ROMANIA

Informative Bulletin

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National Agency for Medicines and Medical Devices

Decisions of the NAMMD Scientific Council

Medicinal product batches recalled during the 1st quarter of 2012

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 4th quarter of 2011

Medicinal products authorised for marketing by the NAMMD during the 4th quarter of 2011

EMA newly centrally authorised medicinal products for which the European Commission issued decisions during the 4th quarter of 2011

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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National Medicines Agency of the EC Administrative Procedure for Official Batch Release of Biological Products shall be repealed.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.

(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.

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

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 (Ph.Eur, WHO, MA or in-house)**
Eg.: 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 (Ph. Eur., WHO, MA or in house)**
E.g. 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 (e.g. 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 No. 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 No. 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

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.

[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.

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: .....

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: .....
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 No. 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 No. 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)

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.

[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.

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
e.g. 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: .....

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: .....

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 No. 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 d

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 No. 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

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

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 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 No. 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 temp. of rbc: .....
Incubation time and temp. 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 No.(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 no.(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 No. (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: .....

Appearance
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 no.(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: .....

Bacterial endotoxins
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: .....
No. & 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 No. 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 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 No. 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 (e.g. 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

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/16/88 Ref				
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/16/88 Ref			
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.			

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: .....
Date of 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:

Residual infectious virus

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

Test for neuraminidase (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 No. 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 No. 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. 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: .....

3.2.1.1.2. 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.

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

3.2.1.2.3 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 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: .....

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.

Ovalbumin

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

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° (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 No. 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 No. 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 No. 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 No. 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 No. 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 No. 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]
- 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.

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

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: .....

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. 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 No. 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 No. 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 batches 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 Virus seed lots

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 No. 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 No. 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.

or

(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 Virus seed lots

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 SI
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 No. 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 No. 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: ml 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 No. 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: ……

DECISION

No. 4/07.03.2012

on approval of Regulations for handling of proposed “umbrella” trade names and other trade names for medicinal products for human use, as related to food supplements, cosmetic products and medical devices

In accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, the Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 1123/18.08.2010, as amended through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 07.03.2012, adopts the following

Decision

Article 1. - The Regulations for handling of proposed “umbrella” trade names and other trade names for medicinal products for human use, as related to food supplements, cosmetic products and medical devices are approved according to the annex which is integral part of this decision.

Article 2. - On the date of this decision coming into force, the Regulations for handling of proposed “umbrella” trade names and other trade names for medicinal products for human use, as related to food supplements and cosmetic 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. 4/07.03.2012)

Regulations for handling of proposed "umbrella" trade names and other trade names for medicinal products for human use, as related to food supplements, cosmetic products and medical devices

Art. 1. – Considering the late issues on the market of medicinal products for human use, in relation to food supplements and cosmetics, related to "umbrella" trade names or even to the same trade names of medicinal products for human use and food supplements/cosmetics, the National Agency for Medicines and Medical Devices hereby issues the following regulations, based on the legal provisions differentiating between medicinal products for human use and products of the aforementioned types:

- Law No. 95/2006, Title XVII – The medicinal product, transposing Directive 2001/83/EC as amended;
- Order of the Minister of Health no. 1069 of 19 June 2007 for approval of Regulations on food supplements;
- Law No. 178/2000 on cosmetic products, as amended;
- Regulation EC no. 1223/2009 on cosmetic products;
- Law No. 176/2000 on medical devices, as amended;
- Order of the Minister of Health no. 1453/2005 on approval of the Guidelines for "umbrella" trade names;
- Scientific Council Decision No. 2/2008 on approval of the Guideline on the trade name of medicinal products for human use;
- Scientific Council Decision No. 14/2010 on approval of National Medicines Agency policy concerning resolution of proposed "umbrella" trade names and other trade names.

Art. 2. – The following shall not be accepted as regards medicinal products for human use:

1) The proposal of an "umbrella" trade name, in case the respective "umbrella" segment can also be found in the trade name of a food supplement, cosmetic product or medical device marketed by the same legal entity.

2) The maintaining of an approved "umbrella" trade name as of its placement on the market, performed by the same legal entity, of a food supplement, cosmetic product or medical device containing the respective "umbrella" segment in its trade name.

In such cases, the Marketing Authorisation Holder is required to submit, within 30 days as of the commencement of the marketing of the food product, cosmetic product or medical device, the applications for variation to

the terms of the marketing authorisations of the respective medicinal products, related to the change of their trade name.
Otherwise, sanctions mentioned under Art. 836 1(i) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, shall be applied.
3) The proposal of the same trade name as owned by a food supplement, cosmetic product or medical device, placed on the market by the same legal entity.
4) The maintaining of the same approved trade name as of placement on the market, performed by the same legal entity, of a food supplement, cosmetic product or medical device with the same trade name.
In such cases, the Marketing Authorisation Holder is required to submit, within 30 days as of placement on the market of the food supplement, cosmetic product or medical device, an application for variation to the terms of the marketing authorisations of the respective medicinal product, concerning the change of its trade name.
Otherwise, sanctions mentioned under Art. 836 1 (i) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended, shall be applied.

DECISION

No. 7/07.03.2012

on repeal of Decision No. 7/09.03.2007 on approval of the content of the manufacturer's batch certificate for a medicinal product exported to countries under the scope of a Mutual Recognition Agreement (MRA)

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 1123/18.08.2010, as amended through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 07.03.2012, in accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Sole article. - SCD No. 7/09.03.2007 on approval of the content of the manufacturer's batch certificate for a medicinal product exported to countries under the scope of a Mutual Recognition Agreement (MRA) shall be repealed.

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

Medicinal product batches recalled during the 1st quarter of 2012

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/ MAH	Batch	Grounds for recall	Action proposed	Date of recall
1	Nurofen 200mg	soft capsules	200mg	ibuprofenum	Reckit Benckiser International Healthcare, Great Britain	1CC 12CC 13CC 6DD 7DD 13DD 2EE	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	19.12.2011
2	Ecalta ®	powder and solvent for concentrate and solution for infusion		anidulafunginum	Ben Venue Laboratories, USA	S10281 X01833 X03673 X05062	Potential risk of particles in the solution	Voluntary recall and destruction	20.12.2011
3	Mycospor cremă, 1%	cream	10mg/g	bifonazol	Bayer Healthcare, Germany	BXNON84, BXPJET6, BXPJFEU, BXPJFG3	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	16.01.2012
4	Mycospor onichoset, unguent	ointment	10mg+ 400mg/g	combinations	Bayer Healthcare, Germany	KP06AB1, KP06LER	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	16.01.2012
5	Mycospor, soluție cutanată, 0.01g/ml	cutaneous solution	0.01g/ml	bifonazol	Bayer Healthcare, Germany	KP07PF3, KP062B1	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	16.01.2012
6	Nutriflex Lipid Plus	emulsion for infusion, bags		combinations	B. Braun Melsungen AG, Germany	113818052 0134A151 0226A151 0324A151 0415A151 111418052 113618051 0411A151	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	17.01.2012
7	Nutriflex Lipid Peri	emulsion for infusion, bags		combinations	B.Braun Melsungen AG, Germany	113868052 0173A151 0284A151 0416A151 111458051 113128052 0033A151 0342A151 0383A152 0461A152 113738052 0265A152 0314A151 0416A151	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	17.01.2012
8	Sotret 10mg	soft capsules	10mg	isotretinoinum	Terapia SA, Romania	2204330	Out-of-specification outcome under parameter "chemically related substances"	Voluntary recall and destruction	23.01.2012
9	Fluimucil 100	granules for oral solution	100mg	acetylcysteinum	Zambon S.A.P., Italy	306248 305094 307250 303977	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	24.01.2012

No.	Product recalled	Pharmaceutical form	Strength	INN	Manufacturer/ MAH	Batch	Grounds for recall	Action proposed	Date of recall
10	Fluimucil 200	granules for oral solution	200 mg	acetylcysteinum	Zambon S.A.P., Italy	304925 304926 307345	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	24.01.2012
11	Fluimucil 600	granules for oral solution	600 mg	acetylcysteinum	Zambon S.A.P., Italy	305941 304035	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	24.01.2012
12	Rispen 3	film-coated tablets	3 mg	risperidonum	Zentiva k.s., Czech Republic	2510211	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	03.02.2012
13	Nutriflex Lipid Plus	emulsion for infusion		combinations	B.Braun Melsungen AG, Germany	114228051	Out-of-specification outcome obtained during stability studies	Recall and destruction	08.02.2012
14	Nutriflex Lipid Peri	emulsion for infusion		combinations	B.Braun Melsungen AG, Germany	114058052 114168052	Needle-like particles found in the solution	Recall and destruction	08.02.2012
15	Verapamil AL 80	film-coated tablets	80mg	verapamilum	Aliud Pharma GmbH, Germany	72255 80972 80973	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	09.02.2012
16	Felodipin AL 10 retard	modified-release tablets	10 mg	felodipinum	Aliud Pharma GmbH, Germany	73812	Voluntary withdrawal performed by the MAH in accordance with Order of the Minister of Health No. 279/30.03.2005	Voluntary recall and destruction	21.02.2012
17	Sinplatin 1 mg/1ml	concentrate for solution for infusion	1mg/1ml	cisplatinum	Sindan Pharma SRL/Actavis SRL, Romania	BT11003A	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	24.02.2012
18	Ultraproct unguent rectal	Rectal ointment	-	combinations	Intendis Manufacturing S.P.A., Italy	94085A, 02093A, 03098B, 11105A, 1211A, 13115A	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	07.03.2012
19	Ceclodyne 125 mg/ml and 250 mg/ml	granules for oral suspension	125mg/ml; 250mg/ml	cefaclorum	Sandoz SRL, Romania	AW0244, AW0813, AX3070. AX3073, AX3074, AX3082, AY4794, AZ1626, BE5413, BG2397, BG2398, BM9736, BM9770. BM9772, BM9771	Out-of-specification outcome obtained during stability studies	Voluntary recall and destruction	07.03.2012
20	Diclofenac AL i.m.	solution for injection	75mg/3ml	diclofenacum	Aliud Pharma GmbH, Germany	81747	Out-of-specification outcome obtained under parameter “colour”	Voluntary recall and destruction	27.03.2012

