Unit: Technical Assessment Unit

Public assessment report for biological products

(ZyVac® MMR)

Administrative information:

Trade name of the medicinal product:	Zyvac® MMR (multidose)
INN (or common name) of the active substance(s):	Live attenuated measles virus (Edmonston Zagreb strain) Propagated on Human Diploid Cells NLT 1000 $CCID_{50}$; live attenuated mumps virus (Hoshino strain) Propagated on Chick Fibroblast Cells NLT 5000 $CCID_{50}$; Live attenuated rubella virus (RA 27/3 strain) Propagated on Human Diploid Cells NLT 1000 $CCID_{50}$.
Manufacturer of the finished product	Zydus Lifesciences Limited, Plot Survey No.23, 25/P, 37, 40/P, 42 to 47, 49 and 50 Sarkhej-Bavla N. H. No. 8A, Opp. Ramdev Masala, Village Changodar, Tal. Sanand, Dist. Ahmedabad - 382213 - Gujarat state, INDIA.
Marketing Authorization holder	Zydus Lifesciences Limited, Plot Survey No.23, 25/P, 37, 40/P, 42 to 47, 49 and 50 Sarkhej-Bavla N. H. No. 8A, Opp. Ramdev Masala, Village Changodar, Tal. Sanand, Dist. Ahmedabad - 382213 – Gujarat state, INDIA.
Applied Indication(s):	ZyVac® MMR is indicated for prevention of Measles, Mumps and Rubella virus infections.
Pharmaceutical form(s) and strength(s):	Freeze dried (Lyophilized Powder) vaccine, Multi-dose Vial (5 ml – 10 dose)
Route of administration	subcutaneous (SC)
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Abs	antibodies
$CCID_{50}$	50% Cell Culture Infectious Dose
CRS	Congenital Rubella Syndrome
GCP	Good clinical practice
ICH	International Council of Harmonization
MMR	Measles, Mumps and Rubella
NLT	Not less than
NZW	New Zealand white
PK	Pharmacokinetics
SC	subcutaneous
TRS	Technical Report Series
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.

ZyVac® MMR Multidose Vial (5 ml – 10 dose) is a sterile, live attenuated, freeze-dried combined vaccine intended for the prevention of measles, mumps and rubella virus infections. The vaccine contains live attenuated measles virus (Edmonston Zagreb strain), mumps virus (Hoshino strain), and rubella virus (RA27/3 strain). The viruses are propagated on MRC-5 human diploid cells for measles and rubella and on chick embryo fibroblast cells for mumps.

Each 0.5 mL dose contains not less than 1000 $CCID_{50}$ of measles virus, 5000 $CCID_{50}$ of mumps virus and 1000 $CCID_{50}$ of rubella virus. The vaccine is administered by subcutaneous injection following reconstitution.

The protective effect is mediated through antigenic stimulation of the immune system, resulting in the induction of virus-neutralizing antibodies against measles, mumps and rubella viruses.

2. Quality aspects:

2.2.1 Introduction

ZyVac® MMR is a live attenuated, freeze-dried combined vaccine containing three viral drug substances: measles virus (Edmonston Zagreb strain), mumps virus (Hoshino strain) and rubella virus (RA27/3 strain). The product is presented as a multidose 10-dose vial for subcutaneous administration after reconstitution with sterile Water for Injection.

The quality assessment covers the manufacture, characterization and control of the three viral drug substances and the finished drug product, including pharmaceutical development, manufacturing process, specifications, analytical procedures, packaging and stability.

2.2.2 Drug Substance (Active ingredient)

- **General information**

The three active substances are:

- **Measles:** Clarified Measles Single Harvest (Bulk), Edmonston Zagreb strain.
- **Mumps:** Clarified and Concentrated Mumps (Bulk), Hoshino strain.
- **Rubella:** Clarified and Concentrated Rubella Single Harvest (Bulk), RA27/3 strain.

