NIB/VVL/CCRV.MMR.MEASLES.RUBELLA/0.1

GUIDANCE MANUAL

ON

QUALITY CONTROL

OF

Viral Vaccines

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AMENDMENT SHEET

S. No.	Date	Page No.	Revision No.	Nature of Amendment Section/details	Authorization

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I would take this opportunity to express my gratitude to all the staff members of viral vaccine laboratory Ms. Gurminder Bindra. Ms. Shalini Tewari, Mr. Subhash Chand, Dr. Manjula Kiran, Mr. Jaipal Meena, Mr. Varun Sharma, Ms. Farha Hasan, Ms. Ila Mathpal, Mr. Saurabh Vaishnav, Ms. Anupama Pandey for providing the valuable inputs in the preparation of the Guidance Manual on Quality Control of CCRV, MMR, Measles, Rubella Vaccine without which the endeavour would not have been possible. I also wish them good luck in their future scientific work.

The encouragement provided by Dr. Surinder Singh, Director (I/c) to prepare this document is deeply acknowledged.

I hope the Guidance Manual on Quality Control of CCRV, MMR, Measles and Rubella vaccines will go a long way in Quality evaluation of these vaccines.

Dr. G.R Soni
Scientist-I & Head
Vaccine Division

FOREWORD

This document has been prepared for the purpose of inviting comments and suggestions from stakeholders of CCRV, MMR, Measles and Rubella Vaccines, Central Drugs Testing Laboratories (CDTL), Indian Pharmacopoeia Commission (IPC), Central Drugs Standard Control Organization (CDSCO), State Drugs Controller, and Academic Institutions involved in activities relating to quality evaluation of above said vaccines

This draft has been prepared in consultation with different pharmacopoeia, WHO Technical Report Series and experience gained by the team during testing of the vaccine. The comments will be considered by the team and will be incorporated accordingly.

This document will be useful to manufacturers, suppliers, NRA and testing laboratories which are involved in assurance of the Quality, Safety and Efficacy of CCRV, MMR, Measles and Rubella vaccines.

The laboratory has a Quality Management System in place and is NABL Accredited in accordance with the standard ISO/IEC 17025; 2005 in the field of biological and chemical testing.

ABBREVIATIONS

BP	British Pharmacopoeia
EP	European Pharmacopoeia
CCID	Cell culture infective dose
CCRV	Cell Culture Rabies Vaccine
CDL	Central Drugs Laboratory
CDSCO	Central Drugs Standard Control Organization
CDTL	Central Drugs Testing Laboratory
CMC	Chemistry Manufacturing and Control
DCG (I)	Drugs Controller General of India
IP	Indian Pharmacopoeia
IPC	Indian Pharmacopoeia Commission
IPRS	Indian Pharmacopoeia Reference Standard
IU	International Unit
LEP	Low Egg Passage
MMR	Measles Mumps Rubella
NABL	National Accreditation Board for Testing and Calibration Laboratories
NLT	Not less than
NCA	National Control Authority
NCL	National Control Laboratory
NIBSC	National Institute of Biological Standards & Control, U.K
SRRDU	Sample Receiving Report and Dispatch Unit
SOP	Standard Operating Procedures
TRS	Technical Report Series
UNICEF	United Nations International Children's Emergency Fund
USP	United States Pharmacopoeia
WHO	World Health Organization

CONTRIBUTORS

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CONTENTS

1. INTRODUCTION

WHO and various Pharmacopoeia regularly review and publish the amendments and address the issues relating to improvement in Quality Control test parameters of various vaccines including CCRV, MMR, Measles, Rubella vaccines. This document will help the stakeholders involved in the quality assurance of CCRV, MMR, Measles, Rubella vaccines.

Vaccines play a significant role in developing the world's economy as they reduce infant mortality and immunize against diseases. They are also cost effective methods of ensuring good health on a long term basis. This in turn leads to greater productivity & contribution to global economy. The global vaccine market is estimated at $32.05 billion in 2013 and is expected to reach $84.44 billion by 2022.

