The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 26th November 2003
EMEA/CPMP/BWP/2758/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

GUIDELINE ON PHARMACEUTICAL ASPECTS OF THE PRODUCT INFORMATION FOR HUMAN VACCINES

DISCUSSION IN THE BWP	**SEPTEMBER 2000 - JUNE 2002**
DISCUSSION IN QRD	**OCTOBER 2000- NOVEMBER 2001**
TRANSMISSION TO CPMP	**JUNE 2002**
RELEASE FOR CONSULTATION	**JULY 2002**
DEADLINE FOR COMMENTS	**OCTOBER 2002**
DISCUSSION IN QRD	**FEBRUARY 2003**
DISCUSSION IN THE BWP	**MARCH 2003- NOVEMBER 2003**
DISCUSSION IN THE QRD	**NOVEMBER 2003**
ADOPTION BY CPMP	**DECEMBER 2003**
DATE FOR COMING INTO OPERATION	**JUNE 2004**

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.eu.int http://www.emea.eu.int

NOTE FOR GUIDANCE ON PHARMACEUTICAL ASPECTS OF THE PRODUCT INFORMATION FOR HUMAN VACCINES

TABLE OF CONTENTS

INTRODUCTION AND SCOPE

This document provides guidance on the content and presentation of the pharmaceutical particulars applicable to the product information (Summary of Product Characteristics (SPC), labelling, and Package Leaflet (PL)) for human vaccines. The need for special guidance arises from the complexity of many aspects of vaccine composition and formulation.

The fundamental requirements for product information particulars for medicines appear in European law, with guidance being found in a number of documents including the following:

- ”Guideline on Summary of Product Characteristics”, “Readability of the label and package leaflet of medicinal products for human use”, and “Packaging information of medicinal products for human use authorised by the Community”, published by the European Commission.

- “Note for guidance on stability testing of new drug substances and products”, “Note for guidance on stability testing of existing drug substances and products”, “Note for guidance on maximum shelf life of sterile products after first opening or following reconstitution”, the QRD product information templates for SPC, label and PL, the “Compilation of QRD decisions on stylistic matters in product information”, and the “Compilation of QRD decisions on the use of terms”, published by the EMEA.

- The European Pharmacopoeia, and the “List of standard terms for pharmaceutical dosage forms, routes of administration, and containers”, published by the European Directorate for the Quality of Medicines.

- For Applications in the centralised procedure general guidance can be found in the “QRD templates with explanatory notes”, published by EMEA.

Applicants are advised to take this Note for Guidance into account when submitting applications for Marketing Authorisation (MA) for new vaccines, and on the occasions of applying for renewals of existing vaccine MAs.

Guidance specific to the product information for influenza vaccines appears in the “Note for Guidance on harmonisation of requirements for influenza vaccines”, published by the EMEA.

SUMMARY OF PRODUCT CHARACTERISTICS

The pharmaceutical sections of the SPC are 1, 2, 3, 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6.

1. NAME OF THE MEDICINAL PRODUCT

The entries under Section 1. in the SPC for vaccines should appear in the following order:

- Invented name,
- [strength],
- pharmaceutical form,
- common name of the product,

and take into account the following guidance:

Trade name of the medicinal product

European Commission rules for trade names for medicinal products should be observed.

Strength

It is acceptable not to include the strength where it is not straightforward.

Pharmaceutical form

Although the SPC Guideline allows the omission of the pharmaceutical form in cases where it is not straightforward, it is recommended that the pharmaceutical form should be stated for all vaccines. The appropriate standard term, or a combination of standard terms, should be used to express the pharmaceutical form.

In the special case of the pre-filled syringe presentation of a vaccine which is also marketed in (a) different container(s), the pharmaceutical form of the pre-filled syringe presentation only should be expressed as "<solution> <suspension> for injection in a pre-filled syringe". In all other cases, the container should not be included in the pharmaceutical form.

