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GUIDELINE ON THE SCIENTIFIC DATA REQUIREMENTS FOR A VACCINE ANTIGEN MASTER FILE (VAMF)

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TABLE OF CONTENTS

1. INTRODUCTION

This Guideline on submission of vaccine antigen master files (VAMFs) is intended to inform Applicants of the implementation of Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC. The Guideline includes scientific requirements for the submission, the evaluation and certification of VAMFs. This document may be reviewed after experience. Separate EMEA Procedural Guidance (Guideline on requirements for Vaccine Antigen Master File (VAMF) certification - EMEA/CPMP/BWP/4548/03) details the procedures for VAMF application and EMEA certification.

Vaccines may contain one or several vaccine antigens. The combination of several antigens into one single product offers obvious advantages in terms of effectiveness, compliance and acceptance. Moreover, the same vaccine antigen may be common to several vaccines of the same Marketing Authorisation Holder (MAH) or to a vaccine of a different MAH. Each MAH will apply for a VAMF certificate in this case. Vaccines are authorised in the European Community via the three existing procedures: centralised, mutual recognition and national. Any change to a particular vaccine antigen may therefore impact on products authorised via both Community procedure(s) and national procedure(s). The extension to 10 more accession EU Member States will introduce significantly greater complexity to current systems. The VAMF procedure is aimed at simplification of existing procedures for the authorisation of vaccines for human use via all authorisation procedures operating in the Community.

The VAMF procedure is not mandatory for the MAH or MA Applicant, but provides clear advantages, provided that the VAMF remains common to all the linked MAs, compared with the situation where vaccine MAHs had to apply for variations for all Marketing Authorisations (MAs) via all authorisation procedures operating in the Community. Such procedures are time, resource, and manpower consuming for both MAHs and competent authorities. The VAMF will now allow the pooling of national expertise, and through the coordination by the EMEA, of a single evaluation of a concerned vaccine antigen.

If, in case of a new and not yet licensed vaccine or new combination product the Applicant decides to opt for vaccine antigen master files, the VAMFs must be submitted for all vaccine antigens in the respective marketing authorisation application.

The VAMF should serve as a stand-alone part of the marketing authorisation dossier and contain all relevant information of a biological, pharmaceutical and chemical nature related to each specific antigen, which constitutes one of the active substances of the medicinal product. In the case of a group of antigens aimed at preventing a single infectious disease e.g. Inactivated poliovirus Serotypes 1, 2 and 3, a VAMF should be submitted for each antigen in the group (see Table of Examples below).

The assessment procedure for certification and variations to a VAMF consists of two steps: First, an assessment of the VAMF application dossier of the Applicant in a system analogous to the centralised procedure, which results in a certificate of compliance to Community legislation, issued by the EMEA. This certificate shall be valid throughout the Community. As a second step, the competent authority that will grant or has granted the MA shall take into account the certification or re-certification variation of the VAMF on the concerned medicinal product.

2. THE PRINCIPLE OF A VAMF

A VAMF is that part of a vaccine Marketing Authorisation Application (MAA) concerning the active substance, including information on the starting materials and reagents, the production process, specification and routine controls, the stability and the viral safety aspects of a vaccine antigen and will not include information on the formulation process or further downstream production steps (See under 3 – The Content of a VAMF).

For a number of vaccines, the same vaccine antigen is used for formulating monovalent and combined vaccine presentations of a given manufacturer. A classical example is a diphtheria antigen that may be used in a series of vaccines such as D, dT, DT, DTPa, dTPa, DTPaHBV, DTPaHBVIPV, DTPa,HBVIPVHib, DTPa+Hib, DTPaIPV, DTPaIPV+Hib, DTPw, DTPw+Hib, DTPwHBV[1]. The VAMF for any given vaccine antigen could also be the VAMF for all of the combinations it is or will be used in, provided that the same data are applicable to these MAs. Then the VAMF certificate issued by the EMEA to the Applicant, will be valid for all the combinations it was approved for or will be extended.

In accordance with Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC, a vaccine MAA contains as many VAMFs as there are antigens included in the vaccine. E.g., in application of this principle, a monovalent tetanus vaccine contains one vaccine antigen aimed at preventing a single disease and therefore would have one VAMF; a combined diphtheria-tetanus vaccine contains two distinct vaccine antigens (in this case aimed at preventing two diseases) and the vaccine has therefore two VAMFs. To further illustrate the interpretation of the VAMF principle outlined above, a number of somewhat more complex examples are given in the table below.

[1] Abbreviations for antigens: D: Diphtheria (paediatric dose), d: Diphtheria (adult dose), T: Tetanus, Pa: Pertussis (acellular), Pw: Pertussis (whole cell), HBV: Hepatitis B, IPV: Inactivated Poliomyelitis, Hib: Haemophilus influenzae b.

Vaccine	Number of VAMFs	Interpretation
Haemophilus b (Hib)	1	Although the Hib vaccine is a poly- or oligo-saccharide conjugated to a protein antigen (e.g. tetanus toxoid or CRM197, a genetically modified diphtheria toxoid) it is considered as one single vaccine antigen.
Inactivated poliomyelitis (IPV)	3	According to the text of Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC and in accordance with the CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97), this vaccine is considered as a combined vaccine containing three distinct antigens (IPV serotypes 1, 2 and 3), aimed at preventing a single disease.
Acellular Pertussis (Pa) Two-component (PT & FHA) Three component (PT, FHA & PRN)	 2 3	According to the text of Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC and in accordance with the CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97), this vaccine is considered as a combined vaccine containing two, or three distinct antigens (PT, FHA, PRN,), aimed at preventing a single disease.
Acellular Pertussis (Pa), (copurified PT, FHA, PRN, Fim 2 & 3)	1	This vaccine contains what is considered to be a single vaccine antigen.
23-valent Pneumococcal Polysaccharide	23	According to the text of Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC and in accordance with the CPMP Note for Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97), this vaccine is considered as a combined vaccine containing 23 distinct antigens aimed at preventing a single disease.
Inactivated cholera vaccine (with heat and formalin inactivated antigens)-	4	This vaccine contains: 1. V. cholerae Inaba, classical biotype (heat-inactivated) 2. V. cholerae Inaba, El Tor biotype (formalin-inactivated) 3. V. cholerae Ogawa, classical biotype (heat-inactivated) 4. V. cholerae Ogawa, classical biotype (formalin-inactivated) 1.& 2. are clearly 2 distinct vaccine antigens (both for the biotype and the inactivation process). 3. & 4.could initially be considered as one single antigen but are considered as two separate antigens due to the two different inactivation processes.

3. THE CONTENT OF A VAMF

A VAMF application submitted by a VAMF Applicant (MA Applicant or MAH) will include an administrative section. Further details of this are provided in the relevant EMEA Procedural Guidance on VAMFs (Guideline on requirements for Vaccine Antigen Master File (VAMF) certification - EMEA/CPMP/BWP/4548/03).

The main body of the submission will consist of the following relevant sections of the MA dossier:

EU CTD (NTA, Vol. 2B, Edition 2001)	
3.2.S1	General information
3.2.S.2	Manufacture
3.2.S.3	Characterisation
3.2.S.4	Control of Drug Substance
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.A.1	Equipment and facilities (as relevant for the S-part)
3.2.A.2	Adventitious agents safety evaluation

It may be useful for both the Applicant and competent authorities if, in the MA dossier, the parts concerned be marked as belonging to a VAMF.