India's huge population places it among the world's largest markets for vaccines. India is already an established player in paedriatic vaccines with various Indian manufacturers contributing to India's emergence as a leading hub for vaccine manufacturing and supply to schemes run by global institutions such as WHO and UNICEF which helped India emerge as a strong global competitor in the vaccines sector without compromising on quality. India is the major supplier of vaccines to UNICEF which in turn supplies 40% of the total vaccine demand for childhood vaccination in more than 100 countries. India produces about 40- 70% of WHO demand for DPT and BCG vaccines and almost 90% of demand for Measles vaccine. Every 2nd child in the world get Measles vaccine manufactured in India. Vaccines from India are exported to more than 151 countries

With the increase in disposable incomes and the launch of new affordable vaccines by both domestic and international companies, the vaccine market is predicted to grow at a rate of 10-13 percent in the next five years. According to 2011 estimates, 60 percent of the global health vaccines are produced in India. The country's vaccine production sector is likely expand to an estimated $871 million by 2016 compared to 2011's value of $350 million. The Indian vaccine market will grow 20% per year. Exports made up 65% of the Indian vaccine market in 2011. Thus, it is very important to maintain high standards of healthcare delivery through vaccines and address immediate challenges to ensure a sustained growth of this sector in the near future by coordination between NIB, Drug Regulatory Authority (CDSCO) & manufacturers.

Depending on the basis of severity, prevalence of diseases & age at dosage India's vaccine market can be classified into 5 different categories- viz UIP vaccines (BCG, DPT, Measles, Polio, TT, pentavalent vaccines), post incident vaccines (Rabies), emerging mandatory vaccines (MMR, Pneumococcal, Meningococcal, HPV, Rota virus), regular optional vaccines (Typhoid, Influenza) and one time optional vaccines (Varicella, Hepatitis A, Cholera).

1. **UIP vaccines**: Vaccines for diseases with high life threating potential and recommended for infants are mostly part of UIP. These vaccines include BCG, DPT, Measles containing vaccine, Polio, TT, pentavalent vaccines etc.
2. **Post incident vaccines**: Diseases which have life threating potential and usage across age groups for example Rabies vaccine.
3. **Emerging mandatory vaccines:** Vaccines for diseases with moderate threating potential and are expected to be included in UIP at some point of

time and usage will become mandatory for example HPV, Rotavirus, MMR, Pneumococcal, Meningococcal vaccines.

4. **Regular optional vaccines** for diseases with low life threating potential i.e. primarily adult vaccines for example Influenza, Typhoid vaccine
5. **One time optional vaccines** for diseases with low life threating potential, for example Hepatitis A, Varicella, Cholera vaccines

2.OBJECTIVE & BACKROUND

The Objective of this document is to provide guidelines to manufactures to assure quality of the CCRV, MMR, Measles and Rubella vaccines for batch release.

Background: Rabies virus belongs to the genus Lyssavirus of the Rhabdoviridae family. Rabies is a zoonotic disease (transmission from animals to humans), and human infection usually occurs following a bite or scratch by an infected animal. Since their development more than four decades ago, concentrated and purified cell-culture and embryonated egg based rabies vaccines (CCVs) have proved to be safe and effective in preventing rabies. Over the years various vaccine strains have evolved viz Flury LEP, Pitman-Moore strain (PM), Wistar rabies PM/WI38-15033M strain, L.Pasteur 2061/Vero Rabies strain for rabies virus.

Measles virus is an enveloped, ribonucleic acid virus of the genus Morbillivirus. Although at least 20 different genotypes have been isolated in various parts of the world, there is only one serotype. Measles is highly contagious, and an infected person will often transmit the virus to over 90% of unprotected close contacts. A number of live, attenuated measles vaccines are available, either as monovalent vaccine or in combination with either rubella vaccine (MR) or mumps and rubella vaccines (MMR). Many of the attenuated strains in use are derived from the Edmonston strain isolated in 1954, including the Schwartz, the Edmonston-Zagreb, and the Moraten strains.

Mumps is an acute disease of children and young adults, caused by a paramyxovirus of which there is only a single serotype. Live attenuated mumps vaccines based on

live attenuated virus strains including the Jeryl-Lynn, RIT 4385, Leningrad-3, Leningrad-Zagreb, Urabe Am9, S79, Rubini, and others, have been available since the 1960s.

The Rubella virus, a togavirus of the genus Rubivirus, is an enveloped singlestranded RNA virus with a single serotype that does not cross-react with other togaviruses. Humans are the only known host, with seasonal epidemics occurring every 5-9 years over a worldwide distribution. Most of the currently licensed vaccines are based on the live, attenuated RA 27/3 strain of rubella virus propagated in human diploid cells.

