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SUMMARY PROTOCOL FOR PRODUCTION AND TESTING OF RUBELLA VACCINE (LIVE)

The following protocol is intended for guidance, and indicates the information that should be provided as a minimum.

The section concerning the final product must be accompanied by a sample of the label, a copy of the leaflet that accompanies the vaccine container, and a certificate from the national control authority of the country in which the vaccine was produced stating that the product meets national requirement as well as the requirements published by WHO.

Source materials (A.4.1)

Strain of rubella virus (A.4.1.1) _____

Cell cultures (A.4.1.2)

Provide information on the source and method of preparation of the cell cultures.

Human diploid cells (A.4.1.3)

Provide information on the source of the manufacturer's working cell bank (MWCB)

Rabbit kidney cell cultures (A.4.1.4)

Provide information on the source and method of preparation of the cell cultures.

Serum used in cell-culture medium (A.4.1.5)

Sterility tests

	bacteria	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Tests for adventitious agents

Methods _____

Date of inoculation _____

Results _____

Trypsin used for preparing cell cultures (A.4.1.6)

Sterility tests

	bacteria	*mycoplasmas*
Date of inoculation	_____	_____
Results	_____	_____

Tests for adventitious agents (including porcine parvoviruses)

Methods _____

Date of inoculation _____

Results _____

Production of the working seed lot (A.4.2)

Summary information

Name and address of manufacturer _____

_____

Virus strain _____

Reference no. of virus seed used to prepare manufacturer's original rubella vaccine that was safe and immunogenic in humans _____

Reference no. of master seed lot _____

No. of passages between the two above seeds _____

Working seed lot

Date of preparation _____

No. of containers prepared _____

Reference no. _____

Conditions of storage _____

History of vaccine strain

Provide a brief account, indicating how the vaccine strain was acquired outlining its history

up to production of the master seed lot, and specifying the criteria on which acceptability for virus production is based.

Certification of working seed lot

Name (typed) and signature of head of production laboratory _____

_____

Certification by the head of the control laboratory of the manufacturer taking overall responsibility for production and control of the working seed lot :

I certify that the working seed lot of rubella vaccine virus no._____ satisfies Part A, sections 2 to 4.4.5,of the Requirements for Rubella Vaccine in Requirements for Biological Substance No. 47 (Requirements for Measles, Mumps and Rubella Vaccines and Combined Vaccine (Live)).

Signature _____

Name (typed) _____

Date _____

Control cell cultures (A.4.3)

Provide information on the control cell cultures corresponding to each single harvest. using extra pages if necessary.

Cell substrate used for production of virus _____

Reference no. of control cell cultures _____

Quantity of cell cultures used as control cultures _____

Period of observation of control cells _____

Test for haemadsorbing viruses (A.4.3.1)

Type of red blood cells _____

Date of test _____

Results _____

Tests for non-haemadsorbing extraneous agents (A.4.3.2)

Cell substrate used for virus growth

Type of cells _____

Date of inoculation _____

Results _____

Simian cells

Type of cells _____

Date of inoculation _____

Results _____

Human cells

Type of cells _____

Date of inoculation _____

Results _____

Additional test if rabbit kidney cells are used for production (A.4.3.3)

Method for detection of *Nosema cuniculi* _____

Date _____

Results _____

Additional tests if human diploid cells are used for production (A.4.3.4)

Identity test

Method _____

Date _____

Results _____

Production and harvest of vaccine virus (A.4.4)

Cells used for vaccine production (A.4.4.1)

Observation of cell cultures before inoculation

Methods _____

Results _____

Antibiotics added (if used) _____

Concentration _____

Single harvests (A.4.4.2)

Report the results of tests on single harvest, using extra pages if necessary.

No. of passages from the primary seed _____

Reference no. of single harvest _____

Sterility tests	*bacteria*	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Virus titration

Cells used for titration _____

Date of inoculation _____

Results _____

Virus pool (A.4.4.3)

Reference no. of virus pool _____

If any test had to be repeated or any abnormal result was observed this must be specified.

Tests for neurovirulence (A.4.2.1)

No. of monkeys in test _____

Species _____

Volume injected _____

No. of monkeys surviving without specific symptoms _____

Results of serological tests _____

Results of histopathological examination (specify findings) _____

Sterility tests	*bacteria*	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Virus titration

Cells used for titration _____

Date of inoculation _____

Results _____

Tests of neutralized virus pool in cell cultures

Species in which neutralizing serum
was prepared and cell substrate in
which immunogen was produced _____

Cells used for virus growth

Type of cells _____

Date of inoculation _____

Results _____

Simian cells

Type of cells _____

Date of inoculation _____

Results _____

Human cells

Type of cells _____

Date of inoculation _____

Results _____

Additional test if rabbit kidney cell cultures are used for production

Volume tested _____

No. of rabbits inoculated _____

No. that survived test _____

Results _____

Clarification of the virus pool (A.4.4.4)

Date of clarification _____

Results of clarification _____

Virus titration

Cells used for titration _____

Date of inoculation _____

Results _____

Sterility tests

	bacteria	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Final bulk (A.4.4.5)

Reference no. of final bulk _____

Total volume of final bulk _____

Added substances (diluent, stabilizer)

and final concentration _____

Residual animal serum proteins

Date _____

Method _____

Results (indicate amount and nature

of serum protein (s) present per

human dose) _____

Sterility tests

	bacteria	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Filling and containers (A.5)

Name and address of manufacturer _____

_____

Proprietary name of vaccine _____

Reference no. of final lot _____

Expiry date _____

No. of containers in the lot _____

No. of doses per container _____

Lot no. of final bulk _____

Date of filing of final containers _____

Control tests on final product (A.6)

Identity test (A.6.1)

Date _____

Method _____

Results _____

Sterility tests (A.6.2)

	bacteria	*fungi*	*mycoplasmas*
Date of inoculation	_____	_____	_____
Results	_____	_____	_____

Virus concentration and thermostability (A.6.3)

Date of inoculation _____

Type of cell cultures _____

	Control (unheated) samples			*Samples incubated at 37°C for 7days*		
	1	*2*	*3*	*1*	*2*	*3*
Virus concentration in each container (in PFU or $CCID_{50}$)	_____			_____		

Mean virus titre per human dose,

with 95% fiducial limits _____ _____

Mean loss in titre due to heat

exposure (in $\log_{10}$ units) _____

Reference preparation

Idenification _____

Theoretical titre _____

Actual titre _____

General safety tests (A.6.4)

Test in mice

Date of inoculation _____

No. of mice tested _____

Volume and route of injection _____

Observation period _____

Results (give details of deaths) _____

Test in guinea-pigs

Date of inoculation _____

No. of guinea-pigs tested _____

Volume and route of injection _____

Observation period _____

Results (give details of deaths) _____

Residual moisture (A.6.5)

Date _____

Method _____

Size of sample _____

Moisture content (%) _____

Inspection of final containers (A.6.6)

Date and result _____

Submission addressed to national control authority for batch release

Name (typed) and signature of head

of production laboratory _____

_____

Date _____

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

I certify that lot no. _____ of rubella vaccine (live) satisfies national requirements and/or Part A of the Requirements for Rubella Vaccine in Requirments for Biological Substances No . 47 (Requirements for Measles, Mumps and Rubella Vaccines and Combined Vaccine (Live)).

Signature _____

Name (typed) _____

Date _____