Common name of the vaccine

The common name should be understood to mean the title of the relevant European Pharmacopoeia monograph, where one exists. In cases where there is no European Pharmacopoeia monograph, the stylistics and precedents of European Pharmacopoeia monograph titles should be observed, including the use of words such as "live", "adsorbed" or "virosome" in parenthesis, if relevant.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The principal entries under Section 2. in the SPC should appear in the following order:

- Qualitative and quantitative declaration of each active substance,
- qualitative and quantitative declaration of any adjuvant or adsorbent present,
- a reference to the list of excipients in Section 6.1,

and take into account the following guidance:

Active substance(s)

The qualitative and quantitative composition, in terms of the presence of the active substance(s), should normally be expressed per dose unit.

For polyvalent vaccines, the active substances would ideally appear in the order of the relevant monograph title of the European Pharmacopoeia, where one exists. However, in the case of a presentation consisting of more than one container or chamber, the composition should be presented on a per container/chamber basis.

Abbreviations for active substance names (including carrier protein) should not be used in the SPC.

Directive 2001/83/EC requires that in Section 2. of SPCs, the usual common name or chemical description of active substances shall be used. As there are no INNs for vaccine antigens, each active substance name should be in conformity with European Pharmacopoeia monograph terminology for vaccine antigens in so far as is possible. For non-pharmacopoeial active substances, the active substance name should ideally be expressed according to its formal Latin/Greek name, or according to the disease being protected against, taking historical and pharmacopoeial precedents for the naming of similar vaccine antigens into account.

Taxonomic names for cellular microorganisms should be italicised. Names of microbial genera should not be abbreviated. Generally, for bacteria and viruses, the strain, serotype or other appropriate sub-species designation should be included in the name of each antigen, if relevant.

The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, including the use of the expression “produced in XXX cells <by recombinant DNA technology>”should be mentioned in the SPC, following the pattern set by the following examples:

- “produced in human diploid (MRC-5) cells”;

- “produced in *Escherichia coli* cells by recombinant DNA technology”;

- “produced in chick-embryo cells”.

For polyvalent vaccines, the information on the cellular system(s) used for production may be presented as (a) footnote(s) within Section 2.

Otherwise, the inclusion of a mention of the production process in vaccine active substance names should normally be restricted to the use of the following terms:

- "live, attenuated" (in the case of vaccines containing living micro-organisms),

- "inactivated" (in the case of vaccines containing killed micro-organisms).

Information on the means used to attenuate or inactivate an active substance should not be given, unless this information is necessary for defining the nature of the active substance, for example in the case of a formaldehyde/heat treated cholera vaccine antigen.

Adjuvants/adsorbents

If an adjuvant or adsorbent is present in the vaccine, it should be included in Section 2. Qualitative and Quantitative Composition. European Pharmacopoeia nomenclature should be employed where possible, with the exception that "aluminium hydroxide, hydrated, for adsorption" may be written as "aluminium hydroxide, hydrated".

Aluminium compounds are normally referred to as adsorbents. The quantitative declaration of aluminium compounds should be in terms of the quantity of Al per dose.

For polyvalent vaccines in particular, and also for monovalent vaccines where this is found convenient, the qualitative and quantitative particulars for the adjuvant(s)/adsorbent(s) may be presented as (a) footnote(s) within Section 2. of the SPC.

Abbreviations for adjuvant/adsorbent names should not be used in the SPC or PL. Where justified, however, abbreviations may be considered for the labelling on space limitation grounds, on condition that any such abbreviations are designated in Section 2.

Multidose preparations

In case of multidose preparation include the following statement: "This is a multidose container. See Section 6.5 for the number of doses per vial".

Reference to the list of excipients

Point 2 of the SPC should conclude with the statement "For excipients, see Section 6.1".

3. PHARMACEUTICAL FORM

The statement of pharmaceutical form appearing in Section 3. should be identical to that appearing in Section 1.

This section should conclude with a description of the product as presented for marketing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The excipients should be listed in accordance with the SPC Guideline using the appropriate common names. As with all excipients, preservatives should be listed qualitatively but not quantitatively in Section 6.1.

