Unit: Technical Assessment Unit

Public assessment report for biological products

*(*Measles and Rubella Vaccine*)*

Administrative information:

Trade name of the medicinal product:	Measles and Rubella Vaccine (Live) (Attenuated, Freeze Dried)
INN (or common name) of the active substance(s):	Measles Virus and Rubella Virus
Manufacturer of the finished product	M/s. Biological E Limited -
Marketing Authorization holder	Queen trading office QTO - Bimag Pharma
Applied Indication(s):	For active immunization against measles and rubella infection in infants, children and young adults at risk
Pharmaceutical form(s) and strength(s):	Powder and Solvent for injection Each 0.5 ml dose of reconstituted vaccine contains: Measles Virus ≥ 1000 $CCID_{50}$ Rubella Virus ≥ 1000 $CCID_{50}$
Route of administration	Subcutaneous injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

AE: Adverse Event
BE: Biological E
CCID50: Cell-culture infective dose 50%
GLP: Good Laboratory Practice
GMT: Geometric Mean Titer
LCL: Lower Confidence Limit
MA: Marketing authorization
MR: Measles and Rubella
Novel : No observed adverse effect level
SAE: Serious Adverse event
SC: subcutaneous
TRS: Technical report series
UCL: Upper confidence limit

WHO: World Health Organization

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

Measles and Rubella Vaccine (Live), (Attenuated, Freeze Dried) (MR Vaccine) is prepared from the live, attenuated strains of Measles virus and Rubella virus. MR vaccine is supplied as follows: 1 dose vial along with diluent (0.5 mL), 5 dose vial along with diluent (2.5 mL) 10 dose vial along with diluent (5 mL). Is it lyophilized powder for subcutaneous Injection upon reconstitution

MR vaccine indicated for active immunization against measles and rubella in infants, Children, adolescents and young adults at risk

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 Bulk (CAM-70)
Structure: Not Applicable
General Properties: Measles bulk is a clear red color suspension. Measles virus is rapidly inactivated by heat, light, acidic pH, ether and trypsin. It has a short survival time (< 2 hours) in the air, or on objects and surfaces.

Rubella Component:

Nomenclature: Rubella virus (Wistar RA 27/3 strain),
Structure: Not Applicable

General properties

Rubella virus bulk is a clear pale-yellow color solution free from foreign particles. The rubella virus is a cubical, single stranded RNA virus, medium sized 70 nm. It is a member of the rubivirus genus in the togaviridae family. Stored at -70°±10°C for 24 months.

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

Manufacturer:

1- Measles Bulk is procured from M/s PT Biofarma, Jalan Pasteur 28 Bandung 40161, Indonesia. PT Biofarma is a leading manufacturer of Measles bulk, which is pre-qualified by WHO for Measles containing vaccines.

2- Rubella virus bulk is developed indigenously by Biological E limited. Plot No. 1, Phase II, S. P. Biotech Park, Kolthur Village, Shameerpet Mandal,

- **Description of Manufacturing Process and Process Controls**.
  - The detailed manufacturing process is mentioned in the MA file along with flow Chart highlighting the process steps and IPC:
  - In-process controls performed during the different stages of the manufacture of measles and Rubella Virus Bulk is provided in MA file
  - **Control of Materials.**
    List of raw materials used in manufacture of Measles Bulk and Rubella Bulk and their specifications with In-house specifications are provided in tables in the MA file.
  - List of biological origin materials used in manufacture of Measles Bulk is provided is provided in tables in the MA file
  - **Controls of Critical Steps and Intermediates**.
    Details of in process controls and control of critical steps in the manufacturing of Rubella Virus Bulk and measles bulk are provided in tables in MA file.
    Detailed Information on control of critical steps and intermediates is provided in MA file.
  - **Process Validation**
    Process Validation is performed for Measles bulk and Rubella bulk manufacturing has been performed for three consecutive batches.
    Approved procedures, raw material, qualified equipment's and trained personnel involved in the study as per GMP requirement
    The list of tests is performed during process validation for Measles and Rubella Virus Bulk manufacture are mentioned in MA File.
    Detailed information about Process Validation and /or evaluation is provided in MA file
  - **Manufacturing Process Development.**
  - Measles bulk is sourced from M/s PT Bio Farma, Indonesia. No major process changes were done.

