DECISION

No. 3/07.03.2012

on approval of Guidelines for use by the National Agency for Medicines and Medical Devices of the EU Administrative Procedure for Official Batch Release of Biological Products

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), set up based on Order of the Minister of Health no. 1123/18.08.2010, as amended by Order of the Minister of Health no. 1601/28.11.2011, reunited on summons of the NAMMD President in the ordinary meeting of 07.03.2012, in accord with Article 12 (5) of Decision of the Romanian Government no. 734/2010 related to the set up and operation of the National Agency for Medicines and Medical Devices, approved as amended, agrees on the following

DECISION

Art. 1. – The Guideline for use by the National Agency for Medicines and Medical Devices of the EU Administrative Procedure for Official Batch Release of biological Products is approved, according to the Annexes which are integral part of this Decision.

Art. 2. - On the date of this decision coming into force, Decision No. 16/15.06.2007 on approval of the Guidelines for use by the National Medicines Agency of the EC Administrative Procedure for Official Batch Release of Biological Products shall be repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices
Acad. Prof. Dr. Leonida Gherasim

ANNEX
(SCD No. 3/07.03.2012)

GUIDELINES
for use by the National Agency for Medicines and Medical Devices of the EU Administrative Procedure for Official Batch Release of Human Biological Medicinal Products

CHAPTER I
Introduction

Article 1. – This Guideline is a translation into Romanian and adaptation of the European Union (EU) Administrative Procedure for Official Control Authority Batch Release, issued in 2011 by the European Directorate for the Quality of Medicines (EDQM), applicable to the competent authorities in European Union (EU) Member States and states signatories of the Agreement on the European Economic Area (EEA): Norway, Iceland and Liechtenstein.

CHAPTER II
Legal basis

Article 2. - This Guideline implements provisions of Article 826 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing updated provisions of Article 114 of Directive 2001/83/EC of the European Parliament and Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Article 3. - Article 826 of Law No. 95/2006 provides that, in the interests of public health, the National Agency for Medicines and Medical Devices (NAMMD) may require submission of samples in view of the testing, by its own laboratory or a laboratory certified/approved by the NAMMD, prior to the marketing in Romania of immunological medicinal product batches or human blood/plasma-derived products.

Article 4. - The EU Administrative procedure for the Official Control Authority Batch Release (OCABR) consists of analytical controls, document review and issuance of the Official Immunological Medicinal Product Batch Release Certificate.

Article 5. - In the case of compliant testing and document review results, the NAMMD shall issue the batch release certificate, according to the template in Annex II.

Article 6. - This Guideline is applicable to immunological medicinal products or human blood/plasma-derived products manufactured in Romania, in third countries or EU Member States for which the Official Control Authority Batch Release has not been carried out and which are only marketed in Romania.

Article 7. – The official batch release of immunological medicinal products and human blood/human plasma-derived products is additional to the batch release that must be carried out by the manufacturer for a given batch in accordance with Article 760 of Law No. 95/2006 transposing Article 51 of Directive 2001/83/EC, as amended.

Article 8. – (1) The National Agency for Medicines and Medical Devices is included in the list of EU Official Medicines Control Laboratories (OMCLs), currently carrying out official batch release.

(2) The list mentioned under (1) is available from the European Directorate for the Quality of Medicines and HealthCare (EDQM), Department of Biological Standardisation, OMCL Networks and HealthCare (DBO), OCABR Section of the Council of Europe and it is regularly updated.

(3) The laboratories mentioned under (1) are part of the „Official Medicines Control Laboratories" category cited under Article 826 of Law No. 95/2006, transposing provisions of Article 114 of Directive 2001/83/EC, as amended.

Article 9. – In accordance with provisions of Law No. 95/2006, the NAMMD recognises the Official Control Authority Batch Release carried out in any other EU Member State.

Article 10.- The official batch release for an immunological or human blood/human plasma-derived product carried out by a Control Authority in an EU Member State is valid for all other Member States, Romania included.

Article 11. – The Official Control Authority Batch Release Certificate delivered by a National competent authority is the document used by a Member State, Romania included, to indicate that Official Control Authority Batch Release has taken place.

Article 12. – Although Law No. 95/2006 specifically precludes the NAMMD from carrying out OCABR testing of a batch already released by another Member State, Romania included, post-authorisation testing of this batch, e.g. as part of post-authorisation surveillance, is however not precluded.

Article 13. – (1) The wording of (1) (immunological medicinal products) and (2) (blood and plasma derivatives) under Article 826 of Law No. 95/2006 are almost identical, the only difference being the mention in (1) only of the phrase: "*in case of a batch manufactured in another Member State*".

(2) The practical significance of this statement for immunological medicinal products is that, when a batch of immunological medicinal products is manufactured and marketed in Romania, the NAMMD would normally conduct the official batch release.

(3) However, the NAMMD may decide to recognise the official batch release conducted by a control authority in another Member State in case of an immunological medicinal product manufactured in Romania.

(4) Moreover, when a batch of immunological medicinal products is marketed in the Member State where it has been manufactured and that Member State does not require the Official Control Authority Batch Release, then the OMCL in any other Member State may be the testing authority for the purpose of Official Control Authority Batch Release within the European Union of that particular batch.

Article 14. – In accordance with provisions of Article 826 of Law No. 95/2006, for a batch of either immunological medicinal products or human blood/human plasma-derived medicinal product which is to be marketed in Romania and which has undergone the official batch release procedure by the control authority in another Member State, the NAMMD shall not carry out any additional or renewed material control such as further verification and checking of the batch protocol review.

Article 15. – In case of immunological medicinal products and human blood/human plasma-derived products authorised through centralised procedure, a specific official batch release procedure shall be applied by the control authority, which is not described in this Guideline.

Article 16. – (1) In accordance with Article 840 of Law No. 95/2006 transposing Article 123 of Directive 2001/83/EC, whenever Romania decides to prohibit the marketing of an immunological medicinal product or human blood/human plasma-derived product, it shall this decision to the attention of the EMA forthwith.

(2) In accordance with these legal provisions, as well as in the interest of public health, a a mechanism must be in place for the exchange of information concerning non-compliance of

a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma, in line with provisions of Law No. 95/2006 transposing the Directive 2001/83/EC, as amended and according to this Guideline on the Official Control Authority Batch Release.

CHAPTER III
Purpose

Article 17. – Law No. 95/2006 requires recognition within Romania of OCABR carried out by any other Member State.

Article 18. – This Guideline, used by the NAMMD for the Official Control Authority Batch Release of immunological medicinal products and products derived from human blood or human plasma to be marketed in Romania is based on the Administrative Procedure for Official Control Authority Batch Release within the European Economic Area including the European Union

Article 19. – (1) As additional safeguards for the protection of public health, this guideline outlines a system for the exchange of information, amongst all EU competent authorities and the marketing authorisation holders concerned, on batches that do not comply with OCABR testing by a European Union Control Authority.

(2) This Guideline provides, in Annex V, an EU agreed format for OMCL annual reports on official batch release testing.

Article 20. – This Guideline is to be used to facilitate OMCL meeting the requirements of Law No. 95/2006 and to recognise within Romania the Official Control Authority Batch Release within the European Union and its validity; the Guideline also includes the formats for Official Control Authority Batch Release Certificates issued within the EU (Annex II).

Article 21. – This Guideline is also for use by MA holders, providing information on documents used for communications concerning Official Control Authority Batch Release, between the marketing authorisation holder and the competent authorities in the EU Member States.

CHAPTER IV
Principles

Article 22. – (1) Within Romania, an EU Member State in which the Official Control Authority (NAMMD) Batch Release is carried out for all batches of immunological and human blood or plasma-derived medicinal products to be marketed, an Official Control Authority Batch Release Certificate must be issued by a control authority in an EU Member State.

(2) The availability of an Official Control Authority Batch Release Certificate shall show that the batch of medicinal product has been examined and tested by an OMCL within the European Union in accordance with Official Control Authority Batch Release guidelines pertaining to the medicinal product within the European Union and is in compliance with the approved specifications laid down in the relevant monographs of the European Pharmacopoeia (Ph. Eur.) and in the relevant marketing authorisation.

CHAPTER V
Official Batch Release Procedure

Article 23. – (1) Given application to Romania of the official batch release of immunological medicinal products and human blood/human plasma-derived products, the NAMMD informs MAHs that the respective products are to be subjected to OCABR procedures applicable within the EU; in this purpose, the Model letter in Annex I shall be used.

(2) Such NAMMD letter to the MAH shall identify the NAMMD contact person to whom the necessary documents and material for official batch release must be sent.

(3) For batches officially released by another control authority in another Member State, the MAH shall submit the following to the NAMMD:

a) copy of the Official Control Authority Batch Release Certificate issued by the control authority in the Member State concerned;

b) Notification of the intention to market issued according to the form provided in Annex IV.

(4) For batches not officially released by another control authority in another Member State, the MAH shall submit the following to the NAMMD:

- samples relevant to the batch to be marketed in Romania, for laboratory testing purposes;
- summary of the batch protocol according to the form in Annex VI;
- copy of the compliance certificate issued by the manufacturer;
- Notification of the intention to market, in accordance with the form in Annex IV.

(5) The NAMMD shall be notified by the MAH of any new approved variations that have an impact on product specifications or on data supplied in section 3 of the manufacturer's OCABR batch release protocol and relevant for the OMCL in Romania. The MAH shall indicate the date for variation(s) implementation (shall indicate the 1st batch to be affected)[1].

Article 24. For immunological medicinal products and human blood/human plasma-derived products, authorised through centralised procedure, a special batch release procedure shall be applied, outside the scope of this Guideline.

Article 25. - The OCABR procedure employed by the ANM is based on the OCABR employed in the EU and consists of:

a) critical assessment of the batch protocol summary according to the form in Annex VI;

b) tests of the samples exposed by the manufacturer, according to the adequate guidelines.

Article 26. – (1) Normally, OCABR consists only of Phase 1 testing.

(2) In special circumstances, as described under Article 35, Phase 2 testing may be appropriate, which shall only apply as a transitory measure.

Article 27. – The NAMMD completes official batch release within 60 days as of receipt of a complete set of documents and materials, as mentioned under Article 23 (4) as well as of payment of appropriate fees as specified in the Minister of Health Order in force on NAMMD fees.

Article 28. – The NAMMD carries out the official batch release in terms of a quality assurance system based on the ISO 17025 international standard.

Article 29. – If a batch is satisfactory for release, the NAMMD issues an Official Control Authority Batch Release Certificate, giving the details shown in the Model certificate given in Annex II; the certificate is usually written in Romanian.

Article 30. – (1) Shall a batch be found not to comply with the specifications, this information shall be forwarded to the MAH and, by a rapid information exchange mechanism, to specified contact persons (OMCL, competent authorities and the EDQM, Division IV, Batch Release Section) within the EU network.

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[1] If an 'overlap' period with batches using the previously approved MA is expected, the MAH shall inform the NAMMD at this time.

(2) A model notice of non-compliance/failure is presented in Annex III.

(3) Upon request by other Member States, the NAMMD shall provide technical details on the non-compliance found; the same principle applies for manufacturer withdrawal or method deficiencies.

Article 31. – In the particular case where an arrangement has been made between the NAMMD and the manufacturer for parallel batch testing, to perform batch testing in parallel, any batches failing tests and subsequently withdrawn by the manufacturer before completion of the OCABR procedure may not be formally considered as non-compliance; however, the information about the recall shall be circulated within the OCABR network, whenever this occurs in order to avoid the possibility of these batches being submitted for official batch release to another OMCL.

Article 32. – The exchanges of information under Article 30 and 31 of this Guideline are carried out in accordance with Article 839 of Law No. 95/2006 transposing provisions of Article 122 of Directive 2001/83/EC, as amended.

Article 33. – The Official Control Authority Batch Release Certificate is issued for the MAH by the NAMMD.

Article 34. (1) For immunological or human blood/human plasma-derived products intended for marketing in Romania, the marketing authorisation holder of the batch of the medicinal product concerned must ensure that a copy of this certificate issued by a control authority in another Member State is provided to the NAMMD. The corresponding "marketing information form" must also be sent by the marketing authorisation holder to the NAMMD, according to the form presented in Annex IV.

(2) After sending these documents to the NAMMD, the MAH can market the batch in Romania, if, within seven working days, the NAMMD has not raised any objection.

Article 35. There are circumstances requiring Phase 2 testing by an official control authority, such as:

a) a significant change in the manufacturing process;

b) a change in the manufacturing site;

c) the occurrence of adverse reactions;

d) significant inconsistencies in the manufacturing process;

e) changes in the manufacturer’s testing procedures;

f) unexpected variability in the results of quality control test carried out by the manufacturer or the NAMMD;

g) a critical inspection report.

Article 36. – (1) Through the rapid information exchange system, the institution (OMCL, competent authority and/or inspectorates) requiring Phase 2 testing must advise the OMCLs performing OCABR that Phase 2 testing shall be initiated for the product concerned, by informing the specified contact persons and indicating the specific reasons.

(2) Phase 2 testing represents a set of additional tests that are only valid for a transitory period, unless otherwise specified; the latter case will then imply an appropriate revision of the product specific guideline concerned.

CHAPTER VI
Annual report

Article 37. – (1) The NAMMD shall produce an annual report summarising the official batch release testing it has undertaken, which shall be presented in accordance with the Model format in Annex V.

(2) The NAMMD participates in exchange of annual reports which shall be dealt with on the basis of strict confidence between the OMCLs in the network and the EDQM (Division

IV); The EMA and the European Commission shall be informed by the EDQM of any relevant major issues.

ANNEX 1

LETTER TO THE MARKETING AUTHORISATION HOLDER AS REGARDS OFFICIAL CONTROL AUTHORITY BATCH RELEASE FOR BIOLOGICAL MEDICINAL PRODUCTS[2]

1. In accordance with Article 826 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC, as amended, the National Agency for Medicines and Medical Devices (NAMMD) requires that, for each biological product batch, samples and batch protocol summary be submitted for examination for official batch release, in accordance with the Model Templates in Annex VI. The NAMMD examines whether the batch in question is compliant with the approved specifications as set out in the documents submitted for grant of Marketing Authorisation (MA) and with the relevant monographs of the European Pharmacopoeia in force.

