



**COMMITTEE FOR THE MEDICINAL PRODUCT FOR HUMAN USE
(CHMP)**

CONCEPT PAPER on the development of a guideline on live recombinant vector vaccines

AGREED BY VWP/GTWP/BWP/SWP	July 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 July 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2007

Comments should be provided to VWP@emea.europa.eu Fax +44 20 7418 8545

KEYWORDS	Vaccines, live recombinant vector vaccines, prevention of infectious diseases, vector, gene, antigen, viral vector, bacterial vector, virulence.
-----------------	--

1. INTRODUCTION

Vaccines against infectious diseases based on a live micro-organism expressing the antigen of a heterologous infectious agent have been under development for some time. Pox virus expressing various heterologous antigens derived, for example, from HIV or malaria, is a typical example of a live recombinant vector vaccine. Although to date no marketing authorisation for such a vaccine for human use has been granted in the EU, many such vaccine candidates are in clinical development, with at least two in phase III studies. Also, live recombinant veterinary vaccines based on canarypox (e.g. Purevax FeLV) or herpes virus (e.g. Vaxxitek HVT+IBD) have been authorised in the EU and a guideline for Live Recombinant Vector Vaccines for Veterinary Use¹ has been developed by the IWP/CVMP.

2. PROBLEM STATEMENT

Specific guidance for live recombinant human vaccines for the prevention of infectious disease does not exist. The CPMP note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99), which came into effect in 2001, provides guidance for plasmid DNA vaccines and for gene therapy medicinal products. Whilst the guideline alludes to live recombinant vaccines, guidance for them is essentially absent. Within the gene transfer guideline, guidance for viral vectors addresses characteristics such as absence of replication competent viruses, packaging cell lines, and efficiency of transfer, which are relevant to therapeutic products and not to vaccines. When vaccines are addressed, it relates to DNA vaccines, and for viral vectors immunogenicity is a safety issue rather than the desired end-point. Consequently, it is clear that guidance specific for live recombinant vector vaccines is absent, and should be developed.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Although several veterinary vaccines based upon live recombinant vectors have been authorised, no authorised human vaccine of this type exists. However, studies have been reported frequently in the scientific literature over many years – and many of these have entered clinical trials. A Feb 2006 WHO list of vaccines under development² notes that fifteen such vaccines are under clinical investigation, one of which is in phase III, and a further twenty vaccines are undergoing preclinical development or being prepared for phase I trials. In addition, one company has recently announced a successful phase III trial of a yellow fever vector expressing a JE antigen³. The vectors being utilised include viruses such as avian pox, adenovirus, vaccinia, yellow fever, measles, respiratory syncytial and vesicular stomatitis, and bacteria such as salmonella, shigella and BCG. The heterologous antigens being expressed by these vectors include antigens from HIV, malaria, Dengue, WNV, SARS, Ebola, plague and anthrax, i.e. generally against those infectious diseases for which no vaccine exists.

The scope of the guideline will include live viral vectors such as vaccinia, yellow fever and measles viruses, viral vectors with restricted replication in humans due to the species barrier such as avipox, and vectors which have been genetically engineered to be replication-incompetent such as adenoviral vectors deleted in the E1A region, or MVA. Live bacterial vectors also are included within the scope of this concept paper. Consideration needs to be given to the terminology used for these types of vaccines.

Issues that are specific to these vaccines include the level of attenuation of the live recombinant vaccine (often already based upon a live attenuated vaccine strain), the replication restriction of the vaccine vector and its design, the extent of immunity raised against the vector itself (with consequences on the re-use of the vector with other antigens), alteration of the host and tissue tropism of the vector, the possibility of reversion to virulence and the possibility of recombination with wild type strains of the vector. Other issues include the method of manufacture, biosafety, clinical follow-up in a healthy patient population and environmental risk.

4. RECOMMENDATION

It is recommended that a guideline devoted to the quality, safety and efficacy of live recombinant vector vaccines is developed. This would be undertaken by a multi-disciplinary drafting group led by VWP, drawing expertise from the BWP (for quality issues), the SWP (for safety issues) and the GTWP (for non-clinical and clinical issues related to gene therapy/transfer products). The guideline would apply to live recombinant vaccines for prevention and treatment of infectious disease. Points to be covered include scope, genetic development, manufacture, quality control, nonclinical safety testing and clinical assessment specific to these vaccines. Where appropriate, reference will be made to other supporting guidelines such as those pertinent for nonclinical and clinical aspects of vaccines.

5. PROPOSED TIMETABLE

It is anticipated that a draft guideline will be available 12-18 months after adoption of the concept paper and will be released for 6 months external consultation, before finalisation within a further 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

Development of the guideline will be led by the VWP in collaboration with the GTWP, BWP and SWP. A coordinating team will be appointed with representation from the above four working parties. Other relevant working parties, e.g. PhVWP, EWP, PEG and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. GTWP, VWP, BWP and SWP will discuss draft versions at their regular meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline will give applicants and Regulatory Authorities guidance on the assessment of live recombinant vaccines. Such a harmonized approach will contribute to the protection of European patients and to foster the development of live recombinant vaccines within the EU. It will also streamline their clinical development and ultimately marketing authorisation applications via the centralised procedure.

8. INTERESTED PARTIES

Internal/External parties

EMEA: VWP, GTWP, BWP, SWP, EWP, PhVWP, PEG

External consultation: pharmaceutical industry, academic networks and learned societies within the EU.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. CVMP Guideline on Live Recombinant Vector Vaccines for Veterinary Use (EMEA/CVMP/004/04). <http://www.emea.europa.eu/pdfs/vet/imp/000404en.pdf>
2. New vaccines against infectious diseases: Research and development status. IVR, WHO, April 2005, updated 2006. http://www.who.int/entity/vaccine_research/documents/en/Status_Table.pdf
3. Acambis' JE vaccine meets and exceeds primary endpoint in pivotal Phase 3 efficacy trial. <http://www.acambis.com/default.asp?id=1839>