Residues of reagents used in production should not be listed in Section 6.1. Certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should, however, be mentioned in Section 4.3.

For vaccines, which are presented in more than one container or in dual-chamber syringes, the excipients should be listed per container or per chamber.

Abbreviations for excipients should not be used in the SPC or PL. However, where justified by space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are designated in Section 6.1.

Adjuvants and adsorbents should not be listed in Section 6.1. However, if such materials are present in the vaccine, this section should contain a reference to their appearance in Section 2.

6.2 Incompatibilities

Only pharmaceutical (i.e. physical, chemical or biological) incompatibilities should be stated in Section 6.2.

The appropriate standard QRD statement viz. <Not applicable>, <In the absence of compatibility studies, the vaccine must not be mixed with other medicinal products>, or <The vaccine must not be mixed with other medicinal products except those mentioned in Section 6.6> should appear.

Pharmacological incompatibilities of the vaccine such as *in vivo* interactions with other drugs or with food should not appear in Section 6.2 as they belong in the clinical parts of the SPC.

6.3 Shelf life

The shelf-life declaration(s) should be in accordance with the SPC Guideline and with related guidance documents, addressing the shelf lives of un-reconstituted and reconstituted vaccines as necessary.

6.4 Special precautions for storage

The declaration of the precautions for storage should be in accordance with the SPC Guideline and with related guidance documents.

6.5 Nature and contents of container

The declaration of the nature and contents of the container(s) should be in accordance with the SPC Guideline and with related guidance documents.

In the case of multidose presentations, the number of doses per vial should be stated.

6.6 Instructions for use, handling <and disposal>

In the case of vaccines intended for reconstitution, the appearance of the product before reconstitution will be found in Section 3., while the post-reconstitution appearance belongs in 6.6.

For all vaccines, there should also be a direction to examine the appearance of the product before administration. Additional directions should be added as necessary.

Information necessary for the pharmacist or other health professional to prepare the product for administration to the vaccinee should appear in 6.6. However, information necessary for the physician or other health care professional to administer the product to the vaccinee should not appear in Section 6.6, as this information belongs in the clinical sections of the SPC.

In the case of live vaccines, there should, as a minimum, be a direction for disposal of product, materials which have come into contact with the product, and/or waste material, in accordance with local requirements for the proper disposal of such materials.

In the case of inactivated vaccines, there should, as a minimum, be a direction for safe disposal in accordance with local requirements.

LABELLING

European guidance documents and templates provide comprehensive guidance on labelling. For vaccines, the following additional guidance should be taken into account.

Outer Packaging

For the statement of active substances, the active substance(s), and the adjuvant/adsorbent, if present, should be expressed qualitatively, and quantitatively per dose unit, as they appear in Section 2 of the SPC, with the exception that, in the case of space limitations, abbreviations for certain adjuvants or adsorbents, as designated in the SPC, may be acceptable in special circumstances.

For multidose presentations, the number of doses in the container(s) should be stated. Information about the cellular systems used as production substrates may be omitted from the carton labelling. The word "micrograms" should normally be spelled out as such in the labelling, with the exception that, in the case of severe space limitations, it may be acceptable to use "µg" if justified and there are no safety concerns.

The list of excipients should appear on the carton labelling and be expressed as in Section 6.1 of the SPC. However, where there are space limitations, abbreviations for certain excipients, as designated in the SPC, may be acceptable.

For cartons containing ancillary items such as swabs, needles etc, carton labels should include a list of the total contents of the carton.

A full statement of the precautions for disposal of unused product and/or waste material should appear on the carton labelling, unless space considerations prevent this, in which case a reference to the appearance of the disposal directions in the PL is sufficient.

Small immediate packaging

Pharmaceutical form short terms according to the current "List of Standard terms" may be used in case of space limitation, but only if consistently used in all language versions of the label. In cases of severe space limitation, the pharmaceutical form may be omitted.

