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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON DATA REQUIREMENTS TO SUPPORT IN USE STABILITY CLAIMS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

AGREED BY IMMUNOLIGICALS WORKING PARTY	June 2006
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END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2006

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1. INTRODUCTION

Immunological veterinary medicinal products (IVMPs) can be marketed as either single or multidose presentations. Consequently, the number of doses per presentation can vary considerably with some authorised presentations containing as few as 1 dose while others may include as many as 10,000 doses. The recommended routes of administration of these products also vary e.g. some are recommended for administration by injection while others are recommended for oral administration by reconstitution in drinking water or in feed. The time taken to administer the entire contents of these products can vary considerably depending on these factors. Therefore, defining an appropriate in-use shelf-life for each individual product is important in order to ensure the safety and efficacy of the finished product during its use. Furthermore, as IVMPs are susceptible to microbiological contamination (due to biological composition and the environment in which they are being administered), it is also important that the microbial safety of the product during its use is assured.

2. PROBLEM STATEMENT

Directive 2001/82/EC Title II Part 6 'Analytical (physico-chemical, biological or immunological) tests of immunological veterinary medicinal products', Section G: Stability Tests states that:

- In the case of products administered in feed, information shall also be given as necessary on the shelf-life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.
- Where a finished product requires reconstitution prior to administration, details of the proposed shelf-life are required for the product reconstituted as recommended. Data, in support of the proposed shelf-life for the reconstituted product shall be submitted'.

The proposed revised Annex 1 indicates that

- In the case of products administered in **drinking water and/or feed**, information shall also be given as necessary on the shelf-life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.
- The proposed in-use shelf-life must be justified.

Currently there is no clear guidance available as to the data required to support in-use shelf-life claims. As a consequence there is no consistency in the allocation of in-use periods. During mutual recognition procedures this lack of guidance has in the past resulted in inconsistencies in the allocation of the final in-use shelf-life.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The presence of a guidance document in this area would overcome the subjectivity often involved in the allocation of the in-use shelf-life. Furthermore, it would inform the proposed marketing authorisation holder (MAH) of the studies required to support the proposed in-use shelf-life. It would also complement the existing guidance notes which currently only include brief references to this issue i.e.

- 'General Requirements for the Production and Control of Live/Inactivated Mammalian Bacterial and Viral Vaccines for Veterinary Use' state that 'Where a finished product requires reconstitution prior to administration, the vaccine shall be reconstituted with the diluent as recommended and the resulting mixture titrated or tested for potency immediately after reconstitution and again after storage'. Further advice on data requirements is not included in this guideline.
- 'Inclusion of Antimicrobial Preservatives in Immunological Veterinary Medicinal Products' – this guideline outlines the studies required to support the inclusion of a preservative in an immunological and to demonstrate in-use preservative efficacy. Included in this guidance note is a recommendation that multidose parenteral IVMPs should be allocated an in-use shelf life of no longer than one working day (8-10 hours) and that the exact proposed in use shelf life

must be accompanied by a justification based on appropriate stability and microbial safety data. However, details of the appropriate stability data are not given.

- 'Position paper on the maximum in-use shelf-life for medicated drinking water' – this position paper states that stability data must be presented in support of proposed in-use shelf-life for pharmaceutical and immunological veterinary medicinal products which are to be administered via drinking water. Advice on the type of data required is not provided.
- Ph. Eur Monograph 0062 'Vaccines for Veterinary Use' - This monograph states that 'Where applicable, studies on the stability of the reconstituted vaccine are carried out, using the product reconstituted in accordance with the proposed recommendations'. No advice is given on the type of studies that should be conducted.

While clearly many documents specify that data are required to support the claimed in-use shelf-life, there is no clear guidance on exactly what these data requirements are e.g. demonstration of vaccine potency and preservative efficacy at defined temperatures over the recommended in-use period. A guidance document in this area would be of benefit to both applicants and assessors as it would clearly define these requirements. As a result this would remove the current inconsistencies associated with the allocation of in-use shelf-life claims and help ensure that the product remains efficacious, safe and free from microbial contamination during use.

4. RECOMMENDATION

The Immunological Working Party recommends that a guideline is drafted which outlines the data required to justify in-use stability claims.

5. PROPOSED TIMETABLE

Work on first draft:	March 2007
Draft Guideline:	June 2007
Adopted by CVMP for consultation:	October 2007

6. RESOURCE REQUIREMENTS FOR PREPARATION

Appointment of Rapporteur
Adequate time for discussion at IWP
EMEA secretariat to manage the consultation process
Discussions at CVMP

7. IMPACT ASSESSMENT (ANTICIPATED)

- **Impact for Industry and other interested parties:**

Clear guidance as to the data required to support in-use stability claims will benefit proposed MAHs as it will eliminate ambiguity as to the exact data requirements and lead to a harmonised approach from Member States. This will eliminate potentially conflicting viewpoints from being an impediment to the MRP and decentralised procedures.

It is not envisaged that this guideline will impact significantly on MAH in terms of workload, as in many instances MAHs are currently undertaking studies to support in-use stability claims.

The end-user will benefit, as the product will have been shown to be efficacious and safe for the duration of the claimed in-use period.

- **Impact for Regulatory Authorities:**

Clear guidance would be beneficial to regulatory authorities in terms of harmonisation at national and European levels. It would help avoid conflicting opinions and therefore eliminate conflicting viewpoints from being an impediment to the MRP and decentralised procedures.