2. Samples and summary protocols shall be submitted to the Biological Product Evaluation and Control Department of the NAMMD, presented in accordance with procedures in force for official batch release and medicinal product specific relevant guidelines.

i. The samples submitted should have been collected so as to be truly representative of the relevant batch.

ii. Each dosage container submitted should be labelled with the final labelling, unless there are valid reasons stated for not doing so, in which case a specimen of the final label should be provided and every dosage container labelled with the name of the medicinal product, batch number, dosage and the name of the marketing authorisation holder;

iii. Samples from stages other than the final batch stage should be labelled to clearly indicate the stage in the manufacturing process and the date on which the samples were secured, the name of the medicinal product, the batch number (or other appropriate identification) and the name of the marketing authorisation holder;

3. The marketing authorisation holder must ensure that all the samples and necessary documentation have been submitted to allow undertaking of Official Control Authority Batch Release by the NAMMD, i.e.:
   - detailed description of in-process testing, finished product testing and specifications, as included in the MA documentation,
   - test methods including details of reference standards,
   - labels,
   - example of the batch protocol.

   The National Agency for Medicines and Medical Devices may request further information to facilitate the Official Control Authority Batch Release procedure and this shall be provided by the manufacturer.

4. Marketing of the batch shall be accompanied by the Official Control Authority Batch Release Certificate.

[2] To be applied in case of biological products for which an Official Control Authority Batch Release in an EU Member State has not been carried out.

ANNEX II

EU OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE FOR BIOLOGICAL PRODUCTS

THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES – Av. Sănătescu 48, sector 1, 011478 – Bucharest

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OFFICIAL CONTROL AUTHORITY BATCH RELEASE IN ROMANIA – Finished Product Examined under Article 826 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC, as amended and in accordance with the Administrative Procedure for Official Control Authority Batch Release by the National Agency for Medicines and Medical Devices.

Trade name	
International non-proprietary Name / Ph. Eur. name / common name:	
Batch numbers appearing on package and other identification numbers associated with this batch (e.g. batch number of final bulk):	
Type of container	
Total number of containers in this batch	
Number of doses per container	
Date of start of period of validity	
Date of expiry	
Marketing Authorisation Number issued by:	
Name and address of manufacturer	
Name and address of MAH (if different from the manufacturer)	

This batch has been examined using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard. This examination is based on either[3]:

- the relevant Note for Guidance for this product, or, in the absence of the latter,
- the review of the manufacturer's protocol and the appropriate control laboratory tests as indicated in the marketing authorisation application

This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above marketing authorisation and IS RELEASED for the internal market in Romania only.

Signature	
Name and function of signatory	NAMMD President
Date of issue	

Certificate number :

[3] Delete as appropriate.

ANNEX III

NOTICE OF NON-COMPLIANCE

NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES – Av. Sănătescu 48, sector 1, 011478 – Bucharest

NOTICE OF NON-COMPLIANCE – Finished Product

Examined under Article 826 of Law No. 95/2006 on healthcare reform, Title XVII

– The medicinal product, transposing Article 114 of Directive 2001/83/EC, as amended and in accordance with the Administrative Procedure for Official Control Authority Batch Release by the National Agency for Medicines and Medical Devices.

Trade name	
International non-proprietary Name / Ph. Eur. name / common name:	
Batch numbers appearing on package and other identification numbers associated with this batch (e.g. batch number of final bulk):	
Type of container	
Total number of containers in this batch	
Number of doses per container	
Date of expiry	
Marketing Authorisation Number issued by:	
Name and address of manufacturer	
Name and address of MAH (if different from the manufacturer)	

This batch has been examined using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard. This examination is based on either[4]:

- The relevant guideline for this product or, in its absence,
- the review of the manufacturer's protocol and the appropriate control laboratory tests as indicated in the marketing authorisation application.

This batch is **NOT** in compliance with the approved specifications laid down in the Marketing Authorisation/relevant European Pharmacopoeia monographs and **CANNOT BE RELEASED**.

Technical details of this non-compliance are available on request.

Reason for failure (specify non-compliance):

Comments (briefly if relevant):

Signature	
Name and function of signatory	NAMMD President
Date of issue	

Notice number:

…….

[4] Delete as appropriate

ANNEX IV

MARKETING INFORMATION FORM
CONCERNING A BATCH OF BIOLOGICAL PRODUCT FOR HUMAN USE
IN ROMANIA

Model Templates for MAH use

Address:	*Name and address of specified contact person(s) in Romania*

Trade name:	*Trade name of the product in Romania*
Batch number appearing on the market package	*Batch name of the product which is to be marketed in Romania*
Other batch identification numbers associated with this batch (sufficient information shall be provided in order to allow bulk level traceability):	*Filling bulk number, final batch number and packaging batch number*
Number of containers to be marketed in Romania :	
MA Number:	*MA Number in Romania*
Name and address of the MAH:	*MA Holder for the medicinal product marketed in Romania*
Date of start of period of validity:	
Date of expiry in Romania	
Intended date of marketing	

OMCL performing batch release:	
Official Control Authority Batch Release Certificate number:	

I hereby declare that:
- this batch is in compliance with the above marketing authorisation and the relevant European Pharmacopoeia monographs ;
- this batch is the batch referred to in the accompanying batch release certificate.

A copy of the batch release certificate is attached (official, carried out by the control authority or unofficial, issued by the manufacturer).

Signature of qualified person:	
Number of qualified person:	
Date of issue:	

ANNEX V

MODEL FORMAT AND CONTENT OF ANNUAL REPORTS FOR THE NETWORK FOR OMCL - OCABR OF HUMAN BIOLOGICAL MEDICINAL PRODUCTS

TABLE OF CONTENTS

A table of contents shall be included.

PART 1: **GENERAL SECTION**

Introduction – *name and address of the organisation as well as the reporting period covered in the report.*

Section A: Organisation of the OMCL

A.1 General structure (administrative data shall be presented)

A.2 Personnel matters (indicating the name of responsible persons for the different relevant activities)

Section B: Quality Assurance System (system in place, status of external audits/visits)

Progress in developing a quality assurance system, which (for OMCLs) meets the International Standard ISO 17025, shall be mentioned.

PART 2: TECHNICAL SECTION

Section A: Status of application of Article 114 of Directive 2001/83/EC, as amended

A clear statement shall be included on whether article 114 is applied for blood and plasma derivatives and/or vaccines with the relevant national legal provisions noted. (Article 826 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product).

Section B: Summary of batches tested for OCABR and batch traceability

(For Romanian/third country biological products for human use or those coming from the EU Member States for which the official batch release has not been carried out and which are to be marketed in Romania only)

This section contains the total number of medicinal product batches released during the reporting period together with the total number of batches rejected or withdrawn as well as the reason for doing so.

B.1 Summary tables

Example for plasma and blood derivatives

Product type	Trade name	Manufacturer	Number of batches tested	Number of batches released

Total batches tested:

Total batches released:

Example for vaccines

Vaccine type	Trade name	Manufacturer	Number of batches tested	Number of batches released

Total batches tested:
Total batches released:

B.2 Details on batches rejected/withdrawn

Common name	Manufacturer	Trade name	Batch number	Nominal potency (blood products) or number of doses (vaccines)	Number of containers	Expiry date	Date of notice of non-compliance or withdrawal	Reason

Additional details as required; example: any follow up action

B.3 Batch traceability

B3.1 Detailed list of batches tested at the OMCL

Common name	Manufacturer	Trade Name	Batch number	Nominal potency (blood products) or number of doses (vaccines)	Number of containers in the batch	Expiry date	OMCL certificate date	MA number used for release

B3.2 Detailed list of imported batches released by another Member State

Common name	Manufacturer	Trade Name	Batch number	Nominal potency (blood products) or number of doses (vaccines)	Number of containers marketed in the Member State	Expiry date	Release date	Releasing OMCL

Section C: Technical Details of methods applied for OCABR

This section refers to the specification of laboratory test methods performed by the OMCL for the tests listed in the specific guidelines (e.g., whether the test is described in a European Pharmacopoeia monograph, in an MA, in a WHO requirement or is a validated "in-house" method). Also indicate any relevant details, such as the use of test sera from the manufacturer.

Example for blood derivatives

Medicinal product	**Release test(s)**	**Brief description; indicate the type of method (PhEur, WHO, MA or in-house)**
E.g.: Albumine	Appearance	
	Distribution of molecular size	

	Pre-kallikrein activator	

Other relevant details (as necessary)	*E.g. any reference material used, source and identity*	
Factor VIII	Solubility and appearance	
	Potency	
Other relevant details (as necessary)		

Example for vaccines (and vaccine components)

Vaccine component(s)	**Release test(s)**	**Brief description; indicate the type of method (PhEur, WHO, MA or in-house)**
Eg Diphtheria containing vaccines	Potency Identity	
Other relevant details (as necessary)		
Hepatitis A vaccines, including combinations	Potency Identity Antigen content	
Other relevant details (as necessary)		
Hepatitis B vaccines, including combinations	Potency & identity In vitro HBsAg content Purity& identity	
Other relevant details (as necessary)		

Section D: Summary of test results

This section refers to the specifications used for the results to the OCABR tests. Results shall be given, preferably as graphs or figures demonstrating trend analysis (particularly for potency test data) with appropriate and clear indication of the values obtained on the axis as well as the limits of these specifications. Tables of results for every test on every batch are not necessary where graphs are provided. OMCL data shall be compared to manufacturer's data (preferably incorporated into the trend analysis graphs).

An interpretation of the data by the OMCL shall be included.

It is not sufficient to indicate that testing is compliant with the MA or Ph. Eur., the specification for each test shall be given.

Data collected on reference preparations shall be included and reference material shall be clearly identified.

Additional data from the batch protocol shall also be included where relevant.

It is important to provide information on batches failing the requirements; all failing batches shall be reported in section B2. Additional details concerning the batches not released and the reasons for non-compliance, as well as any follow up action may be provided.

Example of dT – Diftavax Sanofi Pasteur vaccine

Specifications Applied (indicate origin - MA or Ph. Eur.)

Final bulk	
Test	*Specification applied*
Potency assay Diphtheria	
Potency assay Tetanus	
Finished product	
Test	*Specification applied*
Aspect	
Identity of Diphtheria compound	
Identity of Tetanus compound	

Potency assay Diphtheria

Insert graph comparing OMCL and manufacturer's results

Additional comments as necessary

Potency assay Tetanus

Insert graph comparing OMCL and manufacturer's results

Additional comments as necessary

Appearance and identity

Summary of results

Additional comments as necessary

Data on reference preparations used

Section E: Developmental Work, Technical Difficulties

Any problems with assays and technical developmental work and suggestions for the improvement/update of relevant guidelines and European Pharmacopoeia monographs shall be mentioned.

Section F: OMCL network activity

Participation in EDQM collaborative studies or PTS studies or any other collaborative studies or performance measuring studies external to the network shall be mentioned.

Section G: Other related activity

OMCLs are encouraged to report any relevant related activity – Post-Market Surveillance study, spot-testing, release for other markets where relevant (eg. WHO, limited national release).

- Each Competent Authority/OMCL imposing OCABR for all marketed products, shall edit annual reports.
- Member States in the OMCL network choosing not to apply OCABR shall fill in at least Part 1 and 2, section A and B.3.2.
- All Member States are encouraged to report any related activity (post-market surveillance studies, spot-testing, release for other markets where relevant (e.g. WHO, limited national release) in Part 2, section G.
- According to the specific activity of the Member State, the Competent Authority/OMCL shall fill in the relevant sections in the annual report.
- Regardless of the product's destination, all OCABR activities shall be covered. The report shall be as brief as possible, but it is important that the necessary information is provided in order to promote transparency and trust within the network, in view of encouraging the mutual recognition according to the European legislation. It is also useful to analyse the general tendencies generated by the manufacturer and the OMCL.
- The reports shall be available to the named contact persons (for vaccines or blood-derived products) 2 weeks prior to the annual meeting, except for some common decisions and statement within the OMCL network.
- Annual reports are not meant to be published and strictly address to the EC/EEA OCABR network for biologic products and secretariat.

ANNEX VI a

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF BCG VACCINES

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph. Eur. monograph 0163 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples shall be supplied to the Official Medicines Control Laboratory performing batch release:

If *in vitro* assays are used: at least 50 single or multiple dose containers from each final lot.

If *in vivo* assays are used: a quantity equivalent to at least 320 single human doses of each new final bulk or of the first final batch filled from it.

The Control Laboratory performs the following tests:
In vivo assays on every new working seed lot:

- test for virulent mycobacteria
- excessive dermal reactivity

In vitro assays on the final batch:

- Appearance
- Identity
- Count of viable units (potency assay)

3. Protocol submission

The protocol submitted by the manufacturer shall reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.
A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monograph of the Ph. Eur. for products of this type. The manufacturer shall omit listed items not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for**

a specific product may differ in detail from the model provided. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests shall be given). Sufficient detail shall be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed shall also be included. Results of qualification tests on reference materials shall be given for each new in-house reference material.

3.1 Summary information on the finished product (final batch):

Trade name: .....

International non-proprietary name (INN)/ Ph. Eur. name/common name (whichever is appropriate): .....

Batch number(s):

Finished product (final batch): .....

Final bulk : .....

Type of container: .....

Total number of containers in this batch: .....

Number of doses per container: .....

Composition/Volume of single human dose: .....

Date of expiry: .....

Date of start of period of validity: .....

Storage temperature: .....

Marketing authorisation number issued by (Member state/EU): .....

Name and address of manufacturer: .....

Name and address of Marketing Authorisation Holder, if different: .....

Human Albumin used in the production (if applicable) batch number, manufacturer: .....

(if this batch has been tested and released by an OMCL, the release certificate shall be provided): .....

3.2 Production information

Site of manufacture: ……..

Date of manufacture: ……..

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on master seed-lots and working seed-lot upon first submission only.

Identification and source of starting materials (particularly any materials of human or animal origin e.g plasma; serum; strain of bacteria; master and working seeds; excipients and preservatives etc.): .....

Preparation date and reference number of seed-lot(s). Date of approval of protocol indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

Tests on starting materials (including origin, bacterial purity, identity, biochemical characteristics, absence of virulent mycobacteria, skin reaction test): .....

Production details, in process controls and dates of tests: .....

3.2.2 Intermediate Stages

Batch number(s) of intermediates: .....

Date(s) of manufacture: .....