The nomenclature and structural information were established in accordance with WHO TRS 840 Annex 3 and the relevant pharmacopoeial requirements.

The measles and rubella viruses are propagated in MRC-5 human diploid cells, while the mumps virus is propagated in chick embryo fibroblast (CEF) cells derived from Specific Pathogen Free (SPF) eggs.

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

- **Description of Manufacturing Process and Process Controls.**

The three viral drug substances are manufactured by **Zydus Lifesciences Limited**, Plot Survey No. 23, 25/P, 37, 40/P, 42–47, 49 & 50, Sarkhej-Bavla N.H. No. 8A, Opp. Ramdev Masala, Village-Changodar, Tal: Sanand, Dist. Ahmedabad – 382 213, Gujarat State, India.

The manufacturing processes involve propagation of the respective attenuated virus strains on the specified cell substrates, harvesting, clarification and, where applicable, concentration to produce the respective bulk drug substances.

- **Control of Materials.**

Raw materials used for the manufacture of the three drug substances are procured from established vendors and controlled for identity, strength and purity. Materials are tested internally according to applicable pharmacopeial or in-house procedures.

The MMR virus seeds are produced and tested in accordance with WHO TRS 840 Annex 3 and Indian Pharmacopoeia requirements. For mumps, the Hoshino strain is propagated in CEF cells derived from SPF eggs.

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

Critical steps and in-process controls are established for the measles, mumps and rubella bulk drug substances. Samples from critical manufacturing steps are tested by Quality Control as part of the in-process control strategy. The dossier identifies CPPs and links them to relevant CQAs.

Controls include relevant parameters such as virus concentration, intact cells, sterility, bovine serum albumin and tests for extraneous agents, mycoplasma and mycobacteria, as applicable to each viral bulk.

- **Process Validation**

Process validation was performed at commercial scale for the manufacturing processes of the three viral drug substances and the drug product. The validation batches consistently complied with the established process and product acceptance criteria, demonstrating that the manufacturing processes are capable of reproducibly producing drug substances and drug product meeting the predefined quality requirements. Overall, the manufacturing processes were considered adequately validated.

- **Manufacturing Process Development.**

Process development included optimization of virus infection, harvest schedule, washing procedures, clarification and concentration. For the measles process, an MOI of 0.02 was identified as optimal, the number of harvests was increased, and clarification using a 5 µm filter and concentration using a 100 kDa PES TFF membrane were implemented.

For mumps, process development was aimed at improving virus yield and concentration of the harvest. The PPQ batches C100335, C100336 and C100359 met the specified acceptance criteria, including virus titre, sterility and BSA content.

- **Characterization.**

The structural and biological characteristics of the three viral drug substances, including strain, propagation substrate and viral identity and concentration, were characterized and controlled in

accordance with the applicable WHO and pharmacopeial requirements. The dossier includes testing for extraneous agents appropriate to the respective substrates.

- **Specification**

Specifications are established for the three viral drug substances and include appropriate controls for identity, potency/virus concentration, purity, sterility, and extraneous agents, with additional microbiological and safety-related tests as applicable. The specifications are based on relevant pharmacopeial, WHO, and in-house methods.

- **Analytical Procedures.**

Analytical procedures for the three viral drug substances are established in the relevant Standard Test Procedures. Methods include visual examination, $CCID_{50}$-based virus titration, immunological identification, microscopic cell counting, ELISA for BSA, direct inoculation sterility testing, cell culture testing for extraneous agents, mycoplasma testing and mycobacteria testing.

Analytical procedure validation was performed in accordance with ICH Q2(R1), with validation protocols and reports provided.

For compendial qualitative tests, such as extraneous-agent testing in cell culture, separate validation was not considered necessary. The avian eggs used for the relevant testing are SPF grade.

- **Batch analysis.**

Batch analysis data were provided for three batches of each viral drug substance. The results were compliant with the predefined specifications and demonstrated consistency of the respective drug substance manufacturing processes.