2.1 Selection of methods.

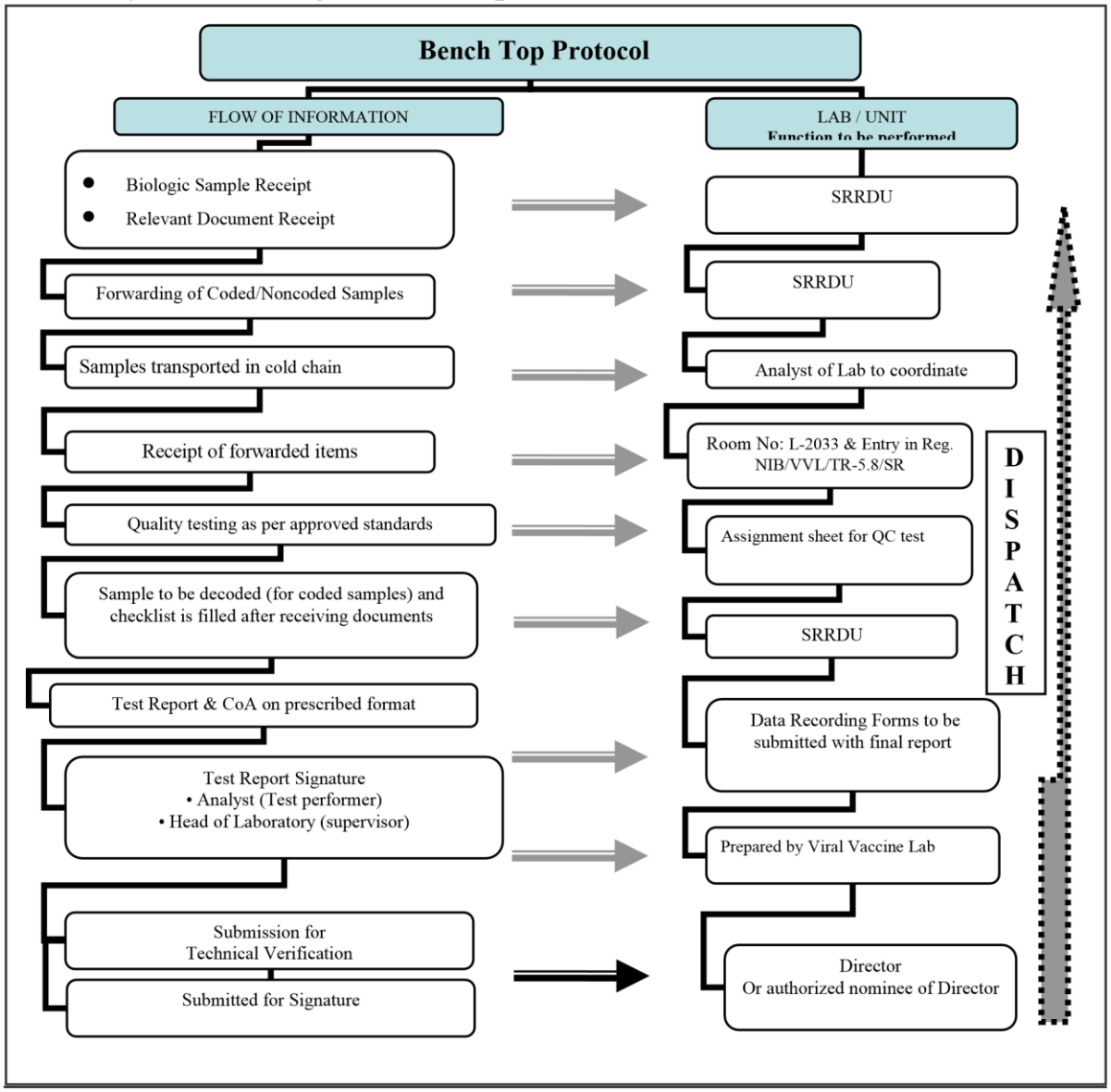
The laboratory uses test methods, which are appropriate for the tests it undertakes and meet the needs of the manufacturer and NRA. Specifications of the test methods are in accordance to respective monograph in the Indian pharmacopoeia 2014 and WHO Technical Report Series for the said vaccine. Laboratory has a well defined test plan with assignment of each test to be conducted by the Analysts.