- Biological E Limited has acquired a facility for carrying out development work on Rubella virus bulk at BE Vaccine, SAS, France. The stage specific process development reports from BE Vaccines, France along with WHO TRS and Pharmacopoeia monographs were used to define the process to be followed for GMP batch manufacturing at Hyderabad
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- **Characterization.**
  Detailed description on Physicochemical Characterization and Biological Characterization of measles and rubella bulks is provided in MA file.
  Preparation and characterization report of Master and Working Cell Banks for measles and rubella is provided in MA file.
- **Specification**
  The specifications related to the release testing of the Measles, mumps and rubella CVP are provided in the MA file according to WHO Expert Committee on Biological Standardization, WHO TRS 840.
- **Analytical Procedures.**
  Analytical method validations for in-house analytical procedures are performed.
  Parameters tested during validation of analytical procedures are provided in the table
  Details of analytical methods validated and tests performed is provided
- **Batch analysis.**
  Description of batches batch results for three consecutive batches of Rubella Virus Bulk are tabulated
- **Reference Standards or Materials.**
  Internal reference control is established in-house and is calibrated against the NIBSC standard of Measles and Rubella**.**
  Establishment report for Internal Control of Measles and Rubella used for estimation of rubella virus content is provided
- **Container closure system**

Primary and secondary materials used for Rubella Virus Bulk and tests performed is provided

Specifications of primary packing and secondary packing are provided in MA file

- **Stability of drug substance**

Approved shelf life

- Measles Virus:

24 months from the date of shipment form PT Biofarma

- Rubella Virus:

24 months

Approved Storage Conditions:

- **Measles Virus: Store at (≤-60°C)**
- **Rubella Virus: Store at (-70±10 °C)**

2.2.3 Drug product:

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

Measles and Rubella Vaccine (Live), (Attenuated, Freeze Dried) (MR Vaccine) is prepared from the live, attenuated strains of Measles virus (CAM-70 Tanabe strain) and rubella virus (RA 27/3). Measles virus is propagated in chicken embryo fibroblast (CEF) cell and rubella virus is propagated in MRC 5 cells.

The vaccine is lyophilized preparation with physical appearance of a white to light yellow compact cake. The vaccine is supplied with diluent (Sodium Chloride for Injection - 0.9% w/v). Sodium Chloride Injection - 0.9% w/v is the diluent used for reconstitution of MR Vaccine. The vaccine is supplied along with the diluent (Sodium Chloride Injection - 0.9% w/v). Only the diluent supplied with the vaccine should be used to reconstitute the vaccine. The diluent is procured from an approved supplier.

Vaccine meets requirements of I.P and WHO

Each single human dose of 0.5 mL after reconstitution contains:

1- Measles virus (CAM-70 strain), propagated in Chicken Embryo Fibroblast cells

2- Rubella virus (Wistar RA 27/3 strain), propagated in MRC 5 cells

3- List of excipients used in the formulation of MR Vaccine, quantity and function is provided (e.g. . Hydrolysed Gelatine, D-Sorbitol, Sucrose and Human Albumin Solution (20% w/v) (as Human Serum Albumin) as stabilizer ..)

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

- Formulation Development

MR Vaccine is developed in-house by Biological E. Limited. The vaccine is formulated with Measles Bulk and Rubella Virus Bulk as bulk antigens and formulation stabilizer is added to ensure the stability of the vaccine. The vaccine meets IP and WHO TRS 840 requirements

- **Physicochemical and Biological Properties**

MR Vaccine has pH between 6.0 to 7.0. The potency of all antigens meets WHO requirements. After reconstitution with diluent, MR Vaccine is a clear colourless to pale yellow coloured liquid free from extraneous visible particles

- **Manufacturing Process Development.**

Manufacturing process (blending, filling and packing) of MR Vaccine is developed and optimized in-house at BE.