Volume, storage temperature, storage time and approved storage period: .....

Production details including number and volume of containers inoculated, date of inoculation date of harvest: .....

In-process controls and dates of tests (including identity, impurity content, safety tests sterility): .....

3.2.2.1 Final bulk vaccine

Batch number: .....

Date of manufacture: .....

Nature of substances added to final bulk and final concentration: .....

Human albumin used in the manufacturing process:

Batch number(s): .....

Manufacturer: .....

Date of release by manufacturer: .....

Stage in the manufacturing process in which this/these batch(es) is used: .....

The information on excipients derived from human blood (e.g. albumin) shall not be less detailed than the information requested for an active ingredient regarding documentation of starting materials as well as specifications and tests on the final product. Nevertheless, if the batch of albumin has been released by an OMCL in accordance with the Official Authority Batch Release procedure, the submission of a copy of the batch release certificate is sufficient.

Bacterial concentration
Method: .....
Specification: .....
Date: .....
Result: .....

Bacterial and fungal contamination:
Method: .....
Media: .....
Date test on: .....
Date test off: .....
Result: .....

Identification
Method: .....
Specification: .....
Date: .....
Result: .....

Count of viable units before freeze drying
Method: .....
Specification: .....
Date: .....
Result: .....

Test for virulent mycobacteria
Method .....
Specification: .....
Date: .....
Result: .....

3.3 Batch of finished product
Batch number: .....
Date of filling: .....
Date of freeze-drying: .....
Type of container: .....
Number of containers after inspection: .....
Filling volume: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Water
Method: .....
Specification: .....
Date: .....
Result: .....

Bacterial concentration
Method: .....
Specification: .....
Date: .....
Result: .....

Test for virulent mycobacteria (if not done on final bulk)
Method: .....
Specification: .....
Date: .....
Result: .....

Excessive dermal reactivity (unless omission allowed after satisfactory results on the working seed batch and 5 consecutive final batches produced from it)
Method: .....
Specification: .....
Date: .....
Result: .....

Bacterial and fungal contamination:
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Identification
Method: .....
Specification: .....
Date: .....
Result: .....

Count of viable units after freeze drying

Method: .....

Specification: .....

Date: .....

Result: .....

Mean survival rate

Method: .....

Specification: .....

Date: .....

Result: .....

Thermal stability

Method .....

Specification: .....

Date: .....

Result: .....

Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch nr._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____

Function: _____

Date: _____

Signature: _____

ANNEX VI b

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF DIPHTHERIA AND TETANUS VACCINE (ADSORBED)

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph. Eur. monograph 0647 (reduced antigen content) or 0444 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the NAMMD performing batch release:

For each new final bulk, the equivalent of at least 100 single human doses (this may be final bulk, single or multiple dose containers).

From each final batch at least 30 samples of containers of finished product (or an equal volume if distributed in multidose containers).

The Control Laboratory performs the following tests:

On every new final bulk:

- Assay for each new component[5]

The assay is not required on subsequent final batches filled from the same final bulk. For the purpose of batch release assay (potency testing), a final bulk vaccine divided over several intermediate containers is considered as one final bulk.

On the final batch:

- Appearance
- Identity (a test for degree of adsorption may serve as the identity test)

3 Protocol submission

[5] The OMCL may limit *in vivo* potency retesting, provided that sufficient data are available showing consistency of potency of the component concerned. Before reduction of the potency testing scheme the OMCL must obtain approval from the other OMCLs by consultation through the network according to the appropriate internal procedure.

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.
A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail is to be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed shall be included. Results of qualification tests on reference materials are given for each new in-house reference material.

The guideline for this vaccine refers to corresponding sections in other guidelines. This cross referral is for the purpose of simplifying the layout of this guideline only. The information provided by the manufacturer in individual protocols must not cross-refer between different products.

3.1 Summary information on the finished product (final batch)

Trade name: .....
International non proprietary name (INN) /
Ph. Eur. name / common name
of product (whichever is appropriate): .....
Batch number(s): .....
Finished product (final batch): .....
Final bulk: .....
Type of container: .....
Total number of containers in this batch: .....
Number of doses per container: .....
Composition/volume of single human dose: .....
Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....
Marketing authorisation number issued by
(Member state/EU): .....
Name and address of manufacturer: .....
Name and address of Marketing
Authorisation Holder if different: .....

3.2 Production information

Site of manufacture: .....

Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master and working seed-lots and cell banks upon first submission only.

For Control Authority Batch Release of Diphtheria, Tetanus, Pertussis (Whole Cell) Combined Vaccine (Adsorbed), refer to the Diphtheria and Tetanus starting materials (section 3.2.1) in the current guideline.

3.2.2 Intermediate stages

For Control Authority Batch Release of Diphtheria, Tetanus, Pertussis (Whole Cell) Combined Vaccine (Adsorbed), refer to guideline for Diphtheria and Tetanus intermediate stages in the current guideline.

- Single harvests : refer to section 3.2.2.1
- Bulk purified diphtheria and/or tetanus toxoid: refer to section 3.2.2.2
- Final Diphtheria, Tetanus bulk vaccine : refer to section 3.2.2.4

3.3 Batch of finished product

Batch no.: .....

Date of filling: .....

Type of container: .....

Number of containers after inspection: .....

Filling volume: .....

<u>Appearance</u>

Method: .....

Specification: .....

Date: .....

Result: .....

<u>Identity</u>

Method: .....

Specification: .....

Date: .....

Result: .....

<u>Extractable volume</u>

Method: .....

Specification: .....

Date: .....

Result: .....

pH

Method: .....

Specification: .....

Date: .....

Result: .....

Aluminium:

Method: .....

Specification: .....

Date: .....

Result: .....

Sterility

Method: .....

Media: .....

Volume inoculated: .....

Date test on: .....

Date test off: .....

Result: .....

Date of start period of validity ....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____

Function: _____

Date: _____

Signature:_____

ANNEX VI c

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF DIPHTHERIA, TETANUS, PERTUSSIS (WHOLE CELL) COMBINED VACCINE (ADSORBED)

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply.
Ph. Eur. monograph 0445 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples shall be supplied to the NAMMD performing batch release:

For each new final bulk the equivalent of at least 100 single human doses (this may be final bulk, single or multiple dose containers).

From each final batch at least 30 samples of containers of finished product (or an equal volume if distributed in multidose containers).

The Control Laboratory performs the following tests:

On every new final bulk:

- Assay (potency) (for each component)[6]
- Specific toxicity for pertussis (CHO cell and endotoxin tests may be used for screening if abnormal results are obtained then the mouse weight gain test is to be used)

(Assay and specific toxicity test is required only whenever a new final bulk has been used. It is not required on subsequent final batches filled from the same final bulk. For the purpose of batch release assay (potency testing), a final bulk vaccine divided over several intermediate containers is considered as one final bulk)

On the final batch:

- Appearance
- Identity (for diphtheria and tetanus toxoid, a test for degree of adsorption may serve as the identity test)

[6] The OMCL may limit *in vivo* potency retesting, provided that sufficient data are available showing consistency of potency of the component concerned. Before reduction of the potency testing scheme the OMCL must obtain approval from the other OMCLs by consultation through the network according to the appropriate internal procedure.

3. Protocol submission

The protocol submitted by the manufacturer shall reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monograph(s) of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests are given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed are also to be included. Results of qualification tests on reference materials shall be given for each new in-house reference material.

3.1 Summary information on the finished product (final batch)

Trade name: .....

International non proprietary name (INN) /
Ph. Eur. name / common name of product
(whichever is appropriate): .....

Batch number(s): .....

Finished product (final batch): .....

Final bulk: .....

Type of container: .....

Total number of containers in this batch: .....

Number of doses per container: .....

Composition/volume of single human dose: .....

Date of expiry: .....

Date of start of period of validity: .....

Storage temperature: .....

Marketing authorisation number issued by
(Member state/EU): .....

Name and address of manufacturer: .....

Name and address of Marketing
Authorisation Holder if different: .....

3.2 Production information

Site of manufacture: .....

Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master seed-lots and working seed-lot upon first submission only.

Identification and source of starting materials
(particularly any materials of human or animal origin eg. strain of bacteria; master, working seeds; excipients and preservatives etc.): .....

Preparation date and reference number of seed-lot(s). Date of approval of protocol indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation (for B. pertussis strain(s), specify serological types)

Tests on starting materials: .....

Production details, in process
controls and dates of tests: .....

3.2.2 Intermediate stages

3.2.2.1 Single harvests

Annex list of single harvests, indicate medium, date of reconstitution of seed-lot ampoule(s), dates of inoculation, time and temperature of incubation, dates of harvests, volumes, results of tests for identity and bacterial purity, method and dates of inactivation, dates and results of tests for inactivation, yields, storage temperatures, storage times and approved storage periods.

For B. Pertussis:

Presence of agglutinogens

Method: .....

Specification: .....

Date: .....

Result: .....

Purity

Method: .....

Specification: .....

Date: .....

Result: .....

Opacity

Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.2 Bulk purified diphtheria or tetanus toxoid

Batch nr: .....
Date of manufacture: .....
Volume, storage temperature, storage time and approved storage period: .....

Toxoid content

Method: .....
Specification: .....
Date: .....
Result (Lf/ml): .....

Absence of diphtheria or tetanus toxin

Method (specify Lf injected): .....
Specification: .....
Date: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Irreversibility of toxoid: *(specify dates of beginning and end of incubation, dates of beginning and end of test, number of animals, volume inoculated into cell culture (for diphtheria only) or injected into animals, number of animals if relevant, test results).*

Method (specify Lf injected): .....
Specification: .....
Date: .....
Result: .....

Antigenic purity

Method: .....
Specification: .....
Date: .....
Result (Lf/mg protein N): .....

3.2.2.3 Inactivated B. pertussis suspension

Batch no.: .....
Date of manufacture: .....
Volume, storage temperature, storage time and approved storage period: .....

Residual live B. pertussis

Method: .....
Media .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Presence of pertussis toxin

Method: .....
Specification: .....
Date: .....
Result: .....

pH

Method: .....
Specification: .....
Date: .....
Result: .....

Identification

Method: .....
Specification: .....
Date: .....
Result: .....

Sterility

Method: .....
Media .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Opacity

Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.4 Final bulk vaccine

Batch no.: .....

Date of manufacture: .....

Volume, storage temperature, storage time and approved storage period: .....

Information on composition of the final bulk: Specify relevant (adsorption, blending) production dates, reference no(s)., volume(s) and concentrations (in Lf/ml for each of Diphtheria and Tetanus, in Opacity Units calculated from single harvests for B. pertussis).

Antimicrobial preservative

Method: .....

Specification: .....

Date: .....

Result: .....

Free formaldehyde

Method: .....

Specification: .....

Date: .....

Result: .....

Sterility

Method: .....

Media: .....

Volume inoculated: .....

Date test on: .....

Date test off: .....

Result: .....

Specific toxicity *(specify number of animals, dates of beginning and end and result of test. For the mouse weight gain test give all relevant details for each of the control and the test group of mice (survival, mean weight on days zero, 3 and 7 after injection) and indicate percentage of weight gain of test group as compared with control group)*

Method: .....

Specification: .....

Date: .....

Result: .....

Assay *(specify strain, sex, weight and number animals, dates, volumes, route and doses of immunisation and challenge (for B. pertussis specify N^{o} of colony forming units in challenge dose), nature, batch N° and potency in International Units of reference vaccine and responses at each dose-level. Express results in International Units, specify confidence interval, slope of parallel line model and outcome of tests for absence of linearity and parallelism)*

Method: .....

Specification: .....
Date test on: .....
Date test off: .....
Result:

.....

3.3 Batch of finished product (final batch)

Batch no.: .....
Date of filling: .....
Type of container: .....
Number of containers after inspection: .....
Filling volume: .....

<u>Appearance</u>
Method: .....
Specification: .....
Date: .....
Result: .....

<u>Identity</u>
Method: .....
Specification: .....
Date: .....
Result: .....

<u>Extractable volume</u>
Method: .....
Specification: .....
Date: .....
Result: .....

<u>pH</u>
Method: .....
Specification: .....
Date: .....
Result: .....

<u>Aluminium</u>
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Degree of adsorption for D and T

Method: .....
Specification: .....
Date: .....
Result: .....
Date of start period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature:_____

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF HEPATITIS B (RDNA) VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph. Eur. monograph 1056 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the NAMMD for batch release:

At least 5 ml of each bulk purified antigen entering into the composition of the final bulk.

At least ten single or multiple dose containers from each final lot and a quantity equivalent to at least ten single human doses of each new final bulk or a lot filled from it.

The Control Laboratory performs the following tests:

On the bulk purified antigen:

- Identity and purity

On the final batch:

- Appearance
- Identity and Assay (the assay serves as an identity test)
  If an *in vitro* assay is used to determine the antigen content, it must be done on the final batch.
  If an *in vivo* assay* is used, this must be done on each new final bulk or on a batch of finished product derived from it**.**
- Monophosphoryl Lipid A (MPL) content (if applicable)

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing

* The OMCL may limit *in vivo* potency retesting, provided that sufficient data are available showing consistency of potency of the component concerned.

Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product (final batch)

Trade name: .....

International non-proprietary name (INN)/
Ph. Eur. name/
common name of product (whichever is appropriate): .....
Batch number(s):

Finished product (final batch): .....

Final bulk: .....
Type of container: .....

Total number of containers in this batch: .....
Number of doses per container: .....

Composition (antigen concentration)/volume
of single human dose: .....
Target group (children or adults): .....
Production cell: .....

Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....

Marketing authorisation number issued by
(Member state/EU): .....
Name and address of manufacturer: .....

Name and address of MA holder if different: ....

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master and working seed-lots and cell banks upon first submission only and whenever a change has been introduced.

3.2.1.1 **Cell banks**

Master cell bank (MCB) lot Nr and preparation date: .....

Population doubling level (PDL) or passage of MCB: .....

Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

Manufacturer's working cell bank (MWCB) lot number: .....

Population doubling level (PDL) or passage of MCB: .....

Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

Production cell lot number: .....

Identification of cell substrate

Method used: .....

Nature and concentration of antibiotics or selecting agent (s) used in production cell culture maintenance medium : .....

Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum): .....

3.2.1.2 Fermentation

Details on production cells (Scaling-up dates):

Date of thawing ampoule of MWCB: .....