2.2 Assuring the Quality of test methods

The laboratory has quality control procedures for monitoring the validity of tests. The resulting data is recorded in a way that the trends are detectable and where practicable, statistical techniques are applied in reviewing of results. This monitoring is planned and reviewed which includes regular use of working reference standards provided by the manufacturer, retesting of test items. Equipment are validated/calibrated to ensure its proper functioning and to maintain the integrity of test data.

3. ASSURING THE QUALITY OF TEST RESULTS

3.1 Policy on handling of test samples



3. 1.1The test plan is prepared and approved which describes the sequence of test from the receipt of samples to release of report by Lab Head for each batch of vaccine sample forwarded for purpose of test and analysis in the laboratory by SRRDU.

3.1.2 The vaccine sample on receipt in the laboratory will be assigned by the Laboratory Head/In-charge to the concerned Analysts. The work assignment for functions and responsibilities are issued to an individual scientific and technical staff for carrying out quality control test and other related laboratory activities. Testing of samples is done to confirm compliance with the requirements and agreed specifications.

3.1.3 Protocols of production, summary protocol and Certificate of analysis of the concerned batch are received from the manufacturer. The check list prepared for the purpose to review manufacturer's documents/protocols is given in Annexure A

4. **DEFINITIONS**

4.1 Final bulk: The homogeneous finished liquid vaccine present in a single container from which the final containers are filled, either directly or through one or more intermediate containers derived from the initial single container.

4.2 Final lot: A number of sealed, final containers that are equivalent with respect to the risk of contamination during filling and, freeze-drying if performed. A final lot should therefore have been filled from a single container and freeze-dried in one continuous working session.

4.3 Working Reference Standard: Manufacturer is to provide working reference standard of vaccine prepared from the same vaccine strain as the tested vaccine and used in parallel to the vaccine tested for:

1. Identification
2. Potency
3. Stability

However in case of CCRV, Measles, Mumps and Rubella national standard is provided by CDL- Kasauli.

4.4 Control test on final lot

As given in Table No.1 to Table 4, manufacturer will provide total quantity of sample to be forwarded to NIB as per the vaccine type. Samples are labeled and retained quantities are kept for future reference. As per the test parameter indicated in Table 1 to Table 4, each container is allocated identification by giving T1, T2….T (n) for vials before the test is initiated.

Tests are performed after reconstitution, except for water content. The diluent supplied or recommended for reconstitution is used.

The vaccine is reconstituted to the concentrations at which it is to be used for injection into humans.

5. **TEST METHOD & TEST VALIDATION:**

5.1 Quality Evaluation

The test methods given in concerned monographs are verified in the laboratory for its repeatability & reproducibility in quantitative test.

5.1.1 Labelling: The product container bears the titer of following Vaccines as

CCRV	NLT 2.5 IU per single human dose
Measles vaccine	NLT 1 x $10^3 CCID_{50}$ per human dose
Rubella vaccine	NLT 1 x $10^3 CCID_{50}$ per human dose
MMR vaccine	NLT 1 x $10^3 CCID_{50}$ per human dose (Measles component) NLT 5 x $10^3 CCID_{50}$ per human dose (Mumps component) NLT 1 x $10^3 CCID_{50}$ per human dose (Rubella component)

On the basis of formulations existing in Indian pharmacopoeia 2014 the tests for quality are carried out and calculations are performed and samples are reported to be of Standard Quality / Not of Standard Quality.

5.1.2 Testing of viral vaccine samples: The product container bears Pharmacopoeial claim or "for WHO supply", on the basis of which the sample is evaluated in accordance with the specifications and the procedure mentioned in IP/ WHO TRS/ method used by manufacturer for the said vaccine. The standard operating procedures (SOP) used in the laboratory for all QC tests are in accordance with IP/ EP/ WHO TRS.

Table 1: Test parameters & Distribution of Quantity of CCRV

S. No	Name of Test	Evaluation parameter	Type of estimation	* Number of Vials	
				Vial (1ml)	Vial ID given
1	Identification and Potency	Potency of virus content in vaccine; identification of virus in the vaccine	Animal based	2	T1-T2
2	Virus inactivation	Complete inactivation of Virus	Animal based	1	T3
3	Sterility (Inter laboratory)	Microbial contamination: fungal/bacterial	Membrane filtration or direct inoculation	2	T4-T5
4	Abnormal toxicity (Inter laboratory)	In-vivo safety	Animal based	7	T6-T12
5	Pyrogen (Inter laboratory)	Endogenous pyrogen	Animal based	3	T13-T15
6	Bacterial endotoxin (Inter laboratory)	Endogenous pyrogen	Gel clot	1	T16
7	Water content	Estimation of water content	Karl Fisher Coulometric	4	T17-T20
8	**Bovine Serum albumin	Bovine serum albumin content	ELISA based	1	T21