Applications for marketing authorisation/marketing authorisation renewal submitted to the NAMMD during the 4th quarter of 2011

During the 4th quarter of 2011, 321 marketing authorisation/renewal applications for medicinal products corresponding to the following therapeutic groups have been received:

A01 – Stomatological preparations
A03 – Drugs for functional gastrointestinal disorders
A05 – Bile and liver therapy
A06 - Laxatives
A08 – Antiobesity preparations (excluding diet products)
A09 – Digestives, including enzymes
A10 – Drugs used in diabetes
A11 - Vitamins
A12 – Mineral supplements
B01 – Antithrombotic agents
B03 – Antianemic preparations
B05 – Blood substitutes and perfusion solutions
C01 – Cardiac therapy
C03 – Diuretics
C05 – Vasoprotectives
C07 – Beta blocking agents
C09 – Agents acting on the renine-angiotensin system
C10 – Lipid modifying agents
D06 – Antibiotics and chemotherapeutics for dermatological use
D10 – Anti-acne preparations
D11 – Other dermatological preparations
G03 – Sex hormones and modulators of the genital system
G04 - Urologicals
J01 – Antibacterials for systemic use
J02 – Antimycotics for systemic use
J05 – Antivirals for systemic use
J07 - Vaccines
L01 – Antineoplastic agents
L02 – Endocrine therapy
L04 - Immunosuppressants
M01 – Anti-inflammatory and antirheumatic products
M05 – Drugs for treatment of bone diseases
N02 - Analgesics
N03 - Antiepileptics

N04 – Anti-Parkinson drugs
N05 – Psycholeptics
N06 – Psychoanaleptics
N07 – Other nervous system drugs
R01 – Nasal preparations
R03 – Drugs for obstructive airway diseases
R05 – Cough and cold preparations
R06 – Antihistamines for systemic use
R07 – Other respiratory system products
S01 – Ophthalmologicals
V03 – All other therapeutic products
XNM – Herbal teas and preparations – external use

Medicinal products authorised for marketing by the NAMMD during the 4th quarter of 2011

INN	Invented name	Pharmaceutical form	Strength	MA Holding Company	Country	MA Number		
ACICLOVIRUM	ACICLOVIR TERAPIA 50mg/g	cream	50mg/g	TERAPIA S.A.	ROMANIA	4096	2011	01
ACIDUM ACETYLSALICYLICUM	ASAPRIN T 500mg	tablets	500mg	AC HELCOR PHARMA S.R.L.	ROMANIA	4149	2011	02
ACIDUM ACETYLSALICYLICUM	ALUPIRIN 75mg	gastro-resistant tablets	75mg	LABORMED PHARMA SA	ROMANIA	3937	2011	01
ACIDUM IBANDRONICUM	HOLMEVIS 50mg	film-coated tablets	50mg	EGIS PHARMACEUTICALS PLC	HUNGARY	3920	2011	03
ACIDUM IBANDRONICUM	HOLMEVIS 1mg/1ml	concentrate for solution for infusion	1mg/1ml	EGIS PHARMACEUTICALS PLC	HUNGARY	3921	2011	01
ACIDUM IBANDRONICUM	HOLMEVIS 2mg/2ml	concentrate for solution for infusion	2mg/2ml	EGIS PHARMACEUTICALS PLC	HUNGARY	3922	2011	01
ACIDUM IBANDRONICUM	HOLMEVIS 6mg/6ml	concentrate for solution for infusion	6mg/6ml	EGIS PHARMACEUTICALS PLC	HUNGARY	3923	2011	03
ACIDUM IBANDRONICUM	OSSICA 2mg	concentrate for solution for infusion	2mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	4088	2011	01
ACIDUM IBANDRONICUM	OSSICA 6mg	concentrate for solution for infusion	6mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	4089	2011	03
ACIDUM IBANDRONICUM	OSSICA 3mg	solution for injection in pre-filled syringe	3mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	4090	2011	02
ACIDUM RISEDRONICUM	RISEDRONAT PFIZER 5mg	film-coated tablets	5mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	4134	2011	04
ACIDUM RISEDRONICUM	RISEDRONAT PFIZER 30mg	film-coated tablets	30mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	4135	2011	03
ACIDUM RISEDRONICUM	RISEDRONAT PFIZER 35mg	film-coated	35mg	PFIZER EUROPE MA	GREAT	4136	2011	06

		tablets		EEIG	BRITAIN			
ACIDUM TIOCTICUM (ALFA-LIPOICUM)	THIOGAMMA 600 INJEKT (see N07XN03)	concentrate for solution for infusion	30mg/ml	WORWAG PHARMA GMBH & CO. KG	GERMANY	4156	2011	03
AMLODIPINUM	AGEN 5	tablets	5mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4024	2011	03
AMLODIPINUM	AGEN 10	tablets	10mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4025	2011	03
AMLODIPINUM	AMLODIPINE MEDOCHEMIE 5mg	tablets	5mg	MEDOCHEMIE LTD.	CYPRUS	4086	2011	01
AMLODIPINUM	AMLODIPINE MEDOCHEMIE 10mg	tablets	10mg	MEDOCHEMIE LTD.	CYPRUS	4087	2011	01
AMLODIPINUM	RECOTENS 5mg	tablets	5mg	ICN POLFA RZESZOW S.A.	POLAND	3930	2011	11
AMLODIPINUM	RECOTENS 10mg	tablets	10mg	ICN POLFA RZESZOW S.A.	POLAND	3931	2011	11
AMLODIPINUM	AMLODIPINA AUROBINDO 5mg	tablets	5mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	3934	2011	19
AMLODIPINUM	AMLODIPINA AUROBINDO 10mg	tablets	10mg	AUROBINDO PHARMA (MALTA) LIMITED	MALTA	3935	2011	19
AMLODIPINUM	VAZOTAL 5mg	tablets	5mg	STADA HEMOFARM S.R.L.	ROMANIA	4099	2011	01
AMLODIPINUM	VAZOTAL 10mg	tablets	10mg	STADA HEMOFARM S.R.L.	ROMANIA	4100	2011	01
AMOXICILLINUM + ACIDUM CLAVULANICUM	ALVONAL 500mg/125mg	film-coated tablets	500mg/ 125mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3846	2011	19
AMOXICILLINUM + ACIDUM CLAVULANICUM	ALVONAL 875mg/125mg	film-coated tablets	875mg/ 125mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3847	2011	19
ANASTROZOLUM	ANASTROZOL KABI 1mg	film-coated tablets	1mg	FRESENIUS KABI ONCOLOGY PLC.	GREAT BRITAIN	4043	2011	06
APOMORFINUM	DACEPTON 10mg/ml	film-coated tablets	10mg/ml	EVER NEURO PHARMA GMBH	GERMANY	3841	2011	07
ATORVASTATINUM	VOREDANIN 10mg	film-coated tablets	10mg	LABORMED PHARMA S.A.	ROMANIA	3962	2011	20
ATORVASTATINUM	VOREDANIN 20mg	film-coated tablets	20mg	LABORMED PHARMA S.A.	ROMANIA	3963	2011	20

ATORVASTATINUM	VOREDANIN 40mg	film-coated tablets	40mg	LABORMED PHARMA S.A.	ROMANIA	3964	2011	20
ATORVASTATINUM	ATORVASTATIN PFIZER 10mg	film-coated tablets	10mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3956	2011	29
ATORVASTATINUM	ATORVASTATIN PFIZER 20mg	film-coated tablets	20mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3957	2011	29
ATORVASTATINUM	ATORVASTATIN PFIZER 40mg	film-coated tablets	40mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3958	2011	29
ATORVASTATINUM	ATORVASTATIN PFIZER 80mg	film-coated tablets	80mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3959	2011	29
ATORVASTATINUM	ATORVILBITIN 10mg	film-coated tablets	10mg	STADA Arzneimittel AG	GERMANY	4017	2011	11
ATORVASTATINUM	ATORVILBITIN 20mg	film-coated tablets	20mg	STADA Arzneimittel AG	GERMANY	4018	2011	11
ATORVASTATINUM	ATORVILBITIN 40mg	film-coated tablets	40mg	STADA Arzneimittel AG	GERMANY	4019	2011	11
AZITHROMYCINUM	AZITROMICINA DORNA 500mg	film-coated tablets	500mg	DORNA FARM S.A.	ROMANIA	4078	2011	02
BENDAMUSTINUM	RIBOVACT 2.5mg/ml	powder for concentrate for solution for infusion	2.5mg/ml	ASTELLAS PHARMA GMBH	GERMANY	3838	2011	04
BETAHISTINUM	BETAHISTINA DICLORHIDRAT ACCORD 8mg	tablets	8mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3973	2011	01
BETAHISTINUM	BETAHISTINA DICLORHIDRAT ACCORD 16mg	tablets	16mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	3974	2011	01
BETAHISTINUM	VERTIMED 8mg	tablets	8mg	MEDOCHEMIE LTD.	CYPRUS	3987	2011	09
BETAHISTINUM	VERTIMED 16mg	tablets	16mg	MEDOCHEMIE LTD.	CYPRUS	3988	2011	09
BETAHISTINUM	VERTIMED 24mg	tablets	24mg	MEDOCHEMIE LTD.	CYPRUS	3989	2011	09
BICALUTAMIDUM	BICALUTAMIDA ALVOGEN 50mg	film-coated tablets	50mg	ALVOGEN ROMANIA S.R.L.	ROMANIA	4101	2011	02
BICALUTAMIDUM	BICALUTAMIDA ALVOGEN 150mg	film-coated tablets	150mg	ALVOGEN ROMANIA S.R.L.	ROMANIA	4102	2011	01
BIPERIDENUM	AKINETON 2mg	tablets	2mg	DESMA GMBH	GERMANY	4133	2011	02
CANDESARTANUM CILEXETIL	CANDESARTAN TORRENT 2mg	tablets	2mg	TORRENT PHARMA GMBH	GERMANY	4068	2011	18