Number of culture flask(s): .....

Dates of passages: .....

Incubation times: .....

Dates of harvesting: .....

3.2.1.3 Control cell cultures if mammalian cells are used for production

Provide information on control cells corresponding to each single harvest.

Ratio or proportion of control to production cell cultures: .....

Period of observation of cultures: .....

Percentage rejected for non specific reasons: .....
Result: .....

Extraneous haemadsorbing viruses

Type(s) of red blood cells: .....
Storage time and tr of rbc: .....
Incubation time and tr of rbc: .....
% of culture tested: .....
Date test on: .....
Date test off: .....
Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....

Type(s) of simian cells: .....

Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type(s) of human cells: .....

Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type(s) of diploid cells: .....
Batch no.. of diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Mycoplasma

Method: .....
Media: .....

Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2 Intermediate stages

Production details, in-process controls and dates of tests. Identification of intermediates e.g. harvests, bulks. Safety tests on intermediates and controls e.g. sterility, adventitious agents, special tests as antigenicity. Details storage conditions.

3.2.2.1 Harvests

Report results of tests for each single fermentation lot, using extra pages if necessary.

Batch number(s): .....

Date of inoculation: .....
Date of harvesting: .....

Volume(s), storage temperature, storage time
and approved storage period: .....

Plasmid retention
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma if mammalian cells are used for production
Method: .....
Media: .....
Volume inoculated: .....

Date test on: .....
Date test off: .....
Result: .....

Antigen content
Method: .....
Specification: .....
Date: .....
Result: .....

Reverse transcriptase assay
Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.2 Purified bulk

Report results of tests for each batch of purified bulk used in further processing.

Batch Nr(s) of purified bulk: .....

Date(s) of purification:
Volume(s), storage temperature, storage time
and approved storage period: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Antigen content
Method: .....
Specification: .....
Date: .....
Result: .....

Total Protein
Method: .....
Specification: .....
Date: .....
Result: .....

Specific activity
Method: .....
Specification: .....
Date: .....
Result: .....

Protein purity (add PAGE photographs, chromatograms, electrophoregrams or other supporting data)
Method: .....
Specification: .....
Date: .....
Result: .....

Residual DNA
Method: .....
Specification: .....
Date: .....
Result: .....

Composition (protein, lipid, polysaccharide)
Method: .....
Specification: .....
Date: .....
Result: .....

Residual chemical(s)
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Additionally, if mammalian cells and animal serum are used for production:
Bovine serum albumin
Method: .....
Specification: .....
Date: .....

Result: .....

3.2.2.3 Adsorbed bulk vaccine

Report results of tests for each batch of purified bulk used in the composition of the final bulk vaccine, using extra pages if necessary

Batch nr(s) of adsorbed bulk vaccine: .....

Adsorption date: .....

Volumes, batch number(s) of all components used during formulation storage temperature, storage time and approved storage period: .....

Degree of adsorption

Method: .....

Specification: .....

Date: .....

Result: .....

Sterility

Method: .....

Media: .....

Volume inoculated: .....

Date test on: .....

Date test off: .....

Result: .....

Free formaldehyde

Method: .....

Specification: .....

Date: .....

Result: .....

Residual chemical(s)

Method: .....

Specification: .....

Date: .....

Result: .....

Adjuvant concentration

Method: .....

Specification: .....

Date: .....

Result: .....

Antimicrobial Preservative

Method: .....

Specification: .....
Date: .....
Result: .....

pH

Method: .....
Specification: .....
Date: .....
Result: .....

Freezing point

Method: .....
Specification: .....
Date: .....
Result: .....

Bacterial endotoxins

Method: .....
Specification: .....
Date: .....
Result: .....

In vitro assay (antigen content)

Method: .....
Batch number of reference vaccine and assigned potency: .....
Date of assay: .....
Validity parameters (linearity, parallelism): .....
Potency result with 95% fiducial limits: .....

In vivo assay (where applicable)

Species, strain, sex, and weight specifications: .....
Dates of vaccination, bleeding: .....
Date of assay: .....
Batch number of reference vaccine and assigned potency: .....
Vaccine doses (dilutions) and number
of animals responding at each dose: .....
ED_{50} of reference and test vaccine: .....
Potency of test vaccine vs. reference vaccine
with 95% fiducial limits: .....
Validity criteria (linearity, parallelism,
precision, ED_{50} between highest and lowest response): .....

3.2.2.4 For vaccines containing MPL

3.2.2.4.1 MPL liquid bulk

Batch no.. and weight of MPL powder used to prepare

the MPL liquid bulk: .....
Batch Nr(s) of MPL liquid bulk: .....
Date(s) of preparation(s): .....
Volume(s), storage temperature,
storage time and approved storage period: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

MPL congener distribution
Method: .....
Specification: .....
Date: .....
Result: .....

MPL content
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Average MPL particle size
Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.4.2 MPL adsorbed bulk
Batch nr(s) of MPL adsorbed bulk: .....
Adsorption date: .....
Batch number(s) of all components
used during adsorption: .....
Volume, storage temperature, storage time and
approved storage period: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Degree of adsorption
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.5 Final bulk vaccine

Report results of tests for each batch of adsorbed bulk.

Batch number of final bulk vaccine: .....

Date of manufacture: .....
Volumes, batch number(s) of all components
used during formulation storage temperature,
storage time and approved storage time period: .....
Batch number(s) and volume(s) of adsorbed bulk vaccine: .....
Batch number(s) and volume(s) of bulk alum diluent: .....
.....

Batch numbers and volumes of adsorbed MPL bulk
used for the formulation of the final bulk vaccine
(if applicable): .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Adjuvant concentration
Method: .....
Specification: .....
Date: .....
Result: .....

Degree of adsorption (if not performed at previous stages)
Method: .....
Specification: .....
Date: .....
Result: .....

Antimicrobial Preservative
Method: .....
Specification: .....
Date: .....
Result: .....

Free formaldehyde
Method: .....
Specification: .....
Date: .....
Result: .....
In vivo assay (if not performed on the final batch)
Species, strain, sex, and weight specifications: .....
Dates of vaccination, bleeding: .....
Date of assay: .....
Batch number of reference vaccine and assigned potency: .....
Vaccine doses (dilutions) and number
of animals responding at each dose: .....
ED_{50} of reference and test vaccine: .....
Potency of test vaccine vs. reference vaccine
with 95% fiducial limits: .....
Validity criteria (linearity, parallelism,
precision, ED_{50} between highest and lowest response): .....

3.3 Batch of finished product (final batch)

Batch number: .....
Date of filling: .....
Type of container: .....
Number of containers after inspection: .....

Filling volume: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Identity of the antigen
Method: .....
Specification: .....
Date: .....
Result: .....

Identity of the MPL (if applicable)
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Extractable volume
Method: .....
Specification: .....
Date: .....
Result: .....

Freezing point
Method: .....
Specification: .....
Date: .....
Result: .....

Adjuvant concentration(s)

Method: .....
Specification: .....
Date: .....
Result: .....

Antimicrobial Preservative
Method: .....
Specification: .....
Date: .....
Result: .....

Degree of adsorption of the antigen
Method: .....
Specification: .....
Date: .....
Result: .....

Free formaldehyde
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Pyrogens or Bacterial endotoxins (according to the MA)
Method: .....
Specification: .....
Date: .....
Result: .....

Degree of adsorption of MPL (if applicable)
Method: .....
Specification: .....
Date: .....
Result: .....

Test for abnormal toxicity
(unless deletion authorised)
Method: .....

Specification: .....
Observation period: .....
Nr & species of animals: .....
Date: .....
Result: .....

In vitro Assay
Method: .....
Specification: .....
Batch number of reference vaccine and assigned potency: .....
Date of assay: .....
Validity parameters (linearity, parallelism): .....
Potency result with 95% fiducial limits: .....

If an *in vivo* assay is used (may be performed on the final bulk):
Species, strain, sex, and weight specifications: .....
Dates of vaccination, bleeding: .....
Date of assay: .....
Batch number of reference vaccine and assigned potency: .....
Vaccine doses (dilutions) and number
of animals responding at each dose: .....
ED_{50} of reference and test vaccine: .....
Potency of test vaccine vs. reference vaccine
with 95% fiducial limits: .....
Validity criteria (linearity, parallelism, precision,
ED_{50} between highest and lowest response): .....
Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no.._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature:_____

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ANNEX VI e

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF INFLUENZA VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph Eur monographs pertaining to this product apply. The Ph. Eur. monographs 0158 (split virion inactivated), 0159 (whole virion inactivated) and 0869 (surface antigen inactivated) are relevant for this product.

These vaccines may contain adjuvant.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the Official Medicines Control Laboratory performing batch release:

At least twenty samples of single or multiple dose final containers.

For adjuvanted vaccines, in the case where the haemagglutinin antigen concentration/identity test is performed on the bulk vaccine before addition of the adjuvant, a volume of that material, equivalent to 20 final doses, must also be submitted to the OMCL.

For purified surface antigen vaccines, an additional 2 ml of monovalent bulk vaccine shall be submitted for the first 5 batches produced from a new influenza strain.
The Control Laboratory performs the following tests:

On the final batch:

- Appearance
- Haemagglutinin antigen concentration/identity test[7] using reference materials currently supplied by NIBSC, UK. Should these be unavailable, reference materials from another officially recognised WHO reference laboratory (eg. TGA-Australia, CBER-USA) may be used. In all cases, the OMCL must use the same source of reagents as the manufacturer as approved in the Marketing Authorisation.
- Bacterial endotoxins

On the first 5 batches of monovalent bulk purified surface antigen vaccine following the introduction of a new influenza strain:

- Purity

[7] In the case of adjuvanted vaccines, if there is interference of the test with the adjuvant, the test may be performed on the bulk vaccine before addition of the adjuvant if approved in the Marketing Authorisation

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product (final lot)

Trade name: .....

International non proprietary name (INN) / Ph Eur name / common name of product (whichever is appropriate): .....

Batch number(s): .....

Finished product (final lot): .....

Final bulk: .....

Type of container: .....

Total number of containers in this batch: .....

Number of doses per container: .....

Composition/volume of single human dose: .....

Prescribed qualitative and quantitative strain composition:

- Strain 1 .....
- Strain 2 .....
- Strain 3 .....

Date of expiry: .....

Date of start of period of validity: .....

Storage temperature: .....

Marketing authorisation number issued by (Member state/EU): .....

Name and address of manufacturer: .....

Name and address of Marketing Authorisation Holder if different: .....

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....
Summary information scheme on batch specific production data including a flowchart, dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission.

Virus seed batches

Virus strain: .....
Source and lot NUMBER of primary seed: .....
Passage history on receipt: .....
Date of receipt: .....
Comments: .....
Storage conditions: .....
Working seed lot NUMBER: .....
Passage history of seed lot(s): .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph Eur monographs and with the Marketing Authorisation: .....
Added antibiotics: .....
Storage conditions of working seed lot(s): .....

Full details on Master and working seed-lots must be provided upon first submission but need not be submitted with the subsequent batches prepared using the same material.
Tests on working seed virus:
Identity

(a) Haemagglutinin
Method: .....
Specification: .....
Date: .....
Result: .....

An example of how this data could be presented as follows:

HI titre				
	Antiserum			
Antigen	Shang/11/87	Sich/2/87	Taiw/1/86	Yam/16/88
A/Shang/11/87(H3N2) Ref				
A/Sich/2/87(H3N2) Ref				

A/Taiw/1/86(H1N1) Ref				
B/Yam/16/88Ref				
A/Shang/11/87 Working seed Lot No...				
A/Sich/2/87 Working seed Lot No...				
A/Taiw/1/86 Working seed Lot No...				
B/Yam/16/88 Working seed Lot No...				

(b) Neuraminidase

Method: .....

Specification: .....

Date: .....

Result: .....

An example of how this data could be presented as follows:

NI titre			
	Antiserum		
Antigen	Anti-N2 NA	Anti-N1 NA	Anti-B NA
A/Shang/11/87(H3N2) Ref			
A/Sich/2/87(H3N2) Ref			
A/Taiw/1/86(H1N1) Ref			
B/Yam/16/88Ref			
A/Shang/11/87 Working seed Lot No....			
A/Sich/2/87 Working seed Lot No...			
A/Taiw/1/86Working seed Lot No...			
B/Yam/16/88 Working seed Lot No....			

Infectivity titre

Method: .....

Specification: .....

Date: .....

Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma

Method: .....
Media: .....
Volume inoculated: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2. Intermediate stages

3.2.2.1 Monovalent virus pool

Virus strain: .....
Batch number(s): .....
Date of inoculation: .....
Date of harvesting: .....
Method of disruption: .....
Date of disruption: .....
Tests for chemicals of disruption: .....
Method of inactivation: .....
Inactivation: Start Date: .....
End Date: .....
Concentration/purification procedure: .....
Added antibiotics: .....
Filtration details (if any): .....
Volume, storage temperature, storage time
and approved storage period: .....
Tests on monovalent virus pool:

<u>Residual infectious virus</u>
Method: .....
Specification: .....
Date: .....
Result: .....
<u>Test for neuraminidase</u> (first three pools only)
Method: .....
Specification: .....
Date: .....

Result: .....

Test for haemagglutinin antigen content
Method: .....
Specification: .....
Date: .....
Result: .....

Identity of haemagglutinin
Method: .....
Specification: .....
Date: .....
Result: .....

Purity (for surface antigen vaccines only)
Method: .....
(e.g.type of PAGE system , reducing/
non reducing conditions) .....
Specification: .....
Date: .....
Result: .....
(e.g. HA, M and NP bands must be identified. Comparison between whole virus and surface antigen preparation must be made)

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.2 Final bulk vaccine
Batch number: .....
Batch number and volume of monovalent
pools used to prepare bulk: .....
Other substances added and volumes: .....
Date of blending: .....
Chemical tests (e. g.preservative; include test for mercury, if appropriate)
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Adjuvant concentration(s) (if applicable) (If not performed on the final lot, as approved in the MA)
Method: .....
Specification: .....
Date: .....
Result: .....

3.3 Batch of finished product (final lot)
Batch number: .....
Date of filling: .....
Type of container: .....
Number of containers after inspection: .....
Filling volume: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Extractable volume
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Adjuvant concentration(s) (if applicable) (may be performed instead on the final bulk if approved in the MA)

Method: .....
Specification: .....
Date: .....
Result: .....