* The number of retained vials is equal to number of vials required for testing

** Under Standardization

Table 2: Test parameters & Distribution of Quantity of MMR

S. No	Name of Test	Evaluation parameter	Type of estimation	* Number of Vials			
				Single dose (0.5ml)	Vial ID given	Ten dose (5ml)	Vial ID given
1	Identification and Potency	Potency of virus content in vaccine; identification of virus in the vaccine	Cell-line based	3	T1-T3	3	T1-T3
2	Stability	Potency of virus content in vaccine exposed at 37°C	Cell-line based	3	T4-T6	3	T4-T6
3	Sterility (Inter laboratory)	Microbial contamination: fungal/bacterial	Membrane filtration or direct inoculation	2	T7-T8	2	T7-T8
4	Abnormal toxicity (Inter laboratory)	In-vivo safety	Animal based	7	T9-T15	1	T9
5	Water content	Estimation of water content	Karl Fisher Coulometric	4	T16-T19	4	T10-T13
6	**Bovine Serum albumin	Bovine serum albumin content	ELISA based	1	T20	1	T14

* The number of retained vials is equal to number of vials required for testing

** Under Standardization

Table 3: Test parameters & Distribution of Quantity of Measles vaccine

S. No	Name of Test	Evaluation parameter	Type of estimation	* Number of Vials			
				Single dose (0.5ml)	Vial ID given	Ten dose (5ml)	Vial ID given
1	Identification and Potency	Potency of virus content in vaccine; identification of virus in the vaccine	Cell-line based	3	T1-T3	3	T1-T3
2	Stability	Potency of virus content in vaccine exposed at 37°C	Cell-line based	3	T4-T6	3	T4-T6
3	Sterility (Inter laboratory)	Microbial contamination: fungal/bacterial	Membrane filtration or direct inoculation	2	T7-T8	2	T7-T8
4	Abnormal toxicity (Inter laboratory)	In-vivo safety	Animal based	7	T9-T15	1	T9
5	Water content	Estimation of water content	Karl Fisher Coulometric	4	T16-T19	4	T10-T13
6	**Bovine Serum albumin	Bovine serum albumin content	ELISA based	1	T20	1	T14

* The number of retained vials is equal to number of vials required for testing

** Under Standardization

Table 4: Test parameters & Distribution of Quantity of Rubella Vaccine

S. No	Name of Test	Evaluation parameter	Type of estimation	* Number of Vials			
				Single dose (0.5ml)	Vial ID given	Ten dose (5ml)	Vial ID given
1	Identification and Potency	Potency of virus content in vaccine; identification of virus in the vaccine	Cell-line based	3	T1-T3	3	T1-T3
2	Stability	Potency of virus content in vaccine exposed at 37°C	Cell-line based	3	T4-T6	3	T4-T6
3	Sterility (Inter laboratory)	Microbial contamination: fungal/bacterial	Membrane filtration or direct inoculation	2	T7-T8	2	T7-T8
4	Abnormal toxicity (Inter laboratory)	In-vivo safety	Animal based	7	T9-T15	1	T9
5	Water content	Estimation of water content	Karl Fisher Coulometric	4	T16-T19	4	T10-T13
6	**Bovine Serum albumin	Bovine serum albumin content	ELISA based	1	T20	1	T14

* The number of retained vials is equal to number of vials required for testing

** Under Standardization

6. REPORTING THE RESULTS CRITERIA FOR ACCEPTANCE OF SAMPLES:

6.1 Types of biological:

Vaccine (freeze dried)/ liquid preparation as per manufacturer's specifications is:

6.1.1 Single dose vial

6.1.2 Multi dose vial

6.2 Condition of packing:

Vaccine should be in

6.2.1 Sealed containers

6.2.2 With proper labels

6.2.3 Supplied in cold chain at 2-8°C.

6.2.4 With minimum 60% shelf life.

6.3 Quantity of samples essential:

Total vials required (Complete testing): As per Table No. 1 to 4

6.4 Documents required

6.4.1 Documents shall be checked as per the check list of documents given in Annexure -A

7. POLICY ON TESTING

7.1 Opening of samples for laboratory test

As per test assignment, the samples are distributed for Inter laboratory testing as well as for testing within Viral vaccine lab.