CANDESARTANUM CILEXETIL	CANDESARTAN TORRENT 4mg	tablets	4mg	TORRENT PHARMA GMBH	GERMANY	4069	2011	18
CANDESARTANUM CILEXETIL	CANDESARTAN TORRENT 8mg	tablets	8mg	TORRENT PHARMA GMBH	GERMANY	4070	2011	18
CANDESARTANUM CILEXETIL	CANDESARTAN TORRENT 16mg	tablets	16mg	TORRENT PHARMA GMBH	GERMANY	4071	2011	18
CANDESARTANUM CILEXETIL	CANDESARTAN TORRENT 32mg	tablets	32mg	TORRENT PHARMA GMBH	GERMANY	4072	2011	18
CANDESARTANUM CILEXETIL	CANDESARTAN CILEXETIL ZENTIVA 4mg	tablets	4mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4118	2011	08
CANDESARTANUM CILEXETIL	CANDESARTAN CILEXETIL ZENTIVA 8mg	tablets	8mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4119	2011	08
CANDESARTANUM CILEXETIL	CANDESARTAN CILEXETIL ZENTIVA 16mg	tablets	16mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4120	2011	08
CANDESARTANUM CILEXETIL	CANDESARTAN CILEXETIL ZENTIVA 32mg	tablets	32mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4121	2011	08
CARVEDILOLUM	CARVEDILOL GRINDEKS 6.25mg	tablets	6.25mg	AS GRINDEKS	LATVIA	3822	2011	01
CARVEDILOLUM	CARVEDILOL GRINDEKS 12.5mg	tablets	12.5mg	AS GRINDEKS	LATVIA	3823	2011	01
CARVEDILOLUM	CARVEDILOL GRINDEKS 25mg	tablets	25mg	AS GRINDEKS	LATVIA	3824	2011	01
CEFUROXIMUM	CEFUROXIMA CEFT LIMITED 125mg	tablets	125mg	CEFT LIMITED	GREAT BRITAIN	3967	2011	11
CEFUROXIMUM	CEFUROXIMA CEFT LIMITED 250mg	tablets	250mg	CEFT LIMITED	GREAT BRITAIN	3968	2011	11
CEFUROXIMUM	CEFUROXIMA CEFT LIMITED 500mg	tablets	500mg	CEFT LIMITED	GREAT BRITAIN	3969	2011	11
CLOPIDOGRELUM	DEPLATT 75mg	film-coated tablets	75mg	TORRENT PHARMA S.R.L.	ROMANIA	3863	2011	04
CLOPIDOGRELUM	TINGREKS 75mg	film-coated tablets	75mg	JSC GRINDEKS	LATVIA	4109	2011	01
COMBINATIONS	MOLAXOLE	powder for oral solution		MEDA AB	SWEDEN	3864	2011	20
COMBINATIONS	NUROFEN RACEALA SI GRIPA 200mg/30mg	film-coated tablets	200mg/ 30mg	RECKITT BENCKISER HEALTHCARE INTERNATIONAL	GREAT BRITAIN	4144	2011	02

				LIMITED				
COMBINATIONS	MOVICOL UNO 6.9g	powder for oral solution	6.9g	NORGINE LIMITED	GREAT BRITAIN	3890	2011	09
COMBINATIONS	PROMATERN	film-coated tablets		BIO EEL S.R.L.	ROMANIA	4157	2011	03
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	DAYLETTE 0.02mg/3mg	film-coated tablets	0.02mg/ 3mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3883	2011	02
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	DAYLLA 0.02mg/3mg	film-coated tablets	0.02mg/ 3mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3884	2011	02
COMBINATIONS (ETINILESTRADIOLUM + DROSPIRENONUM)	ANEEA 0.02mg/3mg	film-coated tablets	0.02mg/ 3mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3885	2011	02
COMBINATIONS (ACIDUM ACETYLSALICYLICUM+ ESOMEPRAZOLUM)	AXANUM 81mg/20mg	capsules	81mg/ 20mg	ASTRAZENECA AB	SWEDEN	3825	2011	07
COMBINATIONS (BECLOMETASONUM+ FORMOTEROLUM)	FOSTER 100/6micrograms/dose	pressurized solution for inhalation	100/ 6micro-grams/dose	CHIESI PHARMACEUTICALS GMBH	AUSTRIA	4092	2011	02
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	KARBICOMBI 8mg/12.5mg	tablets	8mg/ 12.5mg	KRKA D.D., NOVO MESTO	SLOVENIA	3916	2011	18
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	KARBICOMBI 16mg/12.5mg	tablets	16mg/ 12.5mg	KRKA D.D., NOVO MESTO	SLOVENIA	3917	2011	18
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	KARBICOMBI 32mg/12.5mg	tablets	32mg/ 12.5mg	KRKA D.D., NOVO MESTO	SLOVENIA	3918	2011	18
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	KARBICOMBI 32mg/25mg	tablets	32mg/ 25mg	KRKA D.D., NOVO MESTO	SLOVENIA	3919	2011	18
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	ATACAND PLUS 16mg/12.5mg	tablets	16mg/ 12.5mg	ASTRA ZENECA AB	SWEDEN	3853	2011	15
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	ATACAND PLUS 32mg/12.5mg	tablets	32mg/ 12.5mg	ASTRA ZENECA AB	SWEDEN	3854	2011	15
COMBINATIONS	ATACAND PLUS	tablets	32mg/	ASTRA ZENECA AB	SWEDEN	3855	2011	14

(CANDESARTANUM CILEXETIL+HCT)	32mg/25mg		25mg					
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDESARTAN HIDROCLOROTIAZIDA TORRENT 8mg/12.5mg	tablets	8mg/ 12.5mg	TORRENT PHARMA S.R.L.	ROMANIA	3868	2011	18
COMBINATIONS (CANDESARTANUM CILEXETIL+HCT)	CANDESARTAN HIDROCLOROTIAZIDA TORRENT 16mg/12.5mg	tablets	16mg/ 12.5mg	TORRENT PHARMA S.R.L.	ROMANIA	3869	2011	18
COMBINATIONS (CIPROFLOXACINUM+ FLUOCINOLONUM)	OTOTIS 3mg/0.5mg/ml	ear drops, solution	3mg/ 0.5mg/ml	TIS FARMACEUTIC S.A.	ROMANIA	4130	2011	01
COMBINATIONS (DIENOGESTUM+ ETINILESTRADIOLUM)	ZENADEA 2mg/0.03mg	film-coated tablets	2mg/ 0.03mg	ZENTIVA K.S.	THE CZECH REPUBLIC	4026	2011	02
COMBINATIONS (DORZOLAMIDUM+ TIMOLOLUM)	OCCULAN 20mg/5mg/ml	eye drops, solution	20mg/ 5mg/ml	PHARMATHEN S.A.	GREECE	4028	2011	03
COMBINATIONS (DORZOLAMIDUM+ TIMOLOLUM)	GLOPTIC 20mg/5mg/ml	eye drops, solution	20mg/ 5mg/ml	GENERICS (UK) LIMITED	GREAT BRITAIN	4004	2011	03
COMBINATIONS (DORZOLAMIDUM+ TIMOLOLUM)	DORZOLAMIDA/TIMOLOL DR. GERHARD MANN 20mg/ml+5mg/ml	eye drops, solution	20mg/ml+ 5mg/ml	DR. GERHARD MANN CHEM.-PHARM.FABRIK GMBH	GERMANY	4022	2011	03
COMBINATIONS (DORZOLAMIDUM+ TIMOLOLUM)	VENTURAX 20mg/5mg/ml	eye drops, solution	20mg/ 5mg/ml	PHARMATHEN S.A.	GREECE	4091	2011	03
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBESARTAN/HIDROCLORO-TIAZIDA RICHTER 150mg/12.5mg	film-coated tablets	150mg/ 12.5mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3908	2011	07
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBESARTAN/HIDROCLORO-TIAZIDA RICHTER 300mg/12.5mg	film-coated tablets	300mg/ 12.5mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3909	2011	07
COMBINATIONS (IRBERSARTANUM+HYDROCHLOROTHIAZIDUM)	IRBESARTAN/HIDROCLORO-TIAZIDA RICHTER 300mg/25mg	film-coated tablets	300mg/ 25mg	GEDEON RICHTER ROMANIA S.A.	ROMANIA	3910	2011	07
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBESARTAN HIDROCLOROTIAZIDA TORRENT 150mg/12.5mg	film-coated tablets	150mg/ 12.5mg	TORRENT PHARMA S.R.L.	ROMANIA	4141	2011	08

COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBESARTAN HIDROCLOROTIAZIDA TORRENT 300mg/12.5mg	film-coated tablets	300mg/ 12.5mg	TORRENT PHARMA S.R.L.	ROMANIA	4142	2011	08
COMBINATIONS (IRBERSARTANUM+ HYDROCHLOROTHIAZIDUM)	IRBESARTAN HIDROCLOROTIAZIDA TORRENT 300mg/25mg	film-coated tablets	300mg/ 25mg	TORRENT PHARMA S.R.L.	ROMANIA	4143	2011	08
COMBINATIONS (LOSARTANUM+ HYDROCHLOROTHIAZIDUM)	LORZITIN 50mg/12.5mg	film-coated tablets	50mg/ 12.5mg	JENSON PHARMACEUTICAL SERVICES LTD	GREAT BRITAIN	4106	2011	17
COMBINATIONS (LOSARTANUM+ HYDROCHLOROTHIAZIDUM)	LORZITIN 100mg/12.5mg	film-coated tablets	100mg/ 12.5mg	JENSON PHARMACEUTICAL SERVICES LTD	GREAT BRITAIN	4107	2011	17
COMBINATIONS (LOSARTANUM+ HYDROCHLOROTHIAZIDUM)	LORZITIN 100mg/25mg	film-coated tablets	100mg/ 25mg	JENSON PHARMACEUTICAL SERVICES LTD	GREAT BRITAIN	4108	2011	17
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM)	AMLESSA 4mg/5mg	tablets	4mg/5mg	KRKA D.D., NOVO MESTO	SLOVENIA	4082	2011	11
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM)	AMLESSA 4mg/10mg	tablets	4mg/10mg	KRKA D.D., NOVO MESTO	SLOVENIA	4083	2011	11
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM)	AMLESSA 8mg/5mg	tablets	8mg/5mg	KRKA D.D., NOVO MESTO	SLOVENIA	4084	2011	11
COMBINATIONS (PERINDOPRILUM+ AMLODIPINUM)	AMLESSA 8mg/10mg	tablets	8mg/10mg	KRKA D.D., NOVO MESTO	SLOVENIA	4085	2011	11
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PERINDOPRIL/INDAPAMIDA MYLAN 2.5mg/0.625mg	film-coated tablets	2.5mg/ 0.625mg	GENERICS (UK) LTD.	GREAT BRITAIN	4020	2011	07
COMBINATIONS (PERINDOPRILUM+ INDAPAMIDUM)	PERINDOPRIL/INDAPAMIDA MYLAN 5mg/1.25mg	film-coated tablets	5mg/ 1.25mg	GENERICS (UK) LTD.	GREAT BRITAIN	4021	2011	07
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VANATEX HCT 80mg/12.5mg	film-coated tablets	80mg/ 12.5mg	PHARMACEUTICAL WORKS POLPHARMA S.A.	POLAND	3826	2011	02
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VANATEX HCT 160mg/12.5mg	film-coated tablets	160mg/ 12.5mg	PHARMACEUTICAL WORKS POLPHARMA S.A.	POLAND	3827	2011	02

COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	VANATEX HCT 160mg/25mg	film-coated tablets	160mg/ 25mg	PHARMACEUTICAL WORKS POLPHARMA S.A.	POLAND	3828	2011	02
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	CO-AVASSAN 80mg/12.5mg	film-coated tablets	80mg/ 12.5mg	TERAPIA S.A.	ROMANIA	3875	2011	10
COMBINATIONS (VALSARTANUM+ HYDROCHLOROTHIAZIDUM)	CO-AVASSAN 160mg/12.5mg	film-coated tablets	160mg/ 12.5mg	TERAPIA S.A.	ROMANIA	3876	2011	10
COMBINATIONS (VALSARTANUM+HYDROCHLOROTHIAZIDUM)	CO-AVASSAN 160mg/25mg	film-coated tablets	160mg/ 25mg	TERAPIA S.A.	ROMANIA	3877	2011	10
COMBINATIONS (VERAPAMILUM+ TRANDOLAPRILUM)	TARKA 240mg/2mg	modified-release tablets	240mg/ 2mg	ABBOTT GMBH & CO.KG	GERMANY	3940	2011	07
COMBINATIONS (VERAPAMILUM+ TRANDOLAPRILUM)	TARKA 240mg/4mg	modified-release tablets	240mg/ 4mg	ABBOTT GMBH & CO.KG	GERMANY	3941	2011	07
DESOGESTRELUM	SOFTINETTE 0.075mg	film-coated tablets	0.075mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3996	2011	06
DICLOFENACUM	DICLOFENAC TERAPIA 50mg/g	gel	50mg/g	TERAPIA S.A.	ROMANIA	4098	2011	02
DICLOFENACUM	DICLOFENAC TERAPIA 10mg/g	cream	10mg/g	TERAPIA S.A.	ROMANIA	4097	2011	02
DOCETAXELUM	DOCIRENA 20mg/1ml	concentrate for solution for infusion	20mg/1ml	FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	3820	2011	01
DOCETAXELUM	DOCIRENA 80mg/4ml	concentrate for solution for infusion	80mg/4ml	FRESENIUS KABI ROMANIA S.R.L.	ROMANIA	3821	2011	01
DOCETAXELUM	DOCETAXEL GSK 20mg/1ml	concentrate for solution for infusion	20mg/1ml	GLAXOSMITHKLINE (GSK) S.R.L.	ROMANIA	3928	2011	01
DOCETAXELUM	DOCETAXEL GSK 80mg/4ml	concentrate for solution for infusion	80mg/4ml	GLAXOSMITHKLINE (GSK) S.R.L.	ROMANIA	3929	2011	01
DONEPEZILUM	DIVARE 5mg	orodispersible tablets	5mg	ZENTIVA K.S.	THE CZECH REPUBLIC	3861	2011	14

DONEPEZILUM	DIVARE 10mg	orodispersible tablets	10mg	ZENTIVA K.S.	THE CZECH REPUBLIC	3862	2011	14
DONEPEZILUM	DONEPEZIL JACOBSEN 5mg	orodispersible tablets	5mg	JACOBSEN PHARMA AS	DENMARK	4029	2011	03
DONEPEZILUM	DONEPEZIL JACOBSEN 10mg	orodispersible tablets	10mg	JACOBSEN PHARMA AS	DENMARK	4030	2011	03
DORZOLAMIDUM	DOZOTENS 20mg/ml	eye drops, solution	20mg/ml	ICN POLFA RZESZOW S.A.	POLAND	4005	2011	03
DOXAZOSINUM	DOXAZOSINA AUROBINDO 1mg	tablets	1mg	AUROBINDO PHARMA LIMITED	GREAT BRITAIN	3984	2011	14
DOXAZOSINUM	DOXAZOSINA AUROBINDO 2mg	tablets	2mg	AUROBINDO PHARMA LIMITED	GREAT BRITAIN	3985	2011	14
DOXAZOSINUM	DOXAZOSINA AUROBINDO 4mg	tablets	4mg	AUROBINDO PHARMA LIMITED	GREAT BRITAIN	3986	2011	14
DROTAVERINUM	ANTISPASMIN 40mg	tablets	40mg	BIOFARM S.A.	ROMANIA	4093	2011	02
ENALAPRILUM	ENAP 1.25mg/ml	solution for inj./infusion	1.25mg/ml	KRKA, D.D., NOVO MESTO	SLOVENIA	4066	2011	01
ENTACAPONUM	ENTACAPONA MYLAN 200mg	film-coated tablets	200mg	GENERIC (UK) LTD.	GREAT BRITAIN	4049	2011	14
ESCITALOPRAMUM	ESCITALOPRAM SANDOZ 5mg	film-coated tablets	5mg	SANDOZ S.R.L.	ROMANIA	3832	2011	25
ESCITALOPRAMUM	ESCITALOPRAM SANDOZ 10mg	film-coated tablets	10mg	SANDOZ S.R.L.	ROMANIA	3833	2011	25
ESCITALOPRAMUM	ESCITALOPRAM SANDOZ 15mg	film-coated tablets	15mg	SANDOZ S.R.L.	ROMANIA	3834	2011	25
ESCITALOPRAMUM	ESCITALOPRAM SANDOZ 20mg	film-coated tablets	20mg	SANDOZ S.R.L.	ROMANIA	3835	2011	25
ESCITALOPRAMUM	ESCITALOPRAM PFIZER 5mg	film-coated tablets	5mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3849	2011	20
ESCITALOPRAMUM	ESCITALOPRAM PFIZER 10mg	film-coated tablets	10mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3850	2011	20
ESCITALOPRAMUM	ESCITALOPRAM PFIZER 15mg	film-coated tablets	15mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3851	2011	20
ESCITALOPRAMUM	ESCITALOPRAM PFIZER 20mg	film-coated tablets	20mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3852	2011	20
ESOMEPRAZOLUM	ESOMEPRAZOL TEVA 20mg	gastro resistant	20mg	TEVA PHARMACEUTICALS	ROMANIA	3818	2011	14