Critical process parameters and in-process controls have been identified during the process development activities and the same were validated through process validation studies at commercial scale.

- **Container closure system**

MR Vaccine is filled in USP type I amber colored glass vials and closed using Bromo butyl rubber stoppers and sealed by aluminum flip-off seals (13 mm).

Microbiological Attributes

No microbial attributes are used in the formulation of MR Vaccine. However, stabilizers are used in the formulation

- Compatibility.:

Incompatibilities with the dosage devices have not been reported. Compatibility of the container closure system with product is proved in process validation studies and stability studies.

- **Manufacture of the drug product:**

M/s Biological E. Limited, Plot No. 1, Phase II, S. P. Biotech Park, Kolthur Village, Shameerpet Manda which responsible for Formulation, Filling, Packing, Testing & Distribution of Measles and Rubella Vaccine (Live), (Attenuated, Freeze Dried) [MR Vaccine] (Drug Product),

- Control of critical steps and intermediates

Details of In-process controls performed during blending, filling and lyophilization of MR Vaccine are provided

List of Tests Performed at Critical Steps – MR Vaccine is provided in MA file

- Process validation and / or evaluation.

Process validation studies are carried out as per the pre-approved validation protocol. All the critical stages of a product are considered for process validation to assure the consistency of the processes.

All the parameters at different stages of the process such as excipient preparation, blending, filling and lyophilization for final blend and final lot samples for three consecutive batches of MR Vaccine are meeting the acceptance criteria and are found consistent and reproducible

- **Product specification:**
  - Specification of MR vaccine and diluent are provided and tabulated in MA file
    All the specifications comply with WHO, TRS 840 (1994). All the specifications of diluent Sodium Chloride Injection, 0.9 % w/v) complies with Indian Pharmacopoeia.
  - 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.
  - Details of raw materials used as excipients in formulation of Measles and Rubella Vaccine (Live) are listed
  - **Characterization of impurities.**
  - Information on Impurities related to each drug substance is provided in the MA file
    - **Reference Standards or Materials.**
    - The details of In-house Reference Standards are described in the file.
    - **Container closure system.**
      Specifications of primary and secondary packing material of Measles and Rubella Vaccine (Live) is provided in MA file
    - **Stability of the drug product.**

    Based on available stability data:

Approved shelf life: 24 months

After reconstitution: The reconstituted vaccine should be used within six (6) hours.
Diluent: 48 months

Approved Storage Conditions:

Finished product:
It is important to protect both the lyophilized and reconstituted vaccine from the light. The vaccine should be stored in the dark at a temperature between (2-8 °C).
Diluent:
The diluent should not be frozen, but should be kept cool. Store at 30±2°C.

3. **Non –clinical aspect:**

- Measles and Rubella Vaccine is a live Attenuated, freeze-dried Ten dose 5 ml vial. Each reconstituted dose of 0.5 mL contains Measles virus (CAM-70 strain) and Rubella virus (Wister RA 27/3 strain) each at ≥1000 $CCID_{50}$. The vaccine is indicated for active immunization against Measles and Rubella viruses. It prevents infection by Measles and rubella viruses by causing the body to produce its own protection (antibodies) against the viral infection, and in the event of infection, this protects the individual against systemic infection. WHO prequalified it for use on *24/09/2019.*

- **Pharmacology:** Human is the only host for both measles and rubella viruses. So, adequate immunogenicity is done in human beings. Immunogenicity data are fully discussed in the Clinical Module.

- **Pharmacokinetics:**
- Pharmacokinetic studies are normally not required for vaccines in accordance with WHO TRS 927.

- **Toxicology:**

Data revealed that the acute toxicity of Measles and Rubella Vaccine (Live, Freeze dried) after single dose administration through SC route to Sprague Dawley rats and Swiss Albino mice was well tolerated and did not produce any toxicity after single dose (0.5 mL/animal) administration. Moreover, repeated dose toxicity studies to assess the toxic potential of Measles and Rubella Vaccine when administered through SC route to Sprague Dawley Rats on days 1 and 15 with 14 days recovery period after day 28 and in New Zealand White Rabbits on days 1 and 15 with 14 days recovery period after 28th day revealed that Measles and Rubella Vaccine did not produce any significant toxicological manifestations In addition, neurovirulence test for Measles and rubella bulk did not induce any signs of neurovirulence in the brain of cynomolgus monkeys.