Peel-off labelling

MA Holders may consider the addition to the immediate packaging of peel-off labels, which could be used for inserting immunisation details into patient records.

PACKAGE LEAFLET (PL)

European guidance documents and templates provide comprehensive guidance on PLs. As required by Directive 2001/83/EC, the package leaflet should be drawn up in accordance with the SPC, and be written in clear and understandable terms for the user. As in the SPC, abbreviations of terms should not be used, as there are no space limitations in the leaflet.

The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, should be mentioned in the leaflet in a manner consistent with the SPC, including the use of the expression such as "produced in XXX cells <by recombinant DNA technology>".

Complete information regarding instructions for use, handling and disposal by the user should be included in the PL.

The word "micrograms" should be used instead of the abbreviation "µg".

Where an adjuvant or adsorbent is present in a vaccine, the leaflet should include the following or an equivalent statement: “Substance-X is included in this vaccine as an <adjuvant>,<adsorbent>. <Adjuvants> <Adsorbants> are substances included in certain vaccines to accelerate, improve and/or prolong the protective effects of the vaccine”.

ATTACHMENTS

List of attachments

1. Examples of common names for multi-component vaccines
2. Examples of how to present SPC 2. Qualitative and Quantitative Composition.
3. Examples of entries under SPC 6.5 Nature and Contents of Container.

ATTACHMENT 1 - Examples of common names for multi-component vaccines

Diphtheria, tetanus and pertussis vaccine (adsorbed).

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed).

Diphtheria, tetanus, pertussis (acellular, component) and hepatitis B (rDNA) vaccine (adsorbed).

Hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (adsorbed).

Diphtheria, tetanus, pertussis (acellular, component) and haemophilus type b conjugate vaccine (adsorbed).

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA) and poliomyelitis (inactivated) vaccine (adsorbed).

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed).

ATTACHMENT 2 - Examples of how to present SPC 2. Qualitative and Quantitative Composition

Diphtheria, tetanus, pertussis and hepatitis B (rDNA) vaccine (adsorbed)

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than x IU
Tetanus toxoid[1]	not less than x IU
Bordetella pertussis[1] <strain/agglutinogen type> (inactivated)	not less than x IU
Hepatitis B surface antigen [2, 3]	x µg

[1]Adsorbed on aluminium hydroxide, hydrated (x mg Al).

[2]Produced in yeast cells *(Saccharomyces cerevisiae)* by recombinant DNA technology.

[3]Adsorbed on aluminium phosphate (x mg Al).

For excipients, see 6.1

Hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (adsorbed)

1 dose (1 ml) contains:

Hepatitis A virus <strain> (inactivated)[1, 2]	x ELISA Units
Hepatitis B surface antigen [3, 4]	x µg

[1]Produced on human diploid (MRC-5) cells.

[2]Adsorbed on aluminium hydroxide, hydrated (x mg Al).

[3]Produced in yeast cells *(Saccharomyces cerevisiae)* by recombinant DNA technology.

[4]Adsorbed on aluminium phosphate (x mg Al).

For excipients, see 6.1.

Haemophilus type b conjugate and hepatitis B (rDNA) vaccine

1 dose (0.5 ml) contains:

Haemophilus type b polysaccharide	
(polyribosylribitol phosphate)	x µg
conjugated to *Neisseria meningitidis* serogroup B <strain>	
outer membrane protein complex as carrier	y-z µg
Hepatitis B surface antigen[1, 2]	x µg

[1]Produced in recombinant yeast cells *(Saccharomyces cerevisiae)* by recombinant DNA technology.

[2]Adsorbed on aluminium hydroxide, hydrated (x mg Al).