		tablets		S.R.L.				
ESOMEPRAZOLUM	ESOMEPRAZOL TEVA 40mg	gastro resistant tablets	40mg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3819	2011	14
ESOMEPRAZOLUM	ESOMEPRAZOL TORRENT 20mg	gastro resistant tablets	20mg	TORRENT PHARMA S.R.L.	ROMANIA	3865	2011	18
ESOMEPRAZOLUM	ESOMEPRAZOL TORRENT 40mg	gastro resistant tablets	40mg	TORRENT PHARMA S.R.L.	ROMANIA	3866	2011	18
ESTRIOLUM	OVESTIN 1mg/g	cream	1mg/g	N.V. ORGANON	THE NETHERLANDS	4016	2011	01
EXEMESTANUM	INPLAVIA 25mg	film-coated tablets	25mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3837	2011	08
EXEMESTANUM	EXEMESTANE GENERICS 25mg	film-coated tablets	25mg	GENERICS (UK) LTD.	GREAT BRITAIN	3965	2011	08
EXEMESTANUM	EXEMESTAN REGIOMEDICA 25mg	film-coated tablets	25mg	REGIOMEDICA GMBH	GERMANY	3966	2011	06
EXEMESTANUM	NATERAN 25mg	film-coated tablets	25mg	SYNTHON BV	THE NETHERLANDS	3990	2011	04
FENOFIBRATUM	FENOLIP 160mg	capsules	160mg	PHARMASWISS CESKA REPUBLIKA S.R.O.	THE CZECH REPUBLIC	3998	2011	05
FENTANYLUM	ALGOGESIC 12.5micrograms/hour	transdermal patch	12.5micro-grams/hour	ZENTIVA K.S.	THE CZECH REPUBLIC	4006	2011	08
FENTANYLUM	ALGOGESIC 25micrograms/hour	transdermal patch	25micro-grams/hour	ZENTIVA K.S.	THE CZECH REPUBLIC	4007	2011	08
FENTANYLUM	ALGOGESIC 50micrograms/hour	transdermal patch	50micro-grams/hour	ZENTIVA K.S.	THE CZECH REPUBLIC	4008	2011	08
FENTANYLUM	ALGOGESIC 75micrograms/hour	transdermal patch	75micro-grams/hour	ZENTIVA K.S.	THE CZECH REPUBLIC	4009	2011	08
FENTANYLUM	ALGOGESIC 100micrograms/hour	transdermal patch	100micro-grams/hour	ZENTIVA K.S.	THE CZECH REPUBLIC	4010	2011	08
FINASTERIDUM	FINASTERIDA CIPLA UK 5mg	film-coated	5mg	CIPLA UK LTD.	GREAT	3936	2011	01

		tablets			BRITAIN			
FLUCONAZOLUM	DIFLUCAN 10mg/ml	powder for oral suspension	10mg/ml	PFIZER EUROPE MA EEIG	GREAT BRITAIN	4067	2011	01
FLUCONAZOLUM	FLUCONAZOL ROMPHARM 150mg	capsules	150mg	ROMPHARM COMPANY S.R.L.	ROMANIA	3848	2011	01
GABAPENTINUM	GABAPENTINA PFIZER 100mg	capsules	100mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3894	2011	11
GABAPENTINUM	GABAPENTINA PFIZER 300mg	capsules	300mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3895	2011	11
GABAPENTINUM	GABAPENTINA PFIZER 400mg	capsules	400mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3896	2011	11
GELATINA SUCCINILATA	GELASPAN 40mg/ml	solution for infusion	40mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	3979	2011	03
GEMCITABINUM	GEMCITABINA ALVOGEN 200mg	powder for solution for infusion	200mg	ALVOGEN ROMANIA S.R.L.	ROMANIA	4131	2011	01
GEMCITABINUM	GEMCITABINA ALVOGEN 1g	powder for solution for infusion	1g	ALVOGEN ROMANIA S.R.L.	ROMANIA	4132	2011	01
GLICLAZIDUM	GLICLAZIDA JELFA 30mg	prolonged-release tablets	30mg	JELFA PHARMACEUTICAL COMPANY S.A.	POLAND	4128	2011	02
GRANISETRONUM	GRANORED 1mg	film-coated tablets	1mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3839	2011	02
GRANISETRONUM	GRANORED 2mg	film-coated tablets	2mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3840	2011	02
HOMEOPATE	GALSTENA	oral drops, solution		RICHARD BITTNER AG	AUSTRIA	4081	2011	02
HOMEOPATE	GENTOS	sublingual tablets		RICHARD BITTNER AG	AUSTRIA	3960	2011	05
HYDROXYETHYL - AMIDON	INFOHES 60g/L	solution for infusion	60g/l	INFOMED FLUIDS S.R.L.	REPUBLICA SLOVACĂ	4162	2011	02
HYDROXYETHYL - AMIDON	INFOHES 100g/L	solution for infusion	100g/l	INFOMED FLUIDS S.R.L.	REPUBLICA SLOVACĂ	4163	2011	02

IBUPROFENUM	BRUFEN 20mg/ml	oral suspension	20mg/ml	ABBOTT SCANDINAVIA AB	SWEDEN	3881	2011	06
IBUPROFENUM	BRUFEN RETARD 800mg	prolonged-release tablets	800mg	ABBOTT SCANDINAVIA AB	SWEDEN	3880	2011	02
IBUPROFENUM	MIG PEDIATRIC 20mg/ml	oral suspension	20mg/ml	BERLIN-CHEMIE AG (MENARINI GROUP)	GERMANY	3860	2011	02
IBUPROFENUM	IBUPROFEN ARENA 400mg	capsules	400mg	ARENA GROUP S.A.	ROMANIA	3961	2011	01
INDAPAMIDUM	BELAMID 1.5mg	prolonged-release tablets	1.5mg	A&G TRADING S.R.L.	ROMANIA	4129	2011	01
INDAPAMIDUM	SERDIMID 1.5mg	prolonged-release tablets	1.5mg	LABORMED PHARMA S.A.	ROMANIA	4094	2011	02
INDAPAMIDUM	SERDIMID 2.5mg	prolonged-release tablets	2.5mg	LABORMED PHARMA S.A.	ROMANIA	4095	2011	02
IRBESARTANUM	IRBESARTAN JENSON PHARMACEUTICAL SERVICES 75mg	tablets	75mg	JENSON PHARMACEUTICAL SERVICES LTD.	GREAT BRITAIN	4103	2011	14
IRBESARTANUM	IRBESARTAN JENSON PHARMACEUTICAL SERVICES 150mg	tablets	150mg	JENSON PHARMACEUTICAL SERVICES LTD.	GREAT BRITAIN	4104	2011	14
IRBESARTANUM	IRBESARTAN JENSON PHARMACEUTICAL SERVICES 300mg	tablets	300mg	JENSON PHARMACEUTICAL SERVICES LTD.	GREAT BRITAIN	4105	2011	14
IRBESARTANUM	IRBESARTAN TORRENT 75mg	film-coated tablets	75mg	TORRENT PHARMA S.R.L.	ROMANIA	4138	2011	08
IRBESARTANUM	IRBESARTAN TORRENT 150mg	film-coated tablets	150mg	TORRENT PHARMA S.R.L.	ROMANIA	4139	2011	08
IRBESARTANUM	IRBESARTAN TORRENT 300mg	film-coated tablets	300mg	TORRENT PHARMA S.R.L.	ROMANIA	4140	2011	08
IRINOTECANUM	LUDIRADOL 20mg/ml	concentrate for solution for infusion	20mg/ml	EGIS PHARMACEUTICALS PLC	HUNGARY	3900	2011	02
KALII IODIDUM	IODURA DE POTASIU ATB 65mg	tablets	65mg	ANTIBIOTICE S.A.	ROMANIA	4164	2011	01
LACTULOSUM	LAEVOLAC 10g/15ml	oral solution	10g/15ml	FRESENIUS KABI AUSTRIA GMBH	AUSTRIA	3836	2011	05
LATANOPROSTUM	LATANOPROST NTC 50micrograms/ml	eye drops, solution	50micro-grams/ml	NTC S.R.L.	ITALY	3903	2011	03