Equal number of samples are kept as retained samples at recommended storage conditions.

The sample preparation is done in the Biosafety Cabinet Class II A2, wherever required.

8. QUALITY EVALUATION:

Quality evaluation shall be based on various Quality Control Tests, their acceptance criteria and interpretation of results as mentioned in S. No 12.

8.1 Policy on use of control sample:

8.1.1 **Reference vials:** One vial of reference (from manufacturer or national reference) is used for one test which may involve testing of one or more batches.

8.1.2 **Repeat testing (if essential)**: In case of any deviation in the test or objective/ observation of Head, repeat test shall be done with approved competent authority and IAEC approvals.

8.1.3 **Validation of tests**: Records of validation of individual tests shall be maintained in the laboratory.

8.1.4 **Presentation of Results:** Test results shall be mentioned in the test report.

8.2 Verification of Results and Signature:

8.2.1 The results shall be verified by Lab. In-charge/ Head (Supervisor)

8.2.2 Test report of each test shall be signed by analyst (Scientist)

8.3 Policy on calibration of equipment:

8.3.1 Only calibrated equipment of the lab shall be used.

8.3.2 If any fault occurs, it shall be notified to the engineering division for corrective measures as per SOP/QA/14.

8.4 Policy on preparation of report:

8.4.1 **Signature on reports**: Certificate of Analysis shall be signed by analyst and Head of Division.

8.4.2 **Release of Report:** Shall be done by Director or authorized nominee of Director.

8.4.3 **Turnaround time**: Shall be within 45 days from the date of receipt of sample in SRRDU (depending on availability of animals, wherever required).

9.0 POLICY ON RETENTION OF SAMPLES AND REPORT

9.1 No. of samples to be retained: As per test assignment sheets for individual vaccines Table 1 to 4

9.2 Copies of report to be retained: One copy shall be retained by SRRDU in Archives.

10.0 POLICY ON ADMINISTRATIVE REVIEW:

10.1 Reports to be submitted for Administrative Review: The reports shall be submitted as per NIB/QMU/SOP/26/R1.

10.2 Authority for Administrative Review: Expert

11.0 POLICY ON RETENTION OF TEST SAMPLES & REPORT OF BIOLOGICAL SAMPLES

11.1 Duration of retention of samples: Samples shall be retained under specified condition for one year after expiry, in SRRDU. Thereafter the samples are disposed off by the laboratory after verification by Institutional Biosafety Committee.

11.2 Retention of documents: The documents shall be retained in Archives as per NIB/QMU/SOP/26/R1

12. Template Certificate of Analysis:

NATIONAL INSTITUTE OF BIOLOGICALS
(Ministry of Health and Family Welfare)
An ISO 17025:2005 Accredited Institute

-

Dated: 16.10.14

F.NO. N.7
9/2014 -SRRD/VV
Certificate No.

CERTIFICATE OF ANALYSIS

T-2010 & T-2011

Whether Regulatory/ Non Regulatory sample :

Date of sample receipt :

Start date of analysis :

CDR No. :

Analytical Report No. :

Product & Dosage Form :

Name of the manufacturer :

Lot/Batch No. :

Manufacturing Date :

Expiry Date :

S. No.	Test parameter (*Method)*	Specification	Results
1	Potency *(NIH Assay)*	The vaccine complies with the test if the estimated potency is not less than 2.5 IU per single human dose (As per IP 2014)	Complies
2	Virus inactivation *(In vivo*)	Neither symptoms of disease in Central Nervous System nor death occurs in any of animals within 14 days (As per IP 2014)	Complies
3	Sterility *(Membrane filtration)*	No evidence of microbial growth (As per IP 2014)	Complies
4	Abnormal Toxicity *(In vivo)*	None of the animal dies or shows sign of ill health. (As per IP 2014)	Complies
5	Pyrogens *(In Rabbits)*	a. The sum of the responses of group of 3 rabbits does not exceed 1.4°C. b. The response of any individual rabbit should be less than 0.6°C. (As per IP 2014)	Complies
6	Bacterial endotoxin *(Gel clot)*	Less than 25 IU per single human dose (As per IP 2014)	Complies
7	Water content *(Karl Fisher- Coulometric)*	Not more than 3.0 % (As per IP 2014)	Complies

CONCLUSION: The Batch/Lot No. …… of the ……. Cell Cultured Rabies Vaccine **comply** the requirement(s) as per IP 2014. The product is of **Standard Quality**.