For excipients, see 6.1

Rotavirus vaccine

After reconstitution, 1 dose (2.5 ml) contains:

Reassortant rhesus/human rotavirus serotype 1(live, attenuated)	x 10^5pfu[1]
Reassortant rhesus/human rotavirus serotype 2 (live, attenuated)	x 10^5 pfu[1]
Reassortant rhesus/human rotavirus serotype 42 (live, attenuated)	x 10^5 pfu[1]
Rhesus rotavirus serotype 3 (live, attenuated)	x 10^5 pfu[1]

[1]Plaque-forming units

For excipients, see 6.1

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed)

After reconstitution, 1 dose (0.5 ml) contains:

Originally contained in the suspension:

Diphtheria toxoid[1]	not less than x IU
Tetanus toxoid[1]	not less than x IU
Bordetella pertussis <strain/agglutinogen type> antigens	
Pertussis toxoid[1]	x µg
Filamentous haemagglutinin[1]	x µg
Pertactin[1]	x µg
Hepatitis B surface antigen [2, 3]	x µg
Poliovirus (inactivated)	
type 1 < strain>	x D-antigen unit
type 2 <strain>	x D-antigen unit
type 3 <strain>	x D-antigen unit

Originally contained in the powder:

Haemophilus type b polysaccharide

(polyribosylribitol phosphate)[3] x µg

conjugated to tetanus toxoid as carrier protein y-z µg

[1]Adsorbed on aluminium hydroxide, hydrated (x milligrams Al).

[2]Produced in recombinant yeast cells *(Saccharomyces cerevisiae)* by recombinant DNA technology.

[3]Adsorbed on aluminium phosphate (x milligrams Al).

For excipients, see 6.1.

Hepatitis B vaccine (rDNA)

1 dose (1.0 ml) contains:

Hepatitis B surface antigens (S, pre-S1, and pre-S2 protein monomers)[1, 2] x µg

[1]Produced in murine (C127I) cells by recombinant DNA technology.

[2]Adsorbed on aluminium oxide, hydrated (x mg Al).

For excipients, see 6.1.

Measles, mumps and rubella vaccine (live)

After reconstitution, 1 dose (0.5 ml) contains:

Measles virus[1] <strain> (live, attenuated) not less than 1 x 10^3 $CCID_{50}$[2]

Mumps virus[1] <strain> (live, attenuated) not less than 5 x 10^3 $CCID_{50}$[2]

Rubella virus[1] <strain> (live, attenuated) not less than 1 x 10^3 $CCID_{50}$[2]

[1]produced on < cellular system used for production> cells.

[2]The statistically determined quantity of virus expected to infect 50 per cent of a cell culture.

For excipients, see 6.1.

Pneumococcal polysaccharide vaccine (heptavalent, adsorbed)

1 dose (0.5 ml) contains:

Streptococcus pneumoniae, serotype 4, polysaccharide[1]	x µg
Streptococcus pneumoniae, serotype 6B, polysaccharide[1]	x µg
Streptococcus pneumoniae, serotype 9V, polysaccharide[1]	x µg
Streptococcus pneumoniae, serotype 14, polysaccharide[1]	x µg
Streptococcus pneumoniae, serotype 18C, oligosaccharide[1]	x µg
Streptococcus pneumoniae, serotype 19F, polysaccharide[1]	x µg
Streptococcus pneumoniae, serotype 23F, polysaccharide[1]	x µg

[1]Conjugated to CRM_{197} protein as a carrier (total y-z µg per dose), and adsorbed on aluminium hydroxide, hydrated (total 0.5 mg Al per dose).

For excipients, see 6.1.

ATTACHMENT 3 - Examples of entries under SPC 6.5 Nature and Contents of Container

Example

0.5 ml suspension in pre-filled syringe (Type I glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10.

Not all pack sizes may be marketed.

Example

1.0 ml suspension in a vial (type I glass) with stopper (chlorobutyl rubber) with needle, in a pack size of 1.

Example

0.5 ml suspension and 0.5 ml of solution in prefilled syringe (Type I glass) with dual chambers, a plunger stopper (chlorobromobutyl rubber blend), a tip cap (bromobutyl rubber) and a by-pass stopper (bromobutyl rubber), in a pack size of 1.

Example

10ml (20 x 0.5ml doses) suspension in a vial (Type I glass) with stopper (bromobutyl rubber), in a pack size of 1.