Unit: Technical Assessment Unit

Public assessment report for biological products

(Measles, Mumps and Rubella Vaccine Live)

Administrative information:

Trade name of the medicinal product:	Measles, Mumps and Rubella Vaccine Live, Attenuated (Freeze-Dried)
INN (or common name) of the active substance(s):	Measles Virus, Mumps Virus and Rubella Virus
Manufacturer of the finished product	Serum Institute of India Pvt. Ltd, 212/2, Hadapsar, Pune 411028 Maharashtra State – India
Marketing Authorization holder	Serum Institute of India Pvt. Ltd, 212/2, Hadapsar, Pune 411028 Maharashtra State – India
Applied Indication(s):	For active immunization against measles, mumps and rubella infection in humans
Pharmaceutical form(s) and strength(s):	Powder and Solvent for injection Each 0.5 ml dose of reconstituted vaccine contains: Measles Virus not less than 1000 $CCID_{50}$ Mumps Virus not less than 5000 $CCID_{50}$ Rubella Virus not less than 1000 $CCID_{50}$
Route of administration	Subcutaneous injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

MMR	Measles, Mumps and Rubella Vaccine
CVP	Clarified Virus Pool
WHO	World Health Organization
TRS	Technical Report Series
MA	Marketing authorization
ALV	avian leucosis virus
MEM	Minimum Essential Medium
FBS	Fetal Bovine Serum
CVP	Clarified Virus Pool
TRS	Technical Report Series
NOAEL	No observed adverse effect level

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**

   Measles, Mumps and Rubella Vaccine, is live, attenuated (freeze-dried) supplied with diluent for reconstitution. MMR vaccine is available as two dose vial, five doses and ten doses vial. The vaccine is available in a box of 50 vials and each shipper box contains 1200 vials. Diluents (Sterile Water for injection) is available as box of 50 ampoules. Diluents are packed separately.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

Measles Component:

- **Nomenclature:** Measles Vaccine Clarified Virus Pool (CVP), WHO, TRS 840 (1994).
- **Structure:** Active substance in Measles Vaccine CVP is Live, Attenuated Edmonston-Zagreb Measles Virus.
- **General Properties:** Measles Vaccine Clarified Virus Pool is a clear liquid with yellow to yellowish orange color containing measles vaccine virus at a temperature -20ºc or below.

Mumps Component:

- **Nomenclature:** Mumps Vaccine Clarified Virus Pool (CVP), WHO, TRS 840 (1994)

Structure: Active substance in Mumps Vaccine CVP is Live, Attenuated L-Zagreb Mumps Virus**.**

General Properties:

Mumps Vaccine Clarified Virus Pool (CVP), is a clear liquid with yellow to yellowish orange color containing the virus at a temperature -20ºc or below.

Rubella Component:

Nomenclature: Rubella Vaccine Clarified Virus Pool (CVP), WHO, TRS 840 (1994)

Structure: Active substance in Rubella Vaccine CVP is Live, Attenuated Wistar RA 27/3 Rubella Virus .

General Properties:

Rubella Vaccine Clarified Virus Pool (CVP), clear liquid with yellow to yellowish orange color containing the virus at a temperature -20ºc or below.

- **Manufacture, process controls and characterization:**

Manufacturer: Serum Institute of India Pvt. Ltd, 212/2, Hadapsar, Pune 411028 Maharashtra State – India

-Description of Manufacturing Process and Process Controls.

-Measles vaccine is produced using Edmonston-Zagreb Measles vaccine strain and Human Diploid (MRC-5) Cells as a substrate. MRC-5 cel ls at lower passage were obtained from NIBSC, UK.

-Mumps vaccine is produced using L-Zagreb Mu mps vaccine strain and Chicken Embryo Culture as a substrate. Chicken Embryo Culture is prepared from incubated Specific Pathogen Free eggs.

-Rubella vaccine is produced using Wistar RA 27/3 Rubella vaccine strain and Human Diploid (MRC-5) Cells as a substrate obtained from NIBSC.

-The manufacturing and testing are in accordance with W HO, TRS 840 (1994).

-Control of Materials.

List of the raw materials and chemicals used in the manufacturing process and their specification are described in the MA file.

- **Controls of Critical Steps and Intermediates.**

- In-Process Quality Controls tests performed on the Cultures are Description, Microscopic Examination,Test for haemadsorbing viruses, Test for non-haemadsorbing viruses, Identity, Test for Mycoplasma and Test for avian leucosis virus (ALV) (for mumps culture).
- In-Process Quality Controls tests performed on Virus Pool and clarified virus pool of measles, mumps and rubella viruses.

- **Process Validation**

- List of Process Validation activities performed on Clarified Virus Pool of measles, mumps and rubella Vaccine Manufacturing are described in the file.