- **Overall conclusion:** Based on the pharmacology and the toxicology data, **Measles and Rubella Vaccine (live) (Attenuated, freeze dried) Ten dose vial -5ml** is considered acceptable from the preclinical point of view.

4. **Clinical aspect:**

Clinical programme of the product for the proposed indication (active immunization against measles and rubella in infants, children, adolescents and young adults at risk), **included; a Phase-I study** (open label study to assess the safety and tolerability of BE's live attenuated Measles-Rubella vaccine in 4-5 year old healthy children) **and pivotal Phase II/III clinical trial** (Randomised, Comparative, Multicenter Study to Evaluate the Safety and Immunogenicity in 9-12 Month Old Healthy Infants).

Clinical Efficacy:

Immunogenicity:

- There is no statistically significant difference in seroconversion rates between groups against Measles (p-value 0.2873) and Rubella (p-value 0.2606).

- There was no statistically significant difference in proportion of subjects seroconverted between groups at Day 42 (p-value 0.3083 for Measles and p-value 0.3334 for Rubella).

- The primary objective of demonstrating non-inferiority was met with the 95% CI for difference in proportion between treatment arms being -9.09 (LCL) and 2.71 (UCL) for Measles and -5.65 (LCL) and 1.55 (UCL) for Rubella.

- There was no significant difference in proportion of subjects achieving 4-fold increase in anti-Measles and anti-Rubella antibody titers at Day 42 from baseline between groups (p-value 0.0937 and 0.0888 for Measles and Rubella, respectively).

Clinical Safety:

- The safety profile of Biological E's live attenuated MR vaccine was found to be favorable in terms of overall AE, related AE and medically attended AE rates. No SAEs were reported. All the local and systemic AEs reported were mild in intensity. The most commonly observed AEs were in line with the expected AE profile as seen with other available Measles and Rubella containing combination vaccines. No clinically significant changes over time were noted in the laboratory data from baseline. Mean change in vital parameters from baseline were clinically not significant.

- The safety profile of BE's MR vaccine in comparison with SIIL's MR-Vac™ vaccine was found to be favorable in terms of overall AE, related AE and medically attended AE rates. All reported AEs, whether local or systemic, were found to be mild in intensity. No SAEs were reported during the entire study period. Mean change in vital parameters from baseline were not clinically significant.

Benefit/ Risk discussion:

- **Benefits:**

Safety of BE's live attenuated Measles and Rubella vaccine (Live) (Attenuated, freeze dried) was assessed in clinical studies and found to be well tolerated with no safety concerns in 4-5-year-old healthy children and in 9-12-month-old healthy infants.
Non-inferiority of BE's MR vaccine was demonstrated in comparison with commercially available, WHO approved vaccine. There were no clinically significant differences in proportion of subjects' seroprotected between BE's MR Vaccine arms against both Measles and Rubella. There is no statistically significant difference in immunogenicity (GMT) between groups against Measles and Rubella. Hence, BE's MR vaccine is safe and immunogenic.

- **Risks:**

Risks following MR vaccination are mostly mild and transient. Risk associated with MR vaccination like pain at the site of injection, erythema and swelling. Post vaccination hypersensitivity symptoms like pyrexia, irritability, crying, rash and urticaria. All these side effects associated with MR vaccine administration are generally manageable and thus the benefits associated with strong protection against the serious infections outweigh the minor risks as identified above.

In conclusion the overall benefit/risk of Measles and Rubella Vaccine (Live) (Attenuated, Freeze Dried) Ten dose vial -5ml, is favorable for active immunization against measles and rubella in infants, children, adolescents and young adults at risk.

General Conclusion and Recommendations if any

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