Signature of the Analyst

Signature of the Lab Head

Date:

Date:

National Institute of Biologicals
(Ministry of Health & Family Welfare)

An ISO 17025: 2005 Accredited Institute Certificate No.: T- 2010 Certificate No.: T-2011

Dated:

CERTIFICATE OF ANALYSIS

Date of sample receipt :

Start date of analysis :

CDR No. :

Analytical Report No. :

Product & Dosage Form :

Name of the manufacturer :

Lot/Batch No. :

Manufacturing Date :

Expiry Date :

Whether Regulatory/ Non Regulatory sample :

S. No.	Test Parameters *(Method)*	Specification	Results
1.	Identification- Measles *(Cell culture based Bioassay)*	No cytopathic effect observed on susceptible cell cultures after neutralization of vaccine with specific measles antiserum. (IP 2014)	Complies
2.	Identification- Mumps *(Cell culture based Bioassay)*	No cytopathic effect observed on susceptible cell cultures after neutralization of vaccine with specific mumps antiserum. (IP 2014)	Complies
3.	Identification- Rubella *(Cell culture based Bioassay)*	No cytopathic effect observed on susceptible cell cultures after neutralization of vaccine with specific rubella antiserum. (IP 2014)	Complies

4.	Potency *(Cell culture based Bioassay)*	1. Mean potency titer of the Measles virus component is not less than 1 x 10^3CCID$_{50}$ per human dose. 2 .Mean potency titer of the Mumps virus component is not less than 5 x 10^3CCID$_{50}$ per human dose. 3. Mean potency titer of the Rubella virus component is not less than 1 x 10^3CCID$_{50}$ per human dose. (IP 2014)	Complies
5.	Stability *(Cell culture based Bioassay)*	The virus concentration of the heated vaccine held at 37°C for 7 days is not more than 1.0 log $_{10}$ lower than that of the unheated vaccine kept at 2-8^{0}C. (IP 2014)	Complies
6	Sterility *(Membrane Filtration)*	No evidence of microbial growth found. (IP 2014)	Complies
7	Abnormal Toxicity *(In-vivo)*	None of the animals dies or shows sign of ill health. (IP 2014)	Complies
8	Water content *(Karl Fischer- Coulometric)*	Not be more than 3.0 % (IP 2014)	Complies

CONCLUSION: The Batch/Lot No. ……. of the Measles, Mumps, Rubella Vaccine, Live attenuated, (Freeze- Dried) as per requirements of IP 2014 is of **standard quality/ not of standard quality**.

Signature of the Lab. I/c /Head

Signature of the Analyst
Name & Designation:
Date:

Name & Designation:
Date:

National Institute of Biologicals
(Ministry of Health & Family Welfare)

An ISO 17025: 2005 Accredited Institute Certificate No.: T- 2010 Certificate No.: T-2011

Dated:

CERTIFICATE OF ANALYSIS

Date of sample receipt :

Start date of analysis :

CDR No. :

Analytical Report No. :

Product & Dosage Form :

Name of the manufacturer :

Lot/Batch No. :

Manufacturing Date :

Expiry Date :

Whether Regulatory/ Non Regulatory sample :

S. No.	Test Parameters *(Method)*	Specification	Results
1.	Identification *(Cell culture based Bioassay)*	No cytopathic effect observed on susceptible cell cultures after neutralization of vaccine with specific measles antiserum. (IP 2014)	Complies
2.	Potency *(Cell culture based Bioassay)*	Not less than 1 x 10^3CCID$_{50}$ per human dose. (IP 2014)	Complies
3.	Stability *(Cell culture based Bioassay)*	The virus concentration of the heated vaccine held at 37°C for 7 days is not more than 1.0 log $_{10}$ lower than that of the unheated vaccine kept at 2-8^{0}C. (IP 2014)	Complies
4.	Sterility *(Direct inoculation)*	No evidence of microbial growth found. (IP 2014)	Complies
5	Abnormal Toxicity *(In-vivo)*	None of the animals dies or shows sign of ill health. (IP 2014)	Complies
6.	Water content *(Karl Fischer- Coulometric)*	Not be more than 3.0 % (IP 2014)	Complies

CONCLUSION: The Batch/Lot No. …….. of the Measles Vaccine, Live, Attenuated (Freeze- Dried) as per requirements of IP 2014 is of **standard quality/ not of standard quality**.