- **Manufacturing Process Development.**

- The development of the initial Measles, Mumps and Rubella vaccine manufacturing process was performed by Institute of I mmunology , Zagreb prior to technology transfer in 1986.
- Commercial manufacture for the Indian market commenced in 1989.

- **Characterization.**

- Foetal Bovine Serum and Neomycin are the only impurities considered in the process, which is removed by washing of monolayer using MEM without FBS.

- **Specification**

- The specification s related to the release testing of the Measles, mumps and rubella CVP are provided in the MA file.

- **Analytical Procedures.**

- The analytical methods with their validation used for the quality control of the Measles, mumps and Rubella Vaccine CVP are described in details in MA.

- **Batch analysis**

  -Detailed results of the routine tests performed at the time of manufacture on the 3 batches of Measles, mumps and Rubella Vacci ne were provided.
  -All specifications are in compliance with WHO, TRS 840 (1994).

- **Reference Standards or Materials.**

  -The In-house reference standards used for testing of Measles, Mumps and Rubella CVP are calibrated against International Reference Standards.
  -The details of In-house Reference Standards are described in the file.

- **Container closure system**

  Measles and Rubella Vaccine CVPs are stored in sterile plastic disposable bags of 10-liter capacity, While Mumps Vaccine CVPs are stored in sterile plastic polypropylene polycarbonate bottles.

- **Stability of drug substance**

  Detailed stability date of 60 months is described in the MA file.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

  The MMR Vaccine is prepared from the live, attenuated strains of Edmonston -Zagreb measles virus, L-Zagreb (L-Z) mumps virus and Wi star RA 27/3 rubella virus.
  -The measles and rubella viruses are propagated on human diploid cells (HDC) and the mumps virus is grown on chick fibroblasts from SPF eggs.
  -The vaccine is lyophilized and is provided with diluent.
  - The product has the appearance of a yellowish-white dry cake. The vaccine meets the requirements of WHO when tested by the methods outlined in WHO, TRS 840 (1994).

- Pharmaceutical Development including brief description on Components of drug product.

Components of drug product:

Drug Substance: The drug substance of Measles, Mumps and Rubella Vaccine Live, attenuated (Freeze-Dried) is:

Measles Vaccine Clarified Virus Pool Mumps Vaccine Clarified Virus Pool Rubella Vaccine Clarified Virus Pool.

- Formulation Development

There is no formulation in the classical sense except for blending of individual clarified virus pools (CVP s) to achieve the required final bulk titer.
Depending on the need, a blind vaccine is u sed to adjust the titer when CVPs of higher titer are used.

- Overages

For MMR Vaccine 1 doses fill volume is 0.5 ml I Vial and for 10 dose fill volume is l ml /vial Therefore fill volume is calculated as:
For I dose: Required volume is 0.5 ml, and actual fill volume is 0.525 ± 0.025 (4.7% overage) For 10 doses: Required volume is 1.0 ml, and actual fill volume 1.025 ± 0.025 (2.5% overage).

- Physicochemical and Biological Properties

-MMR Vaccine Live, attenuated (Freeze-Dried) is in the form of lyophilized dry cake, yellowish-white in color.
-The vaccine is to be reconstituted with the Sterile Water for Injection.

- Manufacturing Process Development.

-The initial formulation, which was obtained from Institute of immunology, Zagreb, has not been changed since 1987.
-Several experiments were conducted to assess the benefit s of additional quantity of Arginine to the formulation (1989).

- Container closure system and their compatibility.

The vaccine is filled in clear amber tubular vial type I, 50 mm in height Rubber stopper used are 13 mm grey Bromobutyl rubber plugs (V-50) symmetrical with clean and smooth surfaces.
-Aluminium caps are 13 mm Pantone PMS 220 Mauve flip off seal.

- Microbiological Attributes.

Compliance with the specifications for sterility was also shown throughout the shelf life of the product i.e.24 months when stored at recommended temperature of 2°C-8°C, indicating the suitability of the container closure system for prevention of microbial contamination.
-In addition to this seal integrity is also routinely confirmed during media broth fill trials by challenging approximately 100 sample vials with B.*diminuta* after incubation period of 14 days.

- Compatibility.

Stability study of the reconstituted product with diluent provided shows that the product retains the minimum required potency after reconstitution up to 24 hours when stored at 2°C-8°C.

- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities
  Manufacturer: Serum Institute of India Pvt. Ltd, 212/2, Hadapsar, Pune 411028 Maharashtra State – India

  - Control of critical steps and intermediates
  Production process is controlled in a very systematic way at each stage by conducting various In-Process Quality Control tests which are listed & attached in the file.
  -Quality Control tests carried out on MMR Vaccine Final Product are listed & described in the MA file.

  - Process validation and / or evaluation.
  Data on process validations carried out on MMR group of vaccines are described in the file.