LERCANIDIPINUM	LERCANIDIPINA JENSON 10mg	film-coated tablets	10mg	JENSON PHARMACEUTICAL SERVICES LTD	GREAT BRITAIN	3886	2011	10
LERCANIDIPINUM	LERCANIDIPINA JENSON 20mg	film-coated tablets	20mg	JENSON PHARMACEUTICAL SERVICES LTD	GREAT BRITAIN	3887	2011	10
LETROZOLUM	LETROZOL KABI 2.5mg	film-coated tablets	2.5mg	FRESENIUS KABI ONCOLOGY PLC.	MACEDONIA	3882	2011	08
LEVETIRACETAMUM	TRUND 100mg/ml	oral solution	100mg/ml	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	4023	2011	03
LEVETIRACETAMUM	TRUND 250mg	film-coated tablets	250mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	3992	2011	06
LEVETIRACETAMUM	TRUND 500mg	film-coated tablets	500mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	3993	2011	08
LEVETIRACETAMUM	TRUND 750mg	film-coated tablets	750mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	3994	2011	07
LEVETIRACETAMUM	TRUND 1000mg	film-coated tablets	1000mg	GLENMARK PHARMACEUTICALS S.R.O.	THE CZECH REPUBLIC	3995	2011	07
LEVETIRACETAMUM	EPILETAM 250mg	film-coated tablets	250mg	EGIS PHARMACEUTICALS PLC	HUNGARY	4050	2011	09
LEVETIRACETAMUM	EPILETAM 500mg	film-coated tablets	500mg	EGIS PHARMACEUTICALS PLC	HUNGARY	4051	2011	09
LEVETIRACETAMUM	EPILETAM 750mg	film-coated tablets	750mg	EGIS PHARMACEUTICALS PLC	HUNGARY	4052	2011	09
LEVETIRACETAMUM	EPILETAM 1000mg	film-coated tablets	1000mg	EGIS PHARMACEUTICALS PLC	HUNGARY	4053	2011	09
LEVETIRACETAMUM	LEVETIRACETAM DR. REDDY'S 250mg	film-coated tablets	250mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4054	2011	12

LEVETIRACETAMUM	LEVETIRACETAM DR. REDDY'S 500mg	film-coated tablets	500mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4055	2011	12
LEVETIRACETAMUM	LEVETIRACETAM DR. REDDY'S 750mg	film-coated tablets	750mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4056	2011	12
LEVETIRACETAMUM	LEVETIRACETAM DR. REDDY'S 1000mg	film-coated tablets	1000mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4057	2011	12
LINEZOLIDUM	LINEZOLID TEVA 2mg/ml	solution for infusion	2mg/ml	TEVA PHARMA-CEUTICALS S.R.L.	ROMANIA	3867	2011	03
LORATADINUM	ACATALERIC 10mg	tablets	10mg	COSMEDICA SP.Z.O.O.	POLAND	4077	2011	01
LOSARTANUM	VALEZAAR 12.5mg	film-coated tablets	12.5mg	ICN POLFA RZESZOW S.A.	POLAND	3897	2011	01
LOSARTANUM	VALEZAAR 25mg	film-coated tablets	25mg	ICN POLFA RZESZOW S.A.	POLAND	3898	2011	01
LOSARTANUM	VALEZAAR 50mg	film-coated tablets	50mg	ICN POLFA RZESZOW S.A.	POLAND	3899	2011	01
LYNESTRENOLUM	EXLUTON 0.5mg	tablets	0.5mg	N. V. ORGANON	THE NETHERLA NDS	4150	2011	02
MEROPENEMUM	MEROPENEM GSK 500mg	powder for solution for injection/ infusion	500 mg	GLAXOSMITHKLINE (GSK) S.R.L.	ROMANIA	3878	2011	01
MEROPENEMUM	MEROPENEM GSK 1000mg	powder for solution for injection/ infusion	1000 mg	GLAXOSMITHKLINE (GSK) S.R.L.	ROMANIA	3879	2011	01
MESALAZINUM	MEZAVANT 1200mg	prolonged-release gastro resistant tablets	1200mg	SHIRE PHARMACEUTICAL CONTRACTS LTD	GREAT BRITAIN	3831	2011	02
MESALAZINUM	MESALAZINA DUO 400mg	gastro resistant tablets	400mg	DUO FARMACEUTICI S.R.L.	ROMANIA	4079	2011	02
MESALAZINUM	MESALAZINA DUO 800mg	gastro resistant	800mg	DUO FARMACEUTICI S.R.L.	ROMANIA	4080	2011	03

		tablets						
METAMIZOLUM NATRIUM	NOVOCALMIN 300mg	suppositories	300mg	ANTIBIOTICE S.A.	ROMANIA	4015	2011	03
MONTELUKASTUM	SINGULAIR 4mg	granules	4mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	4153	2011	04
NAPROXENUM	EMOXEN 100mg/g	gel	100mg/g	EMO-FARM SP. Z.O.O.	POLAND	4112	2011	03
NATRII PICOSULFAS	PICOSALAX 5mg	tablets	5mg	\FERRING GMBH	GERMANY	4002	2011	02
NATRII PICOSULFAS	PICOSALAX 10mg	tablets	10mg	\FERRING GMBH	GERMANY	4003	2011	02
NEVIRAPINUM	NEVIRAPINA MYLAN 200mg	tablets	200mg	MYLAN S.A.S.	FRANCE	4048	2011	07
NICORANDILUM	NICORANDIL DEXCEL PHARMA 10mg	tablets	10mg	DEXCEL PHARMA LTD.	GREAT BRITAIN	4031	2011	04
NICORANDILUM	NICORANDIL DEXCEL PHARMA 20mg	tablets	20mg	DEXCEL PHARMA LTD.	GREAT BRITAIN	4032	2011	04
OLANZAPINUM	OLANZAPINA BLUEFISH 5mg	orodispersible tablets	5mg	BLUEFISH PHARMACEUTICALS AB	SWEDEN	3904	2011	02
OLANZAPINUM	OLANZAPINA BLUEFISH 10mg	orodispersible tablets	10mg	BLUEFISH PHARMACEUTICALS AB	SWEDEN	3905	2011	02
OLANZAPINUM	OLANZAPINA BLUEFISH 15mg	orodispersible tablets	15mg	BLUEFISH PHARMACEUTICALS AB	SWEDEN	3906	2011	02
OLANZAPINUM	OLANZAPINA BLUEFISH 10mg	orodispersible tablets	10mg	BLUEFISH PHARMACEUTICALS AB	SWEDEN	3905	2011	03
OLANZAPINUM	OLANZAPINA EGIS 5mg	orodispersible tablets	5mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	3842	2011	06
OLANZAPINUM	OLANZAPINA EGIS 10mg	orodispersible tablets	10mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	3843	2011	06
OLANZAPINUM	OLANZAPINA EGIS 15mg	orodispersible tablets	15mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	3844	2011	06
OLANZAPINUM	OLANZAPINA EGIS 20mg	orodispersible tablets	20mg	EGIS PHARMACEUTICALS PLC.	HUNGARY	3845	2011	06

OLANZAPINUM	IRROPIA 5mg	orodispersible tablets	5mg	ROMASTRU TRADING S.R.L.	ROMANIA	4073	2011	01
OLANZAPINUM	IRROPIA 10mg	orodispersible tablets	10mg	ROMASTRU TRADING S.R.L.	ROMANIA	4074	2011	01
OLANZAPINUM	IRROPIA 15mg	orodispersible tablets	15mg	ROMASTRU TRADING S.R.L.	ROMANIA	4075	2011	01
OLANZAPINUM	IRROPIA 20mg	orodispersible tablets	20mg	ROMASTRU TRADING S.R.L.	ROMANIA	4076	2011	01
OLANZAPINUM	WRANELON 5mg	orodispersible tablets	5mg	ADAMED PHARMA S.R.L.	ROMANIA	3980	2011	01
OLANZAPINUM	WRANELON 10mg	orodispersible tablets	10mg	ADAMED PHARMA S.R.L.	ROMANIA	3981	2011	01
OLANZAPINUM	WRANELON 15mg	orodispersible tablets	15mg	ADAMED PHARMA S.R.L.	ROMANIA	3982	2011	01
OLANZAPINUM	WRANELON 20mg	orodispersible tablets	20mg	ADAMED PHARMA S.R.L.	ROMANIA	3983	2011	01
OLANZAPINUM	ZOLASWIFT 5mg	orodispersible tablets	5mg	ZAKLAD FARMACEUTYCZNY ADAMED PHARMA S.A.	POLAND	3975	2011	01
OLANZAPINUM	ZOLASWIFT 10mg	orodispersible tablets	10mg	ZAKLAD FARMACEUTYCZNY ADAMED PHARMA S.A.	POLAND	3976	2011	01
OLANZAPINUM	ZOLASWIFT 15mg	orodispersible tablets	15mg	ZAKLAD FARMACEUTYCZNY ADAMED PHARMA S.A.	POLAND	3977	2011	01
OLANZAPINUM	ZOLASWIFT 20mg	orodispersible tablets	20mg	ZAKLAD FARMACEUTYCZNY ADAMED PHARMA S.A.	POLAND	3978	2011	01
ORLISTATUM	ORLISTAT POLPHARMA 60mg	capsules	60mg	PHARMACEUTICAL WORKS POLPHARMA SA	POLAND	4110	2011	16
ORLISTATUM	ORLISTAT POLPHARMA	capsules	120mg	PHARMACEUTICAL	POLAND	4111	2011	03

