European Medicines Agency
Veterinary Medicines and Inspections

London, 20 July 2006
Doc. Ref. EMEA/CVMP/IWP/205712/2006-CONSULTATION

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON PREPARATION OF MASTER SEEDS TO REPLACE ESTABLISHED MASTER SEEDS ALREADY USED IN AUTHORISED IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS (IVMPS)

AGREED BY IMMUNOLIGICALS WORKING PARTY	June 2006
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	20 July 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2006

Comments should be provided using this template to Jill.Ashley@emea.eu.int /Head of Sector - Veterinary Marketing Authorisation Procedures

Fax +44 20 7418 8447

KEYWORDS	Master Seeds, TSE Guideline

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

1. INTRODUCTION

The production of vaccines usually is based on seed lots. For this purpose, a seed lot system is established at the manufacturers, where a Master Seed (MS) is used to derive Working Seeds (WS) from it. The WS is used as starting micro-organism to produce the final vaccine. In certain circumstances,, the MS must be replaced, usually because either the seed material is depleted or because of new regulatory requirements. Normally, the introduction of a new MS requires a new Marketing Authorisation application. A number of Marketing Authorisation Holders (MAHs) have in such cases withdrawn the product from the market, rather than make new applications. The implementation of EC Directive 99/104/ECto establish freedom of TSE resulted in a number of products disappearing from the market, which has made the availability of vaccines an even more pressing issue.

2. PROBLEM STATEMENT

Replacement of MSs will normally require a new application, but some borderline cases, as the examples presented below, require special treatment:

- The MS of a well established vaccine is out of stock and no more working seed is available. The use of the passage of a micro-organism, preceding the original MS (passage X – 1) to establish a "refreshed" MS may be acceptable as variation and should not require a new MA application.

- According to the Note for Guidance on "Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agent via Human and Veterinary Medicinal Products", all IVMPs had to be assessed due to negative impact of material from ruminant origin to the production of starting materials and final products. In some cases, the MS was regarded as possibly contaminated. Therefore, these MSs could not be used anymore. To avoid the loss of the product, MAHs want to go back to the passage preceding the MS and establish a replacement MS, , whenever no Working Seed passage could be used to establish a new MS.

- The Applicant wishes to use a Working Seed to replace a depleted MS and establish that the safety and efficacy profile of the product produced with the new MS is unaffected by this procedure.

If the need for a new MS as described above appears, the MAH has two options: new application or withdrawal of the product from the market, whenever a new application will become too expensive.
To avoid the loss of useful and needed vaccines and with respect to the fact that the described changes of the MS do not create a really new product, the recreation of the MS from a X – 1 (pre Master Seed) passage should be acceptable, provided that no changes in specifications of production, testing, final product composition and in the SPC occur.
The purpose of the intended paper will be to define the data, which have to be provided for a replacement of the MS concerning quality, safety and efficacy in order to ensure that the replacement does not change the final product.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

On the occasion of the review of existing IVMPs, as required by Directive 92/18/EC, and on the reassessment of starting materials concerning the possible contamination with TSE, some MSs are regarded as not being in compliance with the current legislation. Consequently, some products disappeared from the market,.
Establishment of a MS could be performed as follows:
A certain micro-organism is isolated in the field, treated in a laboratory (e.g. passages, clone purification), and pilot tests for efficacy and safety are performed. Whenever a certain passage is

regarded as suitable basis for a vaccine, this passage is established as stock seed. From this stock seed, one or two passages are performed, to create the MS, on which all tests on quality, safety and efficacy are performed.
Replacing a MS, means that a new MS is passaged from stock seed.

As the approach to the replacement of a MS varies, a harmonised and pragmatic approach is necessary throughout the EU.
The requirements to be fixed in the future guideline should mention all tests on quality, safety and efficacy, being necessary for the replacement. It must be demonstrated, that the characteristics of the MS remain unchanged in terms of genetic stability, immunogenicity, safety to vaccinated and unvaccinated animals etc.
There is a need to compare the "new" MS with the "old" MS or WS derived from it and to justify that the final product derived from both preparations are in conformity.
It is the goal of the intended guideline to identify the key tests, which will allow a decision on the conformity. It is not intened to require a full retesting, which will be contraproductive, wherever a product should be maintained on the market.

4. RECOMMENDATION

The working party recommends to draft a guideline on the requirements to be fulfilled whenever the replacement of a MS is inevitable. The scientific requirements on quality, safety and efficacy data for such a variation should be defined, with respect to the revised Annex I of Directive 2004/28/EC.

5. PROPOSED TIMETABLE

Work on first draft:	October 2006
Draft Guideline:	March 2007
Adopted by CVMP for consultation:	June 2007

6. RESOURCE REQUIREMENTS FOR PREPARATION

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

7. IMPACT ASSESSMENT (ANTICIPATED)

The proposed guideline will have significant consequences for MAHs and veterinarians, as it should provide for the possibility of retaining more IVMPs on the EU market. If no procedure is established for replacing a MS it could result in a number of vaccines disappearing from the market. For authorities and MAHs , the proposed guideline will give advice on which data will be necessary in order to replace a MS. This will lead to a harmonised approach.