Degree of adsorption of each type (if applicable)
Method: .....
Specification: .....
Date: .....
Result: .....

Particle size (if applicable)
Method: .....
Specification: .....
Date: .....
Result: .....

Antimicrobial preservative
Method: .....
Specification: .....
Date: .....
Result: .....

Identity for haemagglutinin
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Haemagglutinin antigen content (if there is interference of the test with the adjuvant, test may be performed on bulk vaccine before addition of the adjuvant if approved in the MA)
Method: .....
Specification: .....
Date: .....
Result: .....

Total protein (this test may be performed on bulk vaccine)

Method: .....
Specification: .....
Date: .....
Result: .....

Ovalbumin (this test may be performed on final bulk vaccine)
Method: .....
Specification: .....
Date: .....
Result: .....

Bacterial endotoxins
Method: .....
Specification: .....
Date: .....
Result: .....
Date of start period of validity

4. Certification
Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature:_____

ANNEX VI f

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF MEASLES, MUMPS AND/OR RUBELLA COMPONENT COMBINED VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph Eur monographs pertaining to this product apply. The Ph. Eur. monograph 1057 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the NAMMD for batch release:

At least twenty single or multiple dose containers of each final batch.

The Control Laboratory performs the following tests:

On the final batch:

- Assay (potency) and thermal stability
- Appearance
- Identity

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed

must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product

Trade name: .....
International non proprietary name (INN) /
Ph Eur name /
common name of product (whichever is appropriate): .....
Batch number(s): .....
Finished product (final batch): .....
Final bulk: .....
Type of container: .....
Total number of containers in this batch: .....
Number of doses per container: .....
Composition/volume of single human dose: .....
Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....
Marketing authorisation number issued by
(Member state/EU): .....
Name and address of manufacturer: .....
Name and address of Marketing
Authorisation Holder if different: .....

Human Albumin used in the production (if applicable)
Batch numbers, manufacturer: .....
(if this batch has been tested and released by
an OMCL, the release certificates must be
provided; for recombinant human albumin
a certificate of analysis must be provided) .....

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....
Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master and working seed-lots and cell banks upon first submission only.

3.2.1.1 Measles component

3.2.1.1.1 <u>Virus seed lots</u>

Virus strain and reference number used to

prepare your licensed measles vaccine: .....
Master seed lot number and preparation date: .....
Number of passages between two seeds mentioned above: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph Eur monographs and with the Marketing Authorisation: .....
Working seed lot number and preparation date: .....
Passage level from Master seed lot: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph Eur monographs and with the Marketing Authorisation: .....

3.2.1.1.2 Cell substrate for virus propagation

3.2.1.1.2.1 If vaccine is produced on human diploid cells

Master cell bank (MCB) number and preparation date: .....
Population doubling level (PDL) or passage of MCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Manufacturer's working cell bank (MWCB) number and preparation date: .....
Population doubling level (PDL) or passage of MWCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Production cell lot number: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells when inoculated with virus seed: .....
Identification of cell substrate: .....
Methods used: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....
Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum): .....

3.2.1.1.2.2 If vaccine is produced on chicken embryos or chick embryo cells

Provide all information about the specific-pathogen-free healthy flock used as the source of the cells.

Tests for infections

Method: .....

Specification: .....

Date: .....

Result: .....

Date of certification: .....

Nature and concentration of antibiotics
used in production cell culture maintenance medium: .....

3.2.1.1.3 Control cell cultures

Provide information on control cells corresponding to each single harvest.

Ratio or proportion of control
to production cell cultures: .....

Period of observation of cultures: .....

Percentage rejected for non-specific reasons: .....

Result: .....

Extraneous haemadsorbing viruses

Type(s) of red blood cells: .....

Storage time and temperature of red blood cells: .....

Incubation time and temperature of red blood cells: .....

% culture tested: .....

Date test on: .....

Date test off: .....

Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....

Type of simian cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....

Date test on: .....

Date test off: .....

% of viable culture at the end: .....

Result: .....

Type of human cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....

Date test on: .....

Date test off: .....

% of viable culture at the end: .....

Result: .....

Type of other cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....

Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test of: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....
Additional tests for avian viruses for production on avian tissues:
……..

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for other avian viruses
Method: .....
Type and batch number of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.1.2 Mumps component

3.2.1.2.1 Virus seed lots
Virus strain and reference number used to prepare your licensed mumps vaccine: .....
Master seed lot number and preparation date: .....
number of passages between two seeds mentioned above: .....

Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Working seed lot number and preparation date: .....
Passage level from Master seed lot: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

3.2.1.2.2 Cell substrate for virus propagation

3.2.1.2.2.1 If vaccine is produced on human diploid cells

Master cell bank (MCB) number and preparation date: .....
Population doubling level (PDL) or passage of MCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Manufacturer's working cell bank (MWCB) number and preparation date: .....
Population doubling level (PDL) or passage of MWCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph Eur monographs and with the Marketing Autorisation: .....
Production cell lot number: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells when inoculated with virus seed: .....
Identification of cell substrate:
Methods used: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....
Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum):

3.2.1.2.2.2 If vaccine is produced on chicken embryos or chick embryo cells

Provide all information about the specific-pathogen-free healthy flock used as the source of the cells.

<u>Tests for infections</u>

Method: .....
Specification: .....
Date: .....
Result: .....
Date of certification: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....

3.2.1.2.3 Control cell cultures

Provide information on control cells corresponding to each single harvest.

Ratio or proportion of control
to production cell cultures: .....
Period of observation of cultures: .....
Percentage rejected for non-specific reasons: .....
Result: .....

Extraneous haemadsorbing viruses

Type(s) of red blood cells: .....
Storage time and temperature of red blood cells: .....
% culture tested: .....
Date test on: .....
Date test off: .....
Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....

Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type(s) of other cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....
Additional tests for avian viruses for production on avian tissues:

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for other avian viruses
Method: .....
Type and batch number of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.1.3 Rubella component

3.2.1.3.1 Virus seed lots
Virus strain and reference number used to prepare your licensed rubella vaccine: .....
Master seed lot number and preparation date: .....
NUMBER of passages between two seeds mentioned above: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Working seed lot number and preparation date: .....
Passage level from Master seed lot: .....

Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

3.2.1.3.2 Cell substrate for virus propagation

Master cell bank (MCB) number and preparation date: .....
Population doubling level (PDL) or passage of MCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Manufacturer's working cell bank (MWCB) number and preparation date: .....
Population doubling level(PDL) or passage of MWCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Production cell lot number: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells when inoculated with virus seed: .....

Identification of cell substrate:

Methods used: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....
Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum):

3.2.1.3.3 <u>Control cell cultures</u>

Provide information on control cells corresponding to each single harvest.

Ratio or proportion of control to production cell cultures: .....
Period of observation of cultures: .....
Percentage rejected for non-specific reasons: .....
Result: .....

<u>Extraneous haemadsorbing viruses</u>

Type(s) of red blood cells: .....
Storage time and temperature of red blood cells: .....
% culture tested: .....
Date test on: .....
Date test off: .....
Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....

Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type(s) of other cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2 Intermediate stages
3.2.2.1 Measles component
3.2.2.1.1 Single Harvests

Batch number(s): .....
Date of inoculation: .....
Date(s) of harvest: .....
Volume(s), storage temperature, storage time and approved storage period: .....
Report results of tests for each single harvest.

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.1.2 Pooled harvests before clarification

Batch number(s): .....
Date(s) of pooling and clarification: .....
Number, dilution medium, volume(s), storage temperature, storage time and approved storage period: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for mycobacterium spp.
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for extraneous agents
Type of simian cells: .....
Quantity of sample inoculated: .....

Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of diploid cells
(if vaccine produced on this cell type): .....
Batch number of diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Safety test in mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Safety test in suckling mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Blind passage in suckling mice
Volume of sample tested: .....
Number of animals inoculated: .....

Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Test for bacteriophage
Method: .....
Volume of sample inoculated: .....
Date test: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....
Additional tests for avian viruses for production in avian tissues:

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for other avian viruses
Method: .....
Type and batch number of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Embryonated chicken eggs
Allantoic route
Method: .....
Volume of sample inoculated: .....
Date test on: .....

Date test off: .....
Result: .....

Yolk sack route
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.1.3 Pooled harvests after concentration and clarification
Batch number(s): .....
Date(s) of concentration and clarification: .....
Volume(s), storage temperature, storage time
and approved storage period: .....

HSA or BSA content
Method: .....
Specification: .....
Date: .....
Result: .....

Test for removal of intact cells
Method: .....
Specification: .....
Date: .....
Result: .....

Protein nitrogen content
Method: .....
Specification: .....
Date: .....
Result: .....

Residual antibiotic content
Calculation: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....

Sufficient details must be provided for any redispensed pooled harvests after concentration and clarification, including storage time and virus concentration.

3.2.2.2 Mumps component
Batch number(s): .....
Date(s) of manufacture: .....
Volume(s), storage temperature, storage time and approved storage period: .....

3.2.2.2.1 Single Harvests
Batch number(s): .....
Date of inoculation: .....
Date(s) of harvest: .....
Volume(s), storage temperature, storage time and approved storage period: .....
Report results of tests for each single harvest.

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.2.2 Pooled harvests before clarification
Batch number(s): .....
Date(s) of pooling and clarification: .....
Number, dilution medium, volume(s), storage temperature, storage time and approved storage period: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for mycobacterium spp.

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for extraneous agents

Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of diploid cells
(if vaccine produced on this cell type): .....
Batch number of diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Safety test in mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Safety test in suckling mice

Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Blind passage in suckling mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Test for bacteriophage
Method: .....
Volume of sample inoculated: .....
Date test: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....
Additional tests for avian viruses for production in avian tissues:

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for other avian viruses
Method: .....
Type and batch number of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Embryonated chicken eggs
Allantoic route
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Yolk sack route
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.2.3 Pooled harvests after concentration and clarification
Batch number(s): .....
Date(s) of concentration and clarification: .....
Volume(s), storage temperature, storage
time and approved storage period: .....

HSA or BSA content
Method: .....
Specification: .....
Date: .....
Result: .....

Test for removal of intact cells
Method: .....
Specification: .....
Date: .....
Result: .....

Protein nitrogen content
Method: .....
Specification: .....
Date: .....

Result: .....

Residual antibiotic content
Calculation: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....

Sufficient details must be provided for any redispensed pooled harvests after concentration and clarification, including storage time and virus concentration.

3.2.2.3. Rubella component
Batch number(s): .....
Date(s) of manufacture: .....
Volume(s), storage temperature, storage time and approved storage period: .....
3.2.2.3.1 Single Harvests
Batch number(s): .....
Date of inoculation: .....
Date(s) of harvest: .....
Volume(s), storage temperature, storage time and approved storage period: .....
Report results of tests for each single harvest.
Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....
3.2.2.3.2 Pooled harvests before clarification
Batch number(s): .....
Date(s) of pooling and clarification: .....

Number, dilution medium, volume(s), storage temperature, storage time and approved storage period: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for mycobacterium spp.
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for extraneous agents

Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Type of diploid cells
(if vaccine produced on this cell type): .....
Batch number of diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....

% of viable culture at the end: .....
Result: .....

Safety test in mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Safety test in suckling mice
Volume of sample tested: .....
Number of animals inoculated: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Blind passage in suckling mice
Volume of sample tested: .....
Number of animals survived: .....
Date test on: .....
Date test off: .....
Specification: .....
Result: .....

Test for bacteriophage
Method: .....
Volume of sample inoculated: .....
Date test: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....

Result: .....

3.2.2.3.3 Pooled harvests after concentration and clarification

Batch number(s): .....
Date(s) of concentration and clarification: .....
Volume(s), storage temperature, storage time and approved storage period: .....

HSA or BSA content
Method: .....
Specification: .....
Date: .....
Result: .....

Test for removal of intact cells
Method: .....
Specification: .....
Date: .....
Result: .....

Residual antibiotic content
Calculation: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....

Sufficient details must be provided for any redispensed pooled harvests after concentration and clarification, including storage time and virus concentration.

3.2.2.4 Final bulk (multivalent)

Batch number: .....
Date of manufacture: .....
Volume, storage temperature, storage time and

approved storage period: .....

Information on composition of the final bulk: Specify relevant production dates (blending), reference number(s) of measles, mumps, rubella harvests, volume(s), dilution medium and volume.

Human albumin used in the manufacturing process:
Batch number(s): .....
Manufacturer: .....
Date of release by manufacturer: .....
Stage in the manufacturing process
in which these batches are used: .....

The information on excipients derived from human blood (e.g. albumin) must not be less detailed than the information requested for an active ingredient regarding documentation of starting materials as well as specifications and tests on the final product. Nevertheless, if the batch of albumin has been released by an OMCL in accordance with the Official Authority Batch Release procedure, the submission of a copy of the batch release certificate is sufficient.

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.3 Batch of finished product
Batch number: .....
Date of filling: .....
Filling Volume: .....
Date of freeze-drying: .....
Freezing temperature: .....
Drying period: .....
Number of vials after inspection: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....

Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Abnormal toxicity (unless deletion authorised)
Method: .....
Specification: .....
Date: .....
Result: .....

Bovine serum albumin
Method: .....
Specification: .....
Date: .....
Result: .....

Residual recombinant human albumin content (by determination and/or by calculation)
Method: .....
Specification: .....
Date: .....
Result: .....

Water
Method: .....
Specification: .....
Date: .....
Result: .....
Residual antibiotic content: .....
Additional test for production in chick embryos:

Ovalbumin
Method: .....

Specification: .....
Date: .....
Result: .....

Assay for **measles** component (provide absolute and, if authorised, relative potency results)

- Date of inoculation .....
- Type of cell culture .....
- Virus concentration
  for each replicate vial
  of vaccine under test .....
  95% fiducial limits of
  mean .....
- Virus concentration
  for each replicate vial after
  storage for 7 days at 37°C .....
  95% fiducial limits of mean .....
- Virus concentration
  for each replicate vial
  of reference vaccine .....
  95% fiducial limits of mean .....
- Batch number of reference
  preparation and assigned potency: .....