	120mg			WORKS POLPHARMA SA				
PANTOPRAZOLUM	PANTOPRAZOL JENSON 20mg	gastroresistant tablets	20mg	JENSON PHARMACEUTICALS LIMITED	GREAT BRITAIN	3829	2011	11
PANTOPRAZOLUM	PANTOPRAZOL JENSON 40mg	gastroresistant tablets	40mg	JENSON PHARMACEUTICALS LIMITED	GREAT BRITAIN	3830	2011	11
PANTOPRAZOLUM	PANTOPRAZOL KRKA 20mg	gastroresistant tablets	20mg	KRKA, D.D., NOVO MESTO	SLOVENIA	4137	2011	13
PARACETAMOLUM	PARACETAMOL SIGILLATA 250mg	film-coated tablets	250mg	SIGILLATA LIMITED	GREAT BRITAIN	3891	2011	11
PARACETAMOLUM	PARACETAMOL SIGILLATA 500mg	film-coated tablets	500mg	SIGILLATA LIMITED	GREAT BRITAIN	3892	2011	11
PARACETAMOLUM	PARACETAMOL SIGILLATA 1000mg	film-coated tablets	1000mg	SIGILLATA LIMITED	GREAT BRITAIN	3893	2011	11
PARICALCITOLUM	PARICALCITOL FRESENIUS 2micrograms/ml	solution for injection	2micro-grams/ml	FRESENIUS MEDICAL CARE NEPHROLOGICA DEUTSCHLAND GM	GERMANY	4041	2011	04
PARICALCITOLUM	PARICALCITOL FRESENIUS 5micrograms/ml	solution for injection	5micro-grams/ml	FRESENIUS MEDICAL CARE NEPHROLOGICA DEUTSCHLAND GM	GERMANY	4042	2011	08
PIOGLITAZONUM	PIOGLITAZONA DR. REDDY'S 15mg	tablets	15mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	3999	2011	07
PIOGLITAZONUM	PIOGLITAZONA DR. REDDY'S 30mg	tablets	30mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4000	2011	07
PIOGLITAZONUM	PIOGLITAZONA DR. REDDY'S 45mg	tablets	45mg	DR. REDDY'S LABORATORIES ROMANIA S.R.L.	ROMANIA	4001	2011	07
PIOGLITAZONUM	PIOGLITAZONA TORRENT 15mg	tablets	15mg	TORRENT PHARMA S.R.L.	ROMANIA	4126	2011	12
PIOGLITAZONUM	PIOGLITAZONA TORRENT 30mg	tablets	30mg	TORRENT PHARMA S.R.L.	ROMANIA	4125	2011	12
PIOGLITAZONUM	PIOGLITAZONA TORRENT 45mg	tablets	45mg	TORRENT PHARMA S.R.L.	ROMANIA	4127	2011	12

PLANTE	CANEPHRON	lozenges		BIONORICA SE	GERMANY	3938	2011	03
PLANTE	CANEPHRON	oral drops, solution		BIONORICA SE	GERMANY	3939	2011	03
PRAMIPEXOLUM	PRAMIPEXOL MYLAN 0.088mg	tablets	0.088mg	GENERICS (UK) LTD.	GREAT BRITAIN	3813	2011	11
PRAMIPEXOLUM	PRAMIPEXOL MYLAN 0.18mg	tablets	0.18mg	GENERICS (UK) LTD.	GREAT BRITAIN	3814	2011	11
PRAMIPEXOLUM	PRAMIPEXOL MYLAN 0.35mg	tablets	0.35mg	GENERICS (UK) LTD.	GREAT BRITAIN	3815	2011	11
PRAMIPEXOLUM	PRAMIPEXOL MYLAN 0.7mg	tablets	0.7mg	GENERICS (UK) LTD.	GREAT BRITAIN	3816	2011	11
PRAMIPEXOLUM	PRAMIPEXOL MYLAN 1.1mg	tablets	1.1mg	GENERICS (UK) LTD.	GREAT BRITAIN	3817	2011	11
PRAMIPEXOLUM	MIGLASEN 0.7mg	tablets	0.7mg	ROMASTRU TRADING S.R.L.	ROMANIA	4058	2011	01
PRAMIPEXOLUM	MIGLASEN 0.18mg	tablets	0.18mg	ROMASTRU TRADING S.R.L.	ROMANIA	4059	2011	01
PRAMIPEXOLUM	MIPARKAN 0.7mg	tablets	0.7 mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	4159	2011	01
PRAMIPEXOLUM	MIPARKAN 0.18mg	tablets	0.18 mg	ZENTIVA, K.S.	THE CZECH REPUBLIC	4158	2011	01
PROGESTERONUM	PROGESTOGEL 10mg/g	gel	10mg/g	LABORATOIRES BESINS INTERNATIONAL	FRANCE	4151	2011	01
PROMESTRIENUM	COLPOTROPHINE 10mg/g	vaginal cream	10mg/g	LABORATOIRE THERAMEX	MONACO	4152	2011	01
PROPOFOLUM	PROPOFOL PFIZER 10mg/ml	emulsion for inj./infusion	10mg/ml	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3901	2011	07
PROPOFOLUM	PROPOFOL PFIZER 20mg/ml	emulsion for injection/ infusion	20mg/ml	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3902	2011	02
PYRITINOLUM	ENCEPHABOL 100mg	lozenges	100mg	MERCK KGAA	GERMANY	4154	2011	03
PYRITINOLUM	ENCEPHABOL 200mg	lozenges	200mg	MERCK KGAA	GERMANY	4155	2011	03
QUETIAPINUM	QUETIAPINA PFIZER 25mg	film-coated tablets	25mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3911	2011	15
QUETIAPINUM	QUETIAPINA PFIZER 100mg	film-coated tablets	100mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3912	2011	15
QUETIAPINUM	QUETIAPINA PFIZER 150mg	film-coated tablets	150mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3913	2011	15

QUETIAPINUM	QUETIAPINA PFIZER 200mg	film-coated tablets	200mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3914	2011	15
QUETIAPINUM	QUETIAPINA PFIZER 300mg	film-coated tablets	300mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3915	2011	16
QUETIAPINUM	Q MIND 50mg	prolonged-release tablets	50mg	TORRENT PHARMA S.R.L.	ROMANIA	3924	2011	08
QUETIAPINUM	Q MIND 200mg	prolonged-release tablets	200mg	TORRENT PHARMA S.R.L.	ROMANIA	3925	2011	08
QUETIAPINUM	Q MIND 300mg	prolonged-release tablets	300mg	TORRENT PHARMA S.R.L.	ROMANIA	3926	2011	08
QUETIAPINUM	Q MIND 400mg	prolonged-release tablets	400mg	TORRENT PHARMA S.R.L.	ROMANIA	3927	2011	08
QUETIAPINUM	QUETIAPINA ACCORD 200mg	prolonged-release tablets	200mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	4113	2011	05
QUETIAPINUM	QUETIAPINA ACCORD 300mg	prolonged-release tablets	300mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	4114	2011	05
QUETIAPINUM	QUETIAPINA ACCORD 400mg	prolonged-release tablets	400mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	4115	2011	05
RABEPRAZOLUM	RACIDOL 10mg	gastro resistant tablets	10mg	TORRENT PHARMA S.R.L.	ROMANIA	3888	2011	02
RABEPRAZOLUM	RACIDOL 20mg	gastro resistant tablets	20mg	TORRENT PHARMA S.R.L.	ROMANIA	3889	2011	02
REMIFENTANILUM	REMIFENTANIL HOSPIRA 1mg	powder for concentrate for solution for injection/ infusion	1mg	HOSPIRA UK LIMITED	GREAT BRITAIN	3948	2011	01
REMIFENTANILUM	REMIFENTANIL HOSPIRA 2mg	powder for concentrate for solution for injection/ infusion	2mg	HOSPIRA UK LIMITED	GREAT BRITAIN	3949	2011	01

REMIFENTANILUM	REMIFENTANIL HOSPIRA 5mg	powder for concentrate for solution for injection/ infusion	5mg	HOSPIRA UK LIMITED	GREAT BRITAIN	3950	2011	01
RILUZOLUM	RILUZOL MYLAN 50mg	film-coated tablets	50mg	GENERICS (UK) LTD.	GREAT BRITAIN	4033	2011	07
RISPERIDONUM	RISPERIDONA MEDOCHEMIE 2mg	film-coated tablets	2mg	MEDOCHEMIE LTD.	CYPRUS	3932	2011	03
RISPERIDONUM	RISPERIDONA MEDOCHEMIE 4mg	film-coated tablets	4mg	MEDOCHEMIE LTD.	CYPRUS	3933	2011	02
RIZATRIPTANUM	MAXALT 5mg	oral lyophilisate	5mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	4039	2011	05
RIZATRIPTANUM	MAXALT 10mg	oral lyophilisate	10mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	4040	2011	05
RIZATRIPTANUM	MAXALT 5mg	tablets	5mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	4037	2011	05
RIZATRIPTANUM	MAXALT 10mg	tablets	10mg	MERCK SHARP & DOHME ROMANIA S.R.L.	ROMANIA	4038	2011	05
ROPIVACAINUM	ROPIVACAINA CLORHIDRAT B BRAUN 2mg/ml	solution for injection	2mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	4060	2011	04
ROPIVACAINUM	ROPIVACAINA CLORHIDRAT B BRAUN 5mg/ml	solution for injection	5mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	4061	2011	04
ROPIVACAINUM	ROPIVACAINA CLORHIDRAT B BRAUN 7.5mg/ml	solution for injection	7.5mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	4062	2011	04
ROPIVACAINUM	ROPIVACAINA CLORHIDRAT B BRAUN 10mg/ml	solution for injection	10mg/ml	B. BRAUN MELSUNGEN AG	GERMANY	4063	2011	04
ROSUVASTATINUM	TINTAROS 5mg	film-coated tablets	5mg	ACTAVIS GROUP PTC EHF	ICELAND	4011	2011	06
ROSUVASTATINUM	TINTAROS 10mg	film-coated tablets	10mg	ACTAVIS GROUP PTC EHF	ICELAND	4012	2011	06
ROSUVASTATINUM	TINTAROS 20mg	film-coated tablets	20mg	ACTAVIS GROUP PTC EHF	ICELAND	4013	2011	06
ROSUVASTATINUM	TINTAROS 40mg	film-coated	40mg	ACTAVIS GROUP PTC	ICELAND	4014	2011	06

