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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
CVMP

CONCEPT PAPER ON THE NEED FOR REQUIRING DATA TO DEMONSTRATE THE INFLUENCE OF MATERNALLY DERIVED ANTIBODIES ON THE VACCINATION OF VERY YOUNG ANIMALS

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Comments should be provided to Jill.Ashley@emea.europa.eu / Head of Sector - Veterinary Marketing Authorisation Procedures
Fax +44 20 7418 8447

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8447
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

INTRODUCTION

Early and continued protection against infectious diseases of animals may be normally achieved with the use of safe and efficacious vaccines administered according to immunization protocols appropriate to target animals. Nevertheless, the efficacy of early life immunization of animals may be hampered by the inhibitory influence of maternally acquired immunity and by a lower and shorter active immune response to vaccines. Special emphasis on the need for demonstrating safety and efficacy of early vaccination of animals is put in annex 1 to Directive 2001/82/EC, as amended. Provisions included in parts 7 (safety) and 8 (efficacy) of the annex, address the need not only for demonstrating the safety of veterinary immunological products in animals of the minimum age intended for vaccination but also for evaluating the influence of maternally acquired immunity on the efficacy of the vaccination. In order to fill a gap of guidance documents, IWP intends to elaborate a concept paper addressing the need for drafting a guidance document aimed to provide a more systematic approach to demonstrate the safety and efficacy of vaccines and vaccination schedules in very young animals.

2 PROBLEM STATEMENT

Passive immunisation of offspring, mainly resulting from maternally derived antibodies (MDAs) transmitted primarily, if not only, with the colostrums, can protect neonate animals after birth, the extent and duration of such a protection being proportional to the amount of antibodies received from their mothers. Early protection conferred by most existing vaccines is largely based on antibody dependent mechanisms and their efficacy is determined by the degree and quality of the antibody response. Although they are known to play the key role in the protective mechanism against infectious diseases during the early life of animals, MDAs may interfere with early active immunity formation to vaccines thus posing major risks of immediate lack of efficacy of these products or hampering the efficacy of vaccination protocols. The degree and duration of interference exerted by MDAs vary greatly and depend on many factors, namely the animal species, the degree of immunity of the mother, the quantity and time of uptake by the neonate after birth, the rate of catabolisation. As a consequence, the age at which the levels of MDAs do not interfere with vaccination and with efficient activation of the animal's own immune system can vary, even on an individual basis. Determining the optimum time for vaccination of offspring is, therefore, of crucial importance in order to balance risks and benefits inherent with the use of vaccines in very young animals.

In the attempt to ensure early protection of young animals at the time of first vaccination, even in presence of MDAs, vaccine producers have started to develop products designed to immunize younger and younger animals and requiring repeated administrations of vaccines. Apart from some reasons for concern from an animal welfare ground, major objections have been raised among Member States during Mutual Recognition Procedure regarding the applicability of recommended vaccination schedules and potential safety and efficacy problems in respect to the increase of the youngest recommended age at vaccination. No specific guidance is currently available on how to fulfil safety and efficacy requirements if vaccination is recommended at a young age at which MDAs may still be present or at which an increased risk of adverse reactions may occur. The intended paper is aimed to give recommendation on how to evaluate the influence of MDAs on the development of protective active immunity, and how to minimize any potential risk related to vaccination of very young animals.

3 DISCUSSION

The challenges for early life immunization of animals are mainly represented by the inhibitory influence of MDAs and by the lower degree of immune response to vaccines due to prenatal development and/or postnatal maturation of immune system. Despite the relevance of these issues on neonatal vaccination, the difficulties encountered in order to clearly define the age at which vaccine induced immunity can consistently take place, are well recognized. Nevertheless, if vaccination is recommended in any animal species at an age when a negative impact on vaccine-induced immunity could be expected, then, the absence of potential interference must be demonstrated (e.g. by showing that, at the age recommended for vaccination, MDAs are no longer detectable in the field population at

that age or by showing that the vaccination performed in animals at the recommended age and possibly possessing maternally acquired antibody develop actively formed immunity similar to animals of the same age without maternally acquired immunity). The proposed guidance will address in particular the degree and duration of interference exerted by MDAs and the resulting impact with the formation of an active immune response upon vaccination when animals are vaccinated at very young age. In this respect, relevant factors will be taken into account, such as vaccine antigen, animal species, degree of immunity of the mother, quantity of acquired maternal immunity by the neonate, type of infection against which the vaccination is intended, type of vaccine (e.g., inactivated or attenuated and degree of attenuation) and route of administration (parenteral versus mucosal administration, e.g. intranasal, spray, etc.). The proposed guidance document is intended to provide the basis for a scientifically sound assessment of the data needed to demonstrate the absence of major immune factors influencing early life antibody responses to vaccines and consistency of vaccination schedules. This guideline is not intended for retroactive application. The need for inclusion/exclusion from the assessment (as it will be proposed in the intended guidance document) of new applications for immunological veterinary medicinal products should be carefully evaluated.

4 RECOMMENDATION

At present, vaccination at an increasingly younger age is often recommended without showing absence of interference with pre-existing MDAs and, as a consequence, the consistency of the proposed vaccination schedule. The IWP recommends that a guideline should be developed in order to provide better indications on how to evaluate the safety and efficacy of early life immunization protocols for target animals. This guideline is deemed to be useful for applicants and assessors.

5 PROPOSED TIMETABLE

The concept paper is intended to be adopted at the April CVMP meeting.
The work on the intended guidance document is expected to start after consideration of comments received during the consultation period. Such an evaluation is reasonably expected to take place during October IWP meeting. A draft guideline is expected to be presented at and discussed by IWP on Q1 2008.

6 RESOURCE REQUIREMENTS FOR PREPARATION

The workload for Rapporteurship can be shared by two members of IWP. Discussions on the intended guidance document are expected to take place during 2-3 IWP meetings and 2 CVMP meetings as a maximum. Additional work can be done by correspondence among members of IWP.

7 IMPACT ASSESSMENT (ANTICIPATED)

The guidance document is not intended to increase the regulatory requirements but should improve the evaluation of data relating to the efficacy of vaccination at a young age and to the possible interference by maternal immunity on the efficacy of vaccines. The benefits from an animal welfare ground are self evident.
Information in SPC should lead to clearer instructions for the veterinarian as user or adviser. The guidance document should also lead to harmonisation of provisions at both national and European levels, thus being useful for regulatory authorities. Industry as well should take advantage from a better guidance on dossier requirements which should also result in more accurate planning of financial resources needed for developing a specific product.

8 INTERESTED PARTIES

Industry, Regulatory Authorities in Member State, Assessors.

9 REFERENCES TO LITERATURE, GUIDELINES ETC

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