Assay for **mumps** component (provide absolute and, if authorised, relative potency results)

- Date of inoculation .....
- Type of cell culture .....
- Virus concentration
  for each replicate vial
  of vaccine under test .....
  95% fiducial limits of mean .....
- Virus concentration
  for each replicate vial after
  storage for 7 days at 37°C .....
  95% fiducial limits of mean .....
- Virus concentration
  for each replicate vial
  of reference vaccine .....
  95% fiducial limits of mean .....
- Batch number of reference
  preparation and assigned potency: .....

Assay for **rubella** component (provide absolute and, if authorised, relative potency results)

- Date of inoculation .....
- Type of cell culture .....
- Virus concentration
  for each replicate vial
  of vaccine under test .....
  95% fiducial limits of mean .....
- Virus concentration
  for each replicate vial after
  storage for 7 days at 37°C .....
  95% fiducial limits of mean .....
- Virus concentration
  for each replicate vial
  of reference vaccine .....
  95% fiducial limits of mean .....
- Batch number of reference
  preparation and assigned potency: .....
  Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature: _____

ANNEX VI g

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF MEASLES VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply. The Ph. Eur. monograph 0213 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the Official Medicines Control Laboratory performing batch release:

At least twenty single or multiple dose containers of each final batch.

The Control Laboratory performs the following tests:
On the final batch:

- Assay (potency) and thermal stability
- Appearance
- Identity

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.
A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow

recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product

Trade name: .....

International non proprietary name (INN) /
Ph. Eur. name / common name of product
(whichever is appropriate): .....

Batch number(s):

Finished product (final batch): .....

Final bulk: .....

Type of container: .....

Total number of containers in this batch: .....

Number of doses per container: .....

Composition/volume of single human dose: .....

Date of expiry: .....

Date of start of period of validity: .....

Storage temperature: .....

Marketing authorisation number issued by
(Member state/EU): .....

Name and address of manufacturer: .....

Name and address of Marketing
Authorisation Holder if different: .....

Human Albumin used in the production (if applicable)
batch number, manufacturer: .....

(if this batch has been tested and released by an
OMCL, the release certificate must be provided): .....

3.2 Production information

Site of manufacture: .....

Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master and working seed-lots and cell banks upon first submission only.

3.2.1.1 Virus seed lots

Virus strain and reference number used to
prepare your licensed measles vaccine: .....

Master seed lot number and preparation date: .....

number of passages between two seeds

mentioned above: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Working seed lot number and preparation date: .....
Passage level from Master seed lot: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

3.2.1.2 Cell substrate for virus propagation

3.2.1.2.1 If vaccine is produced on human diploid cells

Master cell bank (MCB) NUMBER and preparation date: .....
Population doubling level (PDL) or passage of MCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Manufacturer's working cell bank (MWCB) number and preparation date: .....
Population doubling level (PDL) or passage of MWCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Production cell lot number: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells when inoculated with virus seed: .....
Identification of cell substrate: .....
Methods used: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....
Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum):

.....

3.2.1.2.2 If vaccine is produced on chicken embryos or chick embryo cells

Provide all information about the specific-pathogen-free healthy flock used as the source of the cells.

Tests for infections

Method: .....

Specification: .....

Date: .....

Result: .....

Date of certification: .....

Nature and concentration of antibiotics
used in production cell culture maintenance medium: .....

3.2.1.3 Control cell cultures

Provide information on control cells corresponding to each single harvest.

Ratio or proportion of control
to production cell cultures: .....

Period of observation of cultures: .....

Percentage rejected for non-specific reasons: .....

Result: .....

Extraneous haemadsorbing viruses

Type(s) of rbc: .....

Storage time and temperature of rbc: .....

Incubation time and temperature of rbc: .....

% culture tested: .....

Date test on: .....

Date test off: .....

Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....

Type of simian cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....

Date test on: .....

Date test off: .....

% of viable culture at the end: .....

Result: .....

Type of human cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....

Date test on: .....

Date test off: .....

% of viable culture at the end: .....

Result: .....

Type of diploid cells: .....

Quantity of sample inoculated: .....

Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Additional tests for avian viruses for production on chick embryo cells:

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....
Test for other avian viruses

Method: .....
Type and batch NUMBER of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2 Intermediate stages
3.2.2.1 Single Harvests
Batch NUMBER(s): .....
Date of inoculation: .....
Date(s) of harvest: .....
Volume(s), storage temperature, storage time and

approved storage period: .....
Report results of tests for each single harvest.

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on .....
Date test off: .....
Result: .....

3.2.2.2 Pooled harvests before clarification
Batch number(s): .....
Date(s) of pooling and clarification: .....
Number, dilution medium, volume(s), storage
temperature, storage time and approved storage period: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for mycobacterium spp.
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for extraneous agents
Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....
Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....

Date test off: .....
% of viable culture at the end: .....
Result: .....
Type of diploid cells
(if vaccine produced on this cell type): .....
Batch number of diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....
Additional tests for avian viruses for production on chick embryo cells:

Test for Avian Leukosis Virus
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for other avian viruses
Method: .....
Type and batch NUMBER of avian cells: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Embryonated chicken eggs
Allantoic route
Method: .....
Volume of sample inoculated: .....

Date test on: .....
Date test off: .....
Result: .....

Yolk sack route
Method: .....
Volume of sample inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.3 Pooled harvests after concentration and clarification
Batch number(s): .....
Date(s) of concentration and clarification: .....
Volume(s), storage temperature, storage time and approved storage period: .....

HSA or BSA content
Method: .....
Specification: .....
Date: .....
Result: .....

Test for removal of intact cells
Method: .....
Specification: .....
Date: .....
Result: .....

Residual antibiotic content
Calculation: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....
Virus concentration
Date of inoculation: .....
Cells used for titration: .....
Reference preparation: .....
Result: .....

Additional test for production on chick embryo cells:

Ovalbumin
Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.4 Final bulk
Batch number: .....
Date of manufacture: .....
Volume, storage temperature, storage time and
approved storage period: .....
Human albumin used in the manufacturing process:
Batch number(s): .....
Manufacturer: .....
Date of release by manufacturer: .....
Stage in the manufacturing process in
which this batch (s) is used: .....

The information on excipients derived from human blood (e.g. albumin) must not be less detailed than the information requested for an active ingredient regarding documentation of starting materials as well as specifications and tests on the final product. Nevertheless, if the batch of albumin has been released by an OMCL in accordance with the Official Authority Batch Release procedure, the submission of a copy of the batch release certificate is sufficient.

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.3 Batch of finished product
Batch number: .....
Date of filling: .....
Date of freeze-drying: .....
Freezing temperature: .....
Drying period: .....
Type of container: .....
Filling volume: .....
Number of containers after inspection: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Abnormal toxicity (unless deletion authorised)
Method: .....
Specification: .....
Date: .....
Result: .....

Bovine serum albumin
Method: .....
Specification: .....
Date: .....
Result: .....

Water
Method: .....
Specification: .....
Date: .....
Result: .....
Residual antibiotic content: .....

Additional test for production on chick embryo cells:

Ovalbumin

Method: .....

Specification: .....

Date: .....

Result: .....

Assay

-Date of inoculation .....

-Type of cell culture .....

-Virus concentration for each replicate vial of vaccine under test .....

-95% fiducial limits of mean .....

-Virus concentration for each replicate vial after storage for 7 days at 37°C .....

-95% fiducial limits of mean .....

-Virus concentration for each replicate vial of reference vaccine .....

-95% fiducial limits of mean .....

Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____

Function: _____

Date: _____

Signature: _____

ANNEX VI h

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF A PANDEMIC INFLUENZA VACCINE

To be used in the context of the procedure PA/PH/OMCL (04) 60 DEF

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

In the case of a pandemic which requires rapid release of influenza vaccines, OMCLs must follow the procedure for OCABR of immunological medicinal products for human use to be applied in case of a pandemic or a bioterrorism situation (PA/PH/OMCL (2002) 46 2R and the more targeted procedure for pandemic situations PA/PH/OMCL (04) 60 DEF). As such situations will probably involve rapid preparation of material in a high-pressure environment a second independent check on the product would be of added value.

Testing by an OMCL must be done in parallel with testing and release process by the manufacturer and license assessment. Consequently, a specific abridged testing procedure has been put in place. In addition the release process of a pandemic influenza vaccine by OMCLs must be considered as part of a global preparedness plan including in advance:

- collaboration between the WHO collaborating centre (NIBSC) and OMCLs for the standardization of *in vitro* assays (e.g SRD test) or a surrogate test. It is of particular importance during the assessment phase of both the core pandemic dossiers and the pandemic influenza variation dossiers to examine the suitability of classical *in vitro* assays. The possibility of interference of adjuvant in the test must be looked for in advance.
- collaboration between the WHO collaborating centre (NIBSC) and OMCLs for rapid distribution of the calibrated antigen (likely monovalent vaccine) with support from OMCLs on the calibration procedure of the antigen if required.
- collaboration between the OMCLs and manufacturers wherever possible to characterise the working seed lot (i.e. identity, titre, molecular characterisation by NAT). These tests could be carried out by a WHO collaborative centre e.g. NIBSC.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the NAMMD for testing:

- It is highly recommended, when feasibility allows, that the working seed prepared by the manufacturer be sent to NIBSC or a qualified national reference centre for influenza as agreed by the releasing OMCL, for independent testing to confirm the identity. This

must be done in parallel with the beginning of production and using rapid analytical techniques (NAT).

- At least 4 samples of working seed lot (number of samples to be taken under consideration)
- At least twenty samples of single or multiple dose final containers and at least 20 ml of bulk vaccine and monovalent. Nevertheless due to the exceptional circumstances it must be up to the OMCL to define the schedule for testing final batches before batch release (e.g random testing or absence of testing at this level could be acceptable based on case by case rationale). Definition of the schedule applied by the OMCL will take into consideration whether the working seed has undergone independent testing for identification as described above. This is of particular relevance if it is considered to forgo independent testing in view of particular exceptional circumstances.
- The Control Laboratory performs the following tests:

On the Monovalent Virus pool

- Purity (for surface antigen vaccines only)
- In order to save time the OMCL may consider testing for haemagglutinin antigen concentration/identity on the monovalent virus pool in parallel with the manufacturer.

On the final bulk and/or final batch

- Appearance on the final container
- Haemagglutinin antigen concentration/identity (if testing has already been done by the OMCL on the monovalent virus pool, the OMCL may decide whether random testing or no testing is performed on the final bulk/final container).
- Bacterial endotoxin content

3. Protocol submission

In emergency situations procedures must be put in place to shorten as far as possible the delay for protocol submission and review (e.g electronic submission).

In extreme situations, the licensing dossier may not be completed at the time of initiation of the OCABR procedure. In such cases, the final manufacturer's protocol submitted for OCABR, including any differences from the templates provided, as determined by the details of the Marketing Authorisation must be provided to the OMCL concomitantly with the approved marketing authorisation. OCABR cannot be completed until the marketing authorisation has been approved and all elements of the final protocol with the pertinent information regarding the required tests and the specifications outlined in the MA, has been submitted to and evaluated by the releasing OMCL.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

In all cases, the protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

For protocol submission refer to section 3 of the seasonal vaccine guidelines which most resembles the pandemic vaccine, adapting for the number of strains and marketing authorisation specificities as required.

The following seasonal vaccine guidelines are available.

- Cell cultured influenza vaccine (surface antigen inactivated)
- Influenza vaccine
- Influenza vaccine (surface antigen inactivated virosome)
- Live attenuated influenza vaccine

Note for pandemic influenza vaccines:
With respect to the tests on the working seed:

- For the identity tests, if reagents are not available, the NAT test may serve as the identity test)

If noted in the marketing authorisation, tests on the working seed must include:

- Molecular characterisation by NAT methods (indicating; method, specification date and result)
- For reverse genetics derived virus strains: sequencing to monitor any engineered mutations induced into the pathogenic strain.

With respect to the monovalent virus pool:

- For the identity of haemagglutinin if reagents are not available, the test is not performed

With respect to the final bulk/final batch vaccine:

- If no reagents are available for SRD tests, validated alternative tests could be performed such as HPLC or mouse potency test (indicating; method, specification date, result) following the respective marketing authorisation. Unless otherwise approved, when SRD reagents become available the SRD test must be used for batch release.

The manufacturer must omit items listed in the models that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any

materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature:_____

ANNEX VI i

OFFICIAL CONTROL AUTHORITY BATCH RELEASE OF PERTUSSIS VACCINE (ACELLULAR COMPONENT, ADSORBED)

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph Eur monographs pertaining to this product apply. The Ph. Eur. monograph 1356 is relevant for this product

The guideline could also be applied to acellular co-purified and to the combination of acellular pertussis with other components.

Notes:

- *New developments, especially in the field of potency assays, are ongoing and will eventually be reflected in the international requirements for this product. Furthermore, acellular pertussis vaccines produced using different processes are on the market. Therefore, specifications, methods and requirements may be product specific and may evolve in the near future.*
- *For acellular vaccines in combination with Diphtheria, Tetanus, Hepatitis B, Hib or other components, please also refer to the relevant chapters in the specific guidelines for batch release of each of the appropriate combinations.*

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the Official Medicines Control Laboratory performing batch release:

For each new final bulk the equivalent of at least 100 single human doses (this may be final bulk, single or multiple dose containers).

From each final batch at least 30 samples of containers of finished product (or an equal volume if distributed in multidose containers).

The Control Laboratory performs the following tests:
On every new final bulk:

- Assay (immunogenicity in mice)[8]

[8] The OMCL may limit *in vivo* potency retesting, provided that sufficient data are available showing consistency of potency of the component concerned. Before reduction of the potency testing scheme the OMCL must obtain

- Test for residual Pertussis toxin (by the histamine sensitising test in mice) on final bulk (this test is not requested for the product obtained by genetic modification)
- Bacterial endotoxins

Assay and specific toxicity test is required only whenever a new final bulk has been used. It is not required on subsequent final batches filled from the same final bulk. For the purpose of batch release assay (potency testing), a final bulk vaccine divided over several intermediate containers is considered as one final bulk.

On the final batch:
- Appearance
- Identity

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product

Trade name: .....

International non proprietary name (INN) /
Ph. Eur. name /
common name of product (whichever is appropriate): .....

Batch number(s):

Finished product (final batch): .....

Final bulk: .....

Type of container: .....

approval from the other OMCLs by consultation through the network according to the appropriate internal procedure.