		tablets		EHF				
ROSUVASTATINUM	ROSUVASTATINA GENERICS 5mg	film-coated tablets	5mg	GENERICS (UK) LTD T/A MYLAN	GREAT BRITAIN	4122	2011	15
ROSUVASTATINUM	ROSUVASTATINA GENERICS 10mg	film-coated tablets	10mg	GENERICS (UK) LTD T/A MYLAN	GREAT BRITAIN	4123	2011	15
ROSUVASTATINUM	ROSUVASTATINA GENERICS 20mg	film-coated tablets	20mg	GENERICS (UK) LTD T/A MYLAN	GREAT BRITAIN	4124	2011	15
SERTRALINUM	ADJUVIN 50mg	film-coated tablets	50mg	FARMACEUTICA REMEDIA S.A.	ROMANIA	4160	2011	01
SERTRALINUM	ADJUVIN 100mg	film-coated tablets	100mg	FARMACEUTICA REMEDIA S.A.	ROMANIA	4161	2011	01
SILDENAFILUM	SILDENAFIL PFIZER 25mg	film-coated tablets	25mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3872	2011	04
SILDENAFILUM	SILDENAFIL PFIZER 50mg	film-coated tablets	50mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3873	2011	04
SILDENAFILUM	SILDENAFIL PFIZER 100mg	film-coated tablets	100mg	PFIZER EUROPE MA EEIG	GREAT BRITAIN	3874	2011	04
SOLIFENACINUM SUCCINATE	ASOLFENA 5mg	film-coated tablets	5mg	KRKA, TOVARNA ZDRAVIL, D.D.	SLOVENIA	4064	2011	07
SOLIFENACINUM SUCCINATE	ASOLFENA 10mg	film-coated tablets	10mg	KRKA, TOVARNA ZDRAVIL, D.D.	SLOVENIA	4065	2011	07
SOLIFENACINUM SUCCINATE	OSOLFENACARE 5mg	film-coated tablets	5mg	HELM AG	GERMANY	4116	2011	09
SOLIFENACINUM SUCCINATE	OSOLFENACARE 10mg	film-coated tablets	10mg	HELM AG	GERMANY	4117	2011	09
SPIRONOLACTONUM	SPIRONOLACTONA LPH 25mg	capsules	25mg	LABORMED PHARMA S.A.	ROMANIA	4034	2011	02
SPIRONOLACTONUM	SPIRONOLACTONA LPH 50 mg	capsules	50mg	LABORMED PHARMA S.A.	ROMANIA	4035	2011	01
SPIRONOLACTONUM	SPIRONOLACTONA LPH 100mg	capsules	100mg	LABORMED PHARMA S.A.	ROMANIA	4036	2011	01
TAMSULOSINUM	TAMSULOSIN TEVA 400µg	prolonged-release tablets	400µg	TEVA PHARMACEUTICALS S.R.L.	ROMANIA	3997	2011	12
TIANEPTINUM	NELUPTIN 12.5mg	film-coated tablets	12.5mg	LUPIN (EUROPE) LIMITED	GREAT BRITAIN	4027	2011	10

TOLTERODINUM	UROFLOW 1	film-coated tablets	1mg	ZENTIVA K.S.	THE CZECH REPUBLIC	3858	2011	02
TOLTERODINUM	UROFLOW 2	film-coated tablets	2mg	ZENTIVA K.S.	THE CZECH REPUBLIC	3859	2011	02
TOPIRAMATUM	TOPIRAMAT EGIS 25mg	film-coated tablets	25mg	EGIS PHARMACEUTICALS PLC	UK	4044	2011	15
TOPIRAMATUM	TOPIRAMAT EGIS 50mg	film-coated tablets	50mg	EGIS PHARMACEUTICALS PLC	UK	4045	2011	15
TOPIRAMATUM	TOPIRAMAT EGIS 100mg	film-coated tablets	100mg	EGIS PHARMACEUTICALS PLC	UK	4046	2011	12
TOPIRAMATUM	TOPIRAMAT EGIS 200mg	film-coated tablets	200mg	EGIS PHARMACEUTICALS PLC	UK	4047	2011	12
TOPOTECAMUM	TOPOTECAN CIPLA 4mg	powder for solution for infusion	4mg	CIPLA (UK) LTD.	GREAT BRITAIN	3952	2011	02
TOPOTECAMUM	TOPOTECAN CIPLA 1mg	powder for solution for infusion	1mg	CIPLA (UK) LTD.	GREAT BRITAIN	3951	2011	02
TOPOTECAMUM	MICOFENOLAT MOFETIL MYLAN 500mg	film-coated tablets	500mg	GENERICS (UK) LTD	GREAT BRITAIN	3955	2011	36
TRAMADOLUM	TRAMADOL RETARD 100mg	prolonged-release tablets	100mg	KRKA, D.D., NOVO MESTO	SLOVENIA	4146	2011	01
VACCIN H. INFLUENZAE TYPE B	ACT-HIB 10 micrograms/0.5ml	powder and solvent for susp. for inj. in pre-filled syringe	10micro-grams/ 0.5ml	SANOFI PASTEUR S.A.	FRANCE	4148	2011	03
VACCIN HEPATITIC A INACTIVATED	AVAXIM 80 U PEDIATRIC, VACCIN HEPATITIC A INACTIVAT, ADSORBIT	suspension for injection in pre-filled syringe		SANOFI PASTEUR SA	FRANCE	40907	2011	06
VALACYCLOVIRUM	VALTREX 500mg	film-coated tablets	500mg	THE WELLCOME FOUNDATION LIMITED	GREAT BRITAIN	40907	2011	05
VALSARTANUM	DIOVAN 80mg	film-coated	80mg	NOVARTIS PHARMA	GERMANY	40863	2011	30

		tablets		GMBH				
VALSARTANUM	DIOVAN 40mg	film-coated tablets	40mg	NOVARTIS PHARMA GMBH	GERMANY	40863	2011	30
VALSARTANUM	DIOVAN 160mg	film-coated tablets	160mg	NOVARTIS PHARMA GMBH	GERMANY	40863	2011	30
VALSARTANUM	AVASSAN 80mg	film-coated tablets	80mg	TERAPIA S.A.	ROMANIA	40863	2011	06
VALSARTANUM	AVASSAN 40mg	film-coated tablets	40mg	TERAPIA S.A.	ROMANIA	40863	2011	06
VALSARTANUM	AVASSAN 160mg	film-coated tablets	160mg	TERAPIA S.A.	ROMANIA	40863	2011	06
VANCOMYCINUM	VANCOMICINA NATLIP 500mg	powder for concentrate for solution for infusion	500mg	NRIM LIMITED	GREAT BRITAIN	40863	2011	01
VANCOMYCINUM	VANCOMICINA NATLIP 1000mg	powder for concentrate for solution for infusion	1000mg	NRIM LIMITED	GREAT BRITAIN	40863	2011	01

EMA newly centrally authorised medicinal products for which the European Commission has issued decisions during the 4th quarter of 2011

INN	Invented name	Pharmaceutical form	Strength	MA Holding Company	Country	MA Number		
DESLORATADINUM	DESLORATADINE TEVA	film-coated tablets	5mg	TEVA PHARMA B.V.	THE NETHERLANDS	732	2011	13
DESLORATADINUM	DASSELTA	film-coated tablets	5mg	KRKA D.D. NOVO MESTO	SLOVENIA	739	2011	08
LEVETIRACETAMUM	LEVETIRACETAM ACTAVIS 250mg	film-coated tablets	250mg	ACTAVIS GROUP PTC EHF.	ICELAND	713	2011	10
LEVETIRACETAMUM	LEVETIRACETAM ACTAVIS 1000mg	film-coated tablets	1000mg	ACTAVIS GROUP PTC EHF	ICELAND	713	2011	10
LEVETIRACETAMUM	LEVETIRACETAM ACTAVIS 750mg	film-coated tablets	750mg	ACTAVIS GROUP PTC EHF	ICELAND	713	2011	10
LEVETIRACETAMUM	LEVETIRACETAM ACTAVIS 500mg	film-coated tablets	500mg	ACTAVIS GROUP PTC EHF.	ICELAND	713	2011	10
LEVETIRACETAMUM	LEVETIRACETAM ACCORD 250mg	film-coated tablets	250mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	712	2011	07
LEVETIRACETAMUM	LEVETIRACETAM ACCORD 500mg	film-coated tablets	500mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	712	2011	07
LEVETIRACETAMUM	LEVETIRACETAM ACCORD	film-coated	750mg	ACCORD HEALTHCARE	GREAT	712	2011	07

	750mg	tablets		LIMITED	BRITAIN			
LEVETIRACETAMUM	LEVETIRACETAM ACCORD 1000mg	film-coated tablets	1000mg	ACCORD HEALTHCARE LIMITED	GREAT BRITAIN	712	2011	07
LEVETIRACETAMUM	LEVETIRACETAM ACTAVIS GROUP 100mg/ml	oral solution	100mg/ml	ACTAVIS GROUP PTC EHF	ICELAND	738	2011	03
RILPIVIRINUM	EDURANT	film-coated tablets	25mg	JANSSEN CILAG INTERNATIONAL NV	BELGIUM	736	2011	01