- **Product specification:**
  -The analytical procedures used to control excipients described in a Pharmacopoeia are those described in their respective monographs and other excipients are described in the MA file.
  -Compendial tests are used without further validation.
  -All the excipients comply as per the Pharmacopoeia/ I In -house specifications as specified.
  -In the manufacturing of M MR Vaccine, no excipient of human origin is used. The excipients of animal origin are Gelatin and Lactalbum in Hydrolysate.

  -The results of release testing on Filled Containers 1 Dose lots ,10 Doses lots are provided and all shown results were within the specifications. The acceptance criteria and results for the evaluated parameters are provided in the M.A. file.
  - No new impurities are brought during the Final formulation process.
  - All the specifications complies with WHO, TRS 840 (1994). All the specifications of diluent i.e. Sterile Water for Injection complies with Indian Pharmacopoeia.

- **Reference Standards or Materials.**
  The details of In-house Reference Standards are described in the file.

- **Container closure system.**
  MMR Vaccine Live, attenuated (Freeze-Dried) is filled in the Clear amber tubular vial type I, 50 mm in height
  Rubber stopper used are grey Bromo butyl rubber plugs symmetrical with clean and smooth

surfaces.
Aluminium caps are 13 mm PMS 220 Mauve flip off seal.

- **Stability of the drug product.**

-Based on available stability data,
-Real time stability study i.e. at 2°C-8°C proved that the vaccine passes all the test parameters and therefore is stable up to the stated shelf life of 24 months.
-Stability study after reconstitution with the d iluent provided proved that the vaccine retains its minimum required potency up to 24 hours after reconstitution when exposed to 2°C-8°C.

Adventitious agents
The manufacturing process of MMR vaccine is designed to consider sufficient precautions to obviate the risk of adventitious agents being present in the product. The control/ checks are established at various levels in the manufacturing process. The controls repeatedly check and assure the absence of such adventitious agents in the product/ process

3. Non –clinical aspect:
The Measles Mumps and Rubella vaccine is widely used since many years and its role in protection against these viral infections is well established. Accordingly, nonclinical pharmacology studies were not planned.
From the single dose toxicity studies conducted on mice and Beagle dogs, it is found that the candidate vaccine is well tolerated in doses much larger than the expected human dose (80 times in mice and 6.3 times in Beagle dogs). Also in the repeat dose toxicity study the NOAEL in mice is much higher than expected human dose. There was no any abnormality which could be specifically related to the dose of the vaccine or animal gender.

4. Clinical aspect:
The applicant presented 3 controlled Phase III clinical studies C1, C2; N=20 and C3: N=113) assessing immunogenicity and reactogenicity against Trimovax (MMR Aventis) (C1 and C2) and Morupar (C3) (MMR Chiron) , 5 uncontrolled studies (U1, U2; N=84, U3; N=90, U4; N=68 and U5; N=90) assessing immunogenicity and reactogenicity of Tresivac, 2 Phase IV studies (U10 and U11) assessing reactogenicity conducted in India, and 2 Phase IV studies (U12; N=65429 and 12262 (18-24 months) and U13; N=329211 and 46232 (5-7 years) Tresivac vs Unvaccinated respectively) assessing reactogenicity conducted in Egypt. Other studies U3, U4, U5 and U6 assessing reactogenicity were also presented.

Efficacy (Immunogenicity) conclusion:
Controlled and Uncontrolled studies assessing immunogenicity results revealed statistically significant difference between pre and post vaccination GMTs against all 3 components in both the groups. Statistically significant higher seropositivity percentage was observed with SIIL MMR vaccine compared to Chiron MMR vaccine ($P<0.001$) in C3 study. Percentage of subjects

immunogenic for measles was very low in U7 study. In general, Tresivac showed highly immunogenic profile.

In the controlled studies, adverse events which occurred with Tresivac and other standard commercially available vaccines were similar in frequency. Safety results for uncontrolled studies spanned between pain at injection site, fever, catarrhal symptoms, rash and diarrhea. Phase IV safety studies conducted in India reported adverse events similar to the uncontrolled studies in addition to other reported cases e.g (Parotitis, maculopapular rash, Auxillary lymphadenopathy and cough associated with Coryza). Phase IV studies conducted in Egypt reported same type of Adverse events in addition in the Arthralgia in 11 children (0.02%) in U12 compared to none in the unvaccinated group. Also Parotitis was observed in 8059 (2.48%) children compared to 432 (0.94%) in the control group. A case of Epilepsy with suspected by the investigator to be related to the study vaccine was reported in the study group. 93 cases of mumps, 4 cases of measles were observed for the study vaccine versus 29 cases of mumps and 3 cases of measles in the unvaccinated group. One case was reported for meningitis to be reported by the investigator as as not related to the study drug. No single case of rubella or encephalopathy was reported.

The MMR vaccine of Serum Institute of India Ltd efficacious in protection against measles mumps and rubella which is evidenced by induction of adequate 1gG antibody titres in the vaccine recipients.
The vaccine has high safety level as recorded in different studies.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.