Total number of containers in this batch: .....
Number of doses per container: .....
Composition/volume of single human dose: .....
Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....
Marketing authorisation number issued by
(Member state/EU): .....
Name and address of manufacturer: .....
Name and address of Marketing
Authorisation Holder if different: .....

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....

Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master seed-lots and working seed-lot upon first submission only.

Identification and source of starting materials
(particularly any materials of human or animal origin eg. strain of bacteria; master, working seeds; excipients and preservatives etc.): .....
Preparation date and reference number of seed-lot(s). Date of approval of protocol indicating compliance with the requirements of the relevant Ph Eur monographs and with the Marketing Authorisation
Tests on starting materials: .....
Production details, in process
controls and dates of tests: .....

3.2.2 Intermediate stages

3.2.2.1 Single harvests

Annex list of single harvests, indicate medium, date of reconstitution of seed-lot ampoule(s), dates of inoculation, time and temperature of incubation, dates of harvests, volumes, results of tests for identity and bacterial purity, method and dates of inactivation, dates and results of tests for inactivation, yields, storage temperatures, storage times and approved storage periods.

3.2.2.2 Bulk purified components: PT, FHA, Pertactin, Agg

Batch number(s): .....
Date(s) of manufacture: .....
Volume(s), storage temperature, storage time

and approved storage period: .....

3.2.2.2.1 Before detoxification

Identity

Method: .....
Specification: .....
Date: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Purity

Method: .....
Specification: .....
Date: .....
Result: .....

Residual endotoxin content

Method: .....
Specification: .....
Date: .....
Result: .....

Protein content

Method: .....
Specification: .....
Date: .....
Result: .....

Antigen content

Method: .....
Specification: .....
Date:: .....
Result: .....

3.2.2.2.2 After detoxification

Sterility

Method: .....

Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Absence of residual pertussis toxin *(this test is not necessary for the product obtained by genetic modification)*
Method: .....
Specification: .....
Date: .....
Result: .....

Protein content
Method: .....
Specification: .....
Date: .....
Result: .....

Antigen content and ratio antigen/protein
Method: .....
Specification: .....
Date: .....
Result: .....

Residual detoxifying agent and other reagents
Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.3 Final bulk vaccine
Batch. number: .....

Date of manufacture: .....

Volume, storage temperature, storage time
and approved storage period: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....

Result: .....

Antimicrobial preservative
Nature: .....
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Absence of residual pertussis toxin *(specify number , strain and sex of animals; this test is not necessary for the product obtained by genetic modification)*
Method: .....
Dose: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

Irreversibility of toxoid: *(specify dates of beginning and end of incubation, number, strain and sex of animals; this test is not necessary for the product obtained by genetic modification)*
Method: .....
Dose: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

Bacterial endotoxins
Method: .....
Specification: .....
Date: .....
Result: .....

Free formaldehyde
Method: .....
Specification: .....
Date: .....
Result: .....

Assay *(specify strain, sex, weight and number animals, volumes, doses and route of immunisation and date of bleeding, nature, batch number and potency of reference vaccine and antiserum and responses at each dose-level, specify confidence interval and parameters of validity relevant for the statistical model used (e.g. slope of parallel line model and outcome of tests for absence of linearity and parallelism)*

Method: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

3.3 Batch of finished product

Batch number: .....
Date of filling: .....
Type of container: .....
Number of containers after inspection: .....
Filling volume: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Identity
Method: .....
Specification: .....
Date: .....
Result: .....

Extractable volume
Method: .....
Specification: .....
Date: .....
Result: .....

pH
Method: .....
Specification: .....
Date: .....
Result: .....

Aluminium:
Method: .....
Specification: .....

Date: .....
Result: .....
Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Antimicrobial preservative
Method: .....
Specification: .....
Date: .....
Result: .....
Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature: _____

ANNEX VI j

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF RABIES VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph. Eur. monograph 0216 is relevant for this product

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the Official Medicines Control Laboratory performing batch release:
At least thirty single dose containers of each final batch.

The Control Laboratory performs the following tests:
On the final batch:

- Appearance
- Antigen content by SRD test or ELISA test based on glycoprotein
- NIH test for potency: a reduced testing of one final batch out of ten final batches derived from one final bulk is acceptable.
- Bacterial endotoxins
- Pyrogens (if required in the Marketing Authorisation): a reduced testing of at least one final batch and not less than 10% of final batchs derived from one final bulk is acceptable

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.
A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.
Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were

performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product

Trade name: .....
International non proprietary name (INN) /
Ph. Eur. name /
common name of product (whichever is appropriate): .....
Batch number(s): .....
Finished product (final batch): .....
Final bulk: .....
Type of container: .....
Total number of containers in this batch: .....
Number of doses per container: .....
Composition/volume of single human dose: .....

Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....
Marketing authorisation number issued by
(Member state/EU): .....
Name and address of manufacturer: .....
Name and address of Marketing
Authorisation Holder if different .....
Human Albumin used in the production (if applicable)
batch number, manufacturer .....
(if this batch has been tested and released by
an OMCL, the release certificate must be
provided) .....

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....
Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

The information requested below is to be presented on each submission. Full details on Master and working seed-lots and cell banks upon first submission only.

3.2.1.1 <u>Virus seed lots</u>

Virus strain and reference number used to
prepare your licensed rabies vaccine: .....
Master seed lot number and preparation date: .....
number of passages between two seeds
mentioned above: .....
Date of approval of protocols indicating compliance
with the requirements of the relevant Ph. Eur .
monographs and with the Marketing Authorisation: .....
Working seed lot number and preparation date: .....

Passage level from Master seed lot: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....

3.2.1.2 Cell substrate for virus propagation

Master cell bank (MCB) number and preparation date: .....
Population doubling level (PDL) or passage of MCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Manufacturer's working cell bank (MWCB) number and preparation date: .....
Population doubling level (PDL) or passage of MWCB: .....
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. monographs and with the Marketing Authorisation: .....
Production cell lot number: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells when inoculated with virus seed: .....
Identification of cell substrate
Methods used: .....
Nature and concentration of antibiotics used in production of cell culture maintenance medium: .....
Identification and source of starting materials used in preparing production cells including excipients and preservatives (particularly any materials of human or animal origin e.g. albumin; serum): .....

3.2.1.3 Control cell cultures

Provide information on control cells corresponding to each single harvest.
Ratio or proportion of control to production cell cultures: .....
Period of observation of cultures: .....
Percentage rejected for non-specific reasons: .....
Result: .....

Extraneous haemadsorbing viruses
Type(s) of red blood-cells: .....
Storage time and temperature of red blood-cells: .....
Incubation time and temperature of red blood-cells: .....
% culture tested: .....
Date test on: .....
Date test off: .....
Result: .....

Tests on supernatant fluids for other extraneous agents

Date of sampling from production cell cultures: .....
Type of simian cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....
Type of human cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....
Type of human diploid cells: .....
Quantity of sample inoculated: .....
Incubation temperature: .....
Date test on: .....
Date test off: .....
% of viable culture at the end: .....
Result: .....

Mycoplasma

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Sterility

Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2 Intermediate stages

3.2.2.1 Single Harvests

Batch number(s): .....

Date of inoculation: .....
Date(s) of harvest: .....
Volume(s), storage temperature, storage time
and approved storage period: .....

Tests on viral suspension (before concentration, purification, inactivation)

Date of pooling: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Test for virus concentration: infectious titre on cells culture or on animals
Method: .....
Specification: .....
Date: .....
Result: .....

3.2.2.2 Concentrated purified inactivated harvest
Date of concentration: .....
Date and method of purification: .....
Date and method of inactivation: .....

Tests on viral suspension (after concentration, purification, inactivation)

Test for effective inactivation
Amplification test: .....
Specification: .....
Date: .....
Result: .....
Direct inoculation: .....
Specification: .....
Date: .....
Result: .....

Residual DNA
Method: .....
Specification: .....
Date: .....
Result: .....

Bovine serum albumin
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.2.2.3 Final bulk
Batch number .....

Date of manufacture: .....
Volume, storage temperature, storage time and approved storage period: .....
Human albumin used in the manufacturing process:
Batch number(s): .....
Manufacturer: .....
Date of release by manufacturer: .....
Stage in the manufacturing process in which this batch(s) is used: .....

The information on excipients derived from human blood (e.g. albumin) must not be less detailed than the information requested for an active ingredient regarding documentation of starting materials as well as specifications and tests on the final product. Nevertheless, if the batch of albumin has been released by an OMCL in accordance with the Official Authority Batch Release procedure, the submission of a copy of the batch release certificate is sufficient.

Glycoprotein content (if not performed before)
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....

Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

3.3 Batch of finished product

Batch number: .....

Date of filling: .....

Type of container: .....

Number of containers after inspection: .....

Filling Volume: .....

Appearance
Method: .....
Specification: .....
Date: .....
Result: .....

Water
Method: .....
Specification: .....
Date: .....
Result: .....

Bovine serum albumin
Method: .....
Specification: .....
Date: .....
Result: .....

Protein content
Method: .....
Specification: .....
Date: .....
Result: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Pyrogens (if applicable)
Method: .....
Specification: .....

Date: .....
Result: .....

Bacterial endotoxins
Method: .....
Specification: .....
Date: .....
Result: .....

Potency test *(NIH test)*
Species, strain, sex and weight specifications: .....
Challenge Dose (dilution): .....
Dates of vaccination: .....
Date of assay: .....
Batch number of reference vaccine + assigned potency: .....
ED_{50} of reference and test vaccine: .....
Potency of test vaccine (ED_{50} dilution): .....
Validity criteria: .....
Results: .....

Potency test *(in vitro)*
Date of assay: .....
Batch number of reference: .....
Assigned potency of reference: .....
Validity criteria: .....
Results: .....
Date of start of period of validity .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR

Name: _____
Function: _____
Date: _____
Signature:_____

ANNEX VI k

OFFICAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF POLIOMYELITIS VACCINE (ORAL) (OPV) - MONOVALENT BULK

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following *SOP ANMDM DECPB/S/055* transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

Significant differences in neurovirulence between different batches of live oral polio vaccine have been identified and linked to aspects of production including the passage level of the seed. As part of the authorisation procedure, regulatory authorities need to approve each monovalent bulk of oral polio vaccine to be used in blending the final trivalent product.

Assessment of the vaccines by the regulatory authorities includes examination of neurovirulence.

This process requires considerable expertise and as it may be a lengthy process bulks must be submitted for approval well in advance of the date by which they are required for blending. Testing will take more than 60 days.

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph.Eur monograph 0215 is relevant for this product.

2. Sampling and tests to be performed by the Official Medicines Control Laboratory

The samples required depend on the testing option used and must be arranged with the testing OMCL.

Tests to be performed on each batch of monovalent bulk:

Neurovirulence test – An evaluation of neurovirulence must be performed by the OMCL either using option 1 (monkey neurovirulence test) or option 2 (transgenic mouse neurovirulence test).

a) Monkey neurovirulence test, whether this is performed in assessing new seeds, in resolving conflicting results or for other purposes. For the purpose of approval by the NAMMD, this may be:

(a) performed by the NAMMD

or

(b) performed by the manufacturer in which case the histological sections are provided to the Control Authority for a second reading.

or

(c) performed conjointly by the manufacturer and the Control Authority, in which case the histological slides shall be read independently by the manufacturer and the Control Authority.

Whichever option is used, the data in the submitted protocol must be from the manufacturer's assessment.

b) Mouse neurovirulence tests. For the purpose of approval by the NAMMD, this may be:

(a) performed by the NAMMD.

or

(b) performed by manufacturer, observed by National Control Authority staff qualified to perform it, who shall score the animals as a spot check on scoring by the manufacturer according to the procedure outlined in the relevant SOP adopted by the OCABR network. Inoculation shall be observed by the NCA staff on at least 10% of batches and/or at least 1 batch per year. Inoculation must also be observed if the manufacturer has not performed an assay in 6 months or longer.

(c) Where MAPREC (*mutant analysis by polymerase chain reaction and restriction enzyme cleavage*) is part of the approved marketing authorisation, the OMCL must also repeat the MAPREC assay to monitor consistency.

(d) Performed by another OMCL on behalf of the OMCL carrying out the release of the monovalent bulk

At least 10% of the batches (over the 3 types) tested by TgMT for a given manufacturer must be analysed by an independent laboratory.

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.

A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were

performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information

Poliovirus type: .....
Monovalent bulk number: .....
Volume: .....
Storage temperature: .....
Expiry date: .....
Date of start of period of validity: .....
Marketing Authorisation number
issued by (Member State/EU)
for the trivalent final product: .....
Marketing Authorisation number
issued by (Member State/EU)
for monovalent bulk (if applicable): .....
Name and address of manufacturer: .....
Name and address of Marketing
Authorisation Holder if different: .....

3.2 Production information.

Site of manufacture: .....
Date of manufacture: .....
Summary information scheme on batch specific production data including dates of different production stages, different production site(s) where relevant, identification numbers and blending scheme.

3.2.1 Starting materials

3.2.1.1 <u>Virus seed lots</u>

The information requested below is to be presented on each submission. Full details on Master seed-lots and working seed-lots, including manufacturing protocols is to be presented upon first submission only.

Master seed lot number: .....
Passage level from original Sabin virus: .....
Date of approval of protocol indicating
compliance with relevant EP monographs and
with the Marketing Authorisation: .....
Working seed lot number: .....
Passage level from original Sabin virus: .....
Date of approval of protocol indicating
compliance with relevant EP monographs and
with the Marketing Authorisation: .....

3.2.1.2 Production Substrate

3.2.1.2.1 Production on human diploid cells or continuous cell lines

The information requested below is to be presented upon each submission. Full details of the establishment and characterisation of the Master cell-banks and manufacturer's working cell-bank shall be upon first submission only.

Type of human diploid cells: .....
Manufacturer's working cell bank (MWCB) number: .....
Population doubling level (PDL) or passage level of MWCB: .....
Date of approval of protocol indicating compliance with relevant EP monographs and with the Marketing Authorisation: .....
Date of thawing ampoule of MWCB: .....
PDL or passage of production cells: .....
Batch number of production cells: .....
Nature and concentration of antibiotics used in production cell culture maintenance medium: .....

3.2.1.2.2 Production on primary monkey kidney cell cultures

The following information shall be provided for each animal and the production cells derived from that animal used in the process.

Monkey species: .....
Production monkey number: .....
Quarantine batch number: .....
Diagnostic tests and results:

Test for SV40
Method .....
Result .....