Signature of the Analyst
Name & Designation: Date:

Signature of the Lab. I/c /Head Name & Designation:
Date:

National Institute of Biologicals
(Ministry of Health & Family Welfare)

An ISO 17025: 2005 Accredited Institute Certificate No.: T- 2010 Certificate No.: T-2011

Dated:

CERTIFICATE OF ANALYSIS

Date of sample receipt :

Start date of analysis :

CDR No. :

Analytical Report No. :

Product & Dosage Form :

Name of the manufacturer :

Lot/Batch No. :

Manufacturing Date :

Expiry Date :

Whether Regulatory/ Non Regulatory sample :

S. No.	Test Parameters *(Method)*	Specification	Results
1.	Identification *(Cell culture based Bioassay)*	No cytopathic effect observed on susceptible cell cultures after neutralization of vaccine with specific rubella antiserum. (IP 2014)	Complies
2.	Potency *(Cell culture based Bioassay)*	Not less than 1 x 10^3CCID$_{50}$ per human dose. (IP 2014)	Complies
3.	Stability *(Cell culture based Bioassay)*	The virus concentration of the heated vaccine held at 37°C for 7 days is not more than 1.0 log $_{10}$ lower than that of the unheated vaccine kept at 2-8^{0}C. (IP 2014)	Complies
4.	Sterility *(Membrane Filtration)*	No evidence of microbial growth found. (IP 2014)	Complies
5.	Abnormal Toxicity *(In-vivo)*	None of the animals dies or shows sign of ill health. (IP 2014)	Complies
6.	Water content *(Karl Fischer- Coulometric)*	Not be more than 3.0 % (IP 2014)	Complies

CONCLUSION: The Batch/Lot No. ……. of the Rubella Vaccine (Live) I.P, as per requirements of IP 2014 is of **standard quality/ not of standard quality**.

Signature of the Analyst
Name & Designation:
Date:

Signature of the Lab. I/c /Head Name & Designation:
Date:

13. REFERFENCES

13.1	Manual of Laboratory methods for potency testing of vaccines used in the WHO Expanded Programme on Immunization. WHO/BLG/95.1
13.2	WHO/1V/B/05.23 (2005). Guidelines on the International Packing and Shipping of Vaccines
13.3	WHO TRS 745, 941, 840
13.4	Laboratory techniques in Rabies, Fourth Edition, WHO
13.5	Indian Pharmacopoeia (This refers to the current version and addendum of the pharmacopoeia)
13.6	European Pharmacopoeia (This refers to the current version and addendum of the pharmacopoeia)
13.7	Drugs and Cosmetics Act: 1940

ANNEXURE –A

CHECK LIST OF DOCUMENTS

DOCUMENTS REQUIRED TO BE SUBMITTED ALONG WITH SAMPLE OF BATCH FOR QUALITY CONTROL TESTING:

1.1 Indigenous manufacturer:

1.1.1 Forwarding letter from DCG (I) or Port Office/ as per the QC manual of the Institute.

1.1.2 A copy of Manufacturing License.

1.1.3 Batch Release Certificate of Manufacturer for three consecutive batches (for new manufacturer).

1.1.4 Certificate of Analysis of Manufacturer for three consecutive batches (for new manufacturer).

1.1.5 Summary Protocol for Production and Q C Testing.

1.1.6 Manufacturing Protocols for three consecutive batches (for new manufacturer).

1.2 Additional documents from indigenous manufacturer processing imported bulk

1.2.1 **A c**opy of Import License.

1.2.2 Bulk release certificate from National Control Authority.

1.2.3 Certificate of Analysis of bulk.

1.2.4 Manufacturing Protocols

1.2.5 QC test done on final lot.

1. 3 Imported manufacturer:

1. 3.1 Forwarding letter from DCG (I) or port office/ as per the QC manual of the NIB.

1. 3.2 Copy of Import License.
1. 3.3 Batch Release Certificate from the National Control Authority/ country of origin
1. 3.4 Certificate of Analysis of National Control Laboratory
1. 3.5 Summary Protocol for Production and Testing
1. 3.6 List of three countries where the product is sold/marketed.