Test for Spuma viruses
Method .....
Result .....

Test for SIV
Method .....
Result .....

Test for Antibodies to Herpes virus B
Method .....
Result .....
Percentage of monkeys surviving quarantine period: .....
Date of Autopsy and trypsinizing of kidneys: .....
Results of examination at autopsy: .....
Total volume of cells produced: .....
Size and numbers of cultures prepared: .....

Production cell lot number: .....
Nature and concentration of antibiotics
used in production cell culture
maintenance medium: .....
Observation of cells at inoculation: .....
Tests for extraneous agents on primary cell culture supernatant fluids
Tests in primary monkey kidney cells
(same species as that from which primary cell culture is derived)
Species: .....
Volume Tested: .....
Method: .....
Result: .....

Tests in monkey kidney cells (only used if the species from which the primary
cell culture is derived is not susceptible to SV40)
Species: .....
Volume Tested: .....
Method: .....
Result: .....

Tests in rabbit kidney cells
Cell Line used: .....
Serum batch used in nutrient medium: .....
Volume Tested: .....
Method: .....
Result: .....

Test for Measles virus:
Human cell line used: .....
Volume tested: .....
Method: .....
Result: .....

3.2.1.3 Control cell cultures

Provide information on control cells corresponding to each single harvest, using extra pages if necessary.

Production Cell Lot number: .....
Ratio or proportion of control
to production cell cultures: .....
Identity test (for human diploid
cells and continuous cell lines only): .....
Start of observation of cultures: .....
Finish of observation of cultures: .....
% rejected for non-specific reasons: .....
Other Observations: .....

Result: .....

Test for haemadsorbing viruses

Type(s) of red blood-cells: .....
Storage time and temperature of red blood-cells: .....
Incubation time and temperature of red blood-cells: .....
% culture tested: .....
Date test on: .....
Date test off .....
Result: .....

Tests on supernatant fluids for other extraneous agents
Date of sampling from production cell cultures: .....

Testing in simian cells
Type of simian cells: .....
Volume Tested: .....
Incubation temperature: .....
Observation Period: .....
Date test off: .....
Test Method .....
Result: .....

Testing in human cells
Type of human Cells: .....
Volume tested: .....
Incubation temperature: .....
Observation period: .....
Date test off .....
Test Method .....
Result: .....

Testing in Rabbit kidney cells (primary monkey kidney cell production only)
Rabbit kidney cells used: .....
Volume tested: .....
Incubation temperature: .....
Observation period: .....
Date of test off .....
Test Method .....
Result: .....

3.2.2.Intermediate Stages
3.2.2.1 Single Harvests
Batch number: .....
Virus infectivity/cell ratio: .....

Population doubling level or
passage level for virus growth
(human diploid cells or continuous cell lines): .....
Production cell lot number of cells inoculated: .....
Date of inoculation: .....
Temperature of incubation: .....
Period of incubation: .....
Volume harvested: .....
Storage Temperature: .....

Tests for Extraneous Agents
Date of sampling .....

Bacterial and Fungal Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Mycoplasma
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....
Test for mycobacterium spp
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Tests for extraneous agents on neutralized single harvests
Batch number of antiserum used for neutralisation .....
Volume of single harvest neutralised: .....

Test on simian cells (same species as that from production cells were derived)
Monkey species: .....
Production monkey number: .....
Quarantine batch No: .....

Volume sample tested .....
Observation period .....
Date of completion of tests .....
Test method: .....
Result .....

Test on simian cells (only necessary if the species from which the production cells are derived is not susceptible to SV40)

Monkey species: .....
Production monkey number: .....
Quarantine batch No: .....
Volume tested .....
Observation period .....
Test method: .....
Date of completion of tests .....
Result .....

Test for measles virus

Type of human cells .....
Volume tested .....
Observation period .....
Date of completion of tests .....
Test method: .....
Result .....

3.3 Monovalent bulk suspension

Batch number: .....
Composition of bulk suspension: .....

Include information on single harvests used and volumes of each used in the bulk suspension:

Nature and quantity of any stabilizer or preservative added: .....
Final volume of suspension: .....
Date of addition: .....
Date of filling: .....
Date of filtration of bulk: .....
Porosity of filters used: .....
Number and volume of storage containers: .....
Date of sampling bulk suspension: .....

Identity test

Date tested: .....
Method used: .....
Reference virus used: .....

Result for reference virus .....
Result: .....

Virus concentration

Date: .....
Method used .....
Reference virus used: .....
Titre (validity limits) of reference virus: .....
Result .....

Genetic markers

rct 40 marker test

Date of test: .....
Reduction of titre of bulk sample: .....
Negative reference used: .....
Reduction of titre of negative reference: .....
Positive reference used: .....
Reduction of titre of positive reference: .....
Result .....

or

MAPREC Test (for Type 3 only)

Test commencement: .....
Test completion: .....
Individual determinations (% 472-C)
for the bulk sample: .....
Individual determinations (% 472-C)
for the reference .....
Reference values for:
High mutant virus control .....
Low mutant virus control .....
Result .....

Details of the following must also be provided from the last four (minimum) to ten (maximum) tests conducted on the reference preparation:

Test Dates
Individual determinations for the bulk sample
Individual determinations for the reference

Neurovirulence test (report tests as defined in the MA)

Neurovirulence test in monkeys

Date of Test: .....
Species of monkey inoculated .....

Test of serological status of monkey toward poliovirus antibodies.

Method: .....
Specification: .....

Date test on: .....
Date test off: .....
Result: .....
Dose of vaccine virus injected .....
Titre of residual inoculum: .....
Number of monkeys inoculated with test sample: .....
Number of histologically valid monkeys observed: .....
Reference preparation: .....
Dose of reference virus injected: .....
Titre of residual inoculum: .....
Number of monkeys inoculated with reference: .....
Number of histologically valid monkeys observed: .....

Results

Mean lesion score of test sample .....
Mean lesion score of reference .....
Difference between MLS's .....
C1 value of testing laboratory .....

Details of the clinical survey of monkeys during the test must be given

Data forms that show the recording details of the histological observations and assessment must be attached.

Details of the following must also be provided from the last four (minimum) to ten (maximum) tests conducted on the relevant reference preparation for the appropriate poliovirus type:

Date of Test: .....
Reference preparation: .....
Number of inoculated animals: .....
Number of positive animals: .....
Mean Lesion score: .....
Within test Variance (s^2): .....

Neurovirulence test in mice

Source of inoculated mice: .....
Delivery date of mice: .....
Date(s) of inoculation: .....

Pre-inoculation titre for upper dose of vaccine virus inoculated:

.....

Titre of residual inoculum: .....

Pre-inoculation titre for lower dose of vaccine virus inoculated:

.....

Titre of residual inoculum: .....

Pre-inoculation titre for upper dose of reference virus inoculated:

.....

Titre of residual inoculum: .....

Pre-inoculation titre for lower dose of reference virus inoculated:

.....

Titre of residual inoculum: .....

Results

Copies of all of the clinical scoring sheets must be attached to the protocol.

Summary of final clinical scores (by class)
for males in each virus/dose group: .....

Summary of final clinical scores (by class)
for females in each virus/dose group: .....

For both the vaccine and the reference indicate all non-vaccine related deaths for each sex (specify day and probable cause where possible).

Log Odd Ratio value: .....

Details of the following must also be provided from the last four (minimum) to ten (maximum) tests conducted on the relevant reference preparation for the appropriate poliovirus type:

Date of Test .....
Reference preparation .....
Number of inoculated males at each dose .....
Number of inoculated females at each dose .....
Number of males at each dose for each class
of clinical score .....
Number of females at each dose for each class
of clinical score .....
Paralysis rate of males at each dose .....
Paralysis rate of females at each dose .....
Total number of animals inoculated at each dose .....
Total number of animals at each dose for each class of clinical score .....
Updated L1 value (acceptance limit) .....
Updated L2 value (rejection limit) .....

Tests for extraneous agents in rabbits (only for bulks derived from primary monkey kidney cells)

Strain and source of animals .....
Number and weight of animals .....
Date of inoculation .....
Volume and route of inoculation .....
Results (survival numbers etc...) .....

Tests for extraneous agents in guinea-pigs (only for bulks derived from primary monkey kidney cells)

Strain and source of animals .....
Number and weight of animals .....
Date of inoculation .....
Volume and route of inoculation .....

Results (survival numbers etc...) .....

Test for retroviruses (only for monovalent bulk suspensions derived from primary monkey kidney cells)

Date of test: .....

Reference used: .....

Result: .....

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____

Function: _____

Date: _____

Signature:_____

ANNEX VI l

OFFICIAL CONTROL AUTHORITY (NAMMD) BATCH RELEASE OF POLIOMYELITIS VACCINE (ORAL) (OPV) – TRIVALENT VACCINE

1. Introduction

Control Authority (NAMMD) Batch Release of immunological medicinal products is performed within the framework of Article 826 of Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Article 114 of Directive 2001/83/EC of the European Parliament and of the Council on a Community Code relating to medicinal products for human use, as amended, and following SOP ANMDM DECPB/S/055 transposing the current Guideline on EU Administrative Procedure for Official Control Authority Batch Release.

Monovalent bulks are evaluated separately because of the complexity and importance of the testing involved for the safety of the product. The bulks receive separate certificates of approval, which must be supplied along with the samples and protocols for the final product. The OMCL releasing the final product may contact the OMCL that approved the monovalent bulk for further information if required

All general and specific Ph. Eur. monographs pertaining to this product apply. Ph. Eur monograph 0215 is relevant for this product.

2. Sampling and tests to be performed by the Control Laboratory

The following samples must be supplied to the NAMMD for batch release:
At least twenty samples of final containers
The Control Laboratory performs the following tests:

- Assay (potency) and thermal stability
- Appearance
- Identity

3. Protocol submission

The protocol submitted by the manufacturer must reflect all appropriate production steps and controls for a particular product as outlined in the Marketing Authorisation for that specific product.
A **model** protocol is given below to help ensure complete and harmonised protocol A **model protocol** is given below to help ensure complete and harmonised protocol submission. An attempt has been made to list all appropriate production steps and controls as required by the various Marketing Authorisations and the relevant monographs of the Ph. Eur. for products of this type. The manufacturer must omit listed items that are not required by his Marketing Authorisation and include any relevant additional items. It is thus possible that **a protocol for a specific product may differ in detail from the model provided**. The essential point is that **all relevant details demonstrating compliance with the Marketing Authorisation and the Ph. Eur. monographs (if available) for a particular product be given in the protocol submitted**.

Results of the tests are required ("passed" or "failed" is not sufficient, initial results and, where applicable, results of retests must be given). Sufficient detail must be supplied to allow recalculation of test values. Specifications for each test and dates when the tests were performed must also be included. Results of qualification tests on reference materials must be given for each new in-house reference material.

3.1 Summary information on the finished product (final lot)

Trade name: .....
International non-proprietary name (INN)/
Ph. Eur. name/
common name of product (whichever is appropriate): .....
Batch number(s): .....
Finished product (final batch): .....
Final bulk: .....
Type of container: .....
Total number of containers in this batch: .....
Number of doses per container: .....
Composition/volume of single human dose (in drops and/or ml):
Date of expiry: .....
Date of start of period of validity: .....
Storage temperature: .....
Marketing Authorisation number issued by
(Member State/EU): .....
Name and address of manufacturer: .....
Name and address of
Marketing Authorisation Holder if different: .....
Human Albumin used in the production (if applicable)
Batch number, manufacturer:
(if this batch has been tested and released by an OMCL, the release certificate must be provided)

3.2 Production information

Site of manufacture: .....
Date of manufacture: .....
Summary information scheme on batch specific production data including dates of different production stages, identification numbers and blending scheme.

3.2.1 Final bulk vaccine

Batch number: .....

Date of manufacture .....
Bulk numbers of monovalent bulk
suspensions blended in
trivalent vaccine
Type 1 .....
Type 2: .....

Type 3: .....

For each bulk indicate:	Type 1	Type 2	Type 3
Preparation date:	…….	…….	……..
Volume:	…….	…….	……..
Storage temperature:	…….	…….	……..
Storage time:	…….	…….	……..
Approved storage period:	…….	…….	……..
Date of approval of protocol indicating compliance with the requirements of the relevant EP Monographs and with the Marketing Authorization:	…….	…….	……..
OCABR certificate of approval number:	…….	…….	……..
Certificate issued by (releasing authority):	…….	…….	……..
Volume of blended bulk	…….	…….	……..

Nature and volume of stabilizer .....

Total volume of blend .....

Sterility

Method: .....

Media: .....

Volume inoculated: .....

Date test on: .....

Date test off: .....

Result: .....

3.3 Batch of finished product

Batch number

Total volume for final filling .....

Date of final filling .....

Number of vials filled .....

Number of vials after inspection .....

Appearance

Method: .....

Specification: .....

Date test on: .....

Date test off: .....

Result: .....

Identity test

Method: .....

Specification: .....
Date test on: .....
Date test off: .....
Result: .....

pH
Method: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....

Stabiliser concentration
Method: .....
Specification: .....
Date test on: .....
Date test off: .....
Result: .....
Volume in vial: mls and drops: .....

Sterility
Method: .....
Media: .....
Volume inoculated: .....
Date test on: .....
Date test off: .....
Result: .....

Potency assay and thermal stability

	Type 1	Type 2	Type 3
Batch numbers of antiserum used in test:	……..	……..	……..
Date of test:	……..	……..	……..

Test vaccine

	Type 1	Type 2	Type 3	Total Virus
Titre of virus for each replicate of vaccine under test with 95% fiducial limits of mean	……..	……..	……..	……
Total virus titre for each replicate of vaccine under test with 95% fiducial limits of mean (after 48h at 37°C):				……

Reference vaccine

	Type 1	Type 2	Type 3	Total Virus

Titre of individual virus types
for each replicate of reference vaccine
with 95% fiducial limits of mean …….. …….. …….. ……..
Date of start of period of validity ……

4. Certification

Certification by qualified person taking the overall responsibility for production and control of the product:

I herewith certify that _____(*name of the medicinal product*) batch no._____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Law 95/2006 on healthcare reform, Title XVII – The medicinal product, transposing Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition, the NAMMD has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU Administrative Procedure for OCABR.

Name: _____
Function: _____
Date: _____
Signature:_____