- **Reference Standards or Materials.**

Reference materials and standards used for testing the viral drug substances are controlled according to the applicable analytical procedures and pharmacopeial/WHO requirements. The dossier includes the relevant virus seed and working seed documentation and testing.

- **Container closure system**

The viral drug substances are stored in suitable container closure systems under controlled conditions. The proposed systems provide adequate protection of the drug substances during storage and maintain their quality and integrity throughout the intended storage period.

- **Stability of drug substance**

The drug substances are stored under the approved storage conditions and have an established shelf life supported by the submitted stability data.

Approved Storage Conditions:
Clarified Measles Single Harvest Bulk: at or below -70 °C
Clarified and Concentrated Mumps Bulk: at or below -70 °C
Clarified and Concentrated Rubella Single Harvest Bulk: at or below -70 °C

Approved Shelf Life
Clarified Measles Single Harvest Bulk: 36 months
Clarified and Concentrated Mumps Bulk: 36 months
Clarified and Concentrated Rubella Single Harvest Bulk: 36 Months

2.2.3 Drug product:

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

ZyVac® MMR is a sterile, freeze-dried live attenuated vaccine. The lyophilized product is described as a whitish to very light pink cake and forms a clear red-to-purple solution after reconstitution.

Each 0.5 mL dose contains:

- Live attenuated measles virus, Edmonston Zagreb strain(Propagated on Human Diploid Cells): **NLT 1000 $CCID_{50}$**
- Live attenuated mumps virus, Hoshino strain (Propagated on Chick fibroblast Cells): **NLT 5000 $CCID_{50}$**
- Live attenuated rubella virus, RA27/3 strain (Propagated on Human Diploid Cells): **NLT 1000 $CCID_{50}$**

MMR vaccine is formulated with stabilizer 176 and diluent Medium 199. The Stabilizer 176 contains following excipients: Gelatin, D-Sorbitol, Lactose monohydrate, Lactalbumin hydrolysate, Calcium gluconate monohydrate, L-Alanine, L-Histidine, Tricine, Sodium hydroxide (pH adjustment).

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

Components of Drug Product
The three live attenuated viral components are formulated with Stabilizer 176 and diluent Medium 199. The supplied diluent is sterile Water for Injection used for reconstitution. The formulation and excipient composition were evaluated in relation to the stability and potency requirements of the live viral vaccine.

- Formulation Development
The formulation was initially developed for both single-dose and 10-dose multidose presentations. The selection and quantity of the viral components were based on approved MMR vaccines and the

applicable pharmacopeial and WHO TRS 840 requirements, including the minimum virus concentrations per dose.

The formulation remained unchanged from preclinical development through commercial approval.

- Overages

Overages of the three viral components are incorporated during manufacture to compensate for potency loss during the freeze-drying process.

- Physicochemical and Biological Properties

The finished product is a lyophilized cake that reconstitutes to a clear red-to-purple solution. Product controls include reconstitution time and volume, pH, moisture content, viral identification and titre, thermal stability, sterility and other microbiological attributes.

- Manufacturing Process Development.

The manufacturing process was developed and optimized to maintain viral potency and product quality during formulation, filling and lyophilization. Critical process parameters include temperature, mixing speed, pressure and lyophilization conditions, with relevant CQAs including virus concentration, sterility, pH, moisture and appearance.

- Container closure system and their compatibility.

The finished product is filled in **5 mL USP Type I amber glass vials** with **13 mm grey bromobutyl rubber stoppers** and aluminum flip-off seals. The amber glass provides protection for the light-sensitive product. The container closure system has been qualified, including integrity, compatibility and extractables/leachables assessments.

- Microbiological Attributes.

The product is manufactured using aseptic processing. Sterility is controlled through the manufacturing process and container closure integrity. Aseptic process simulation was performed using 3% w/v Soybean Casein Digest Medium, including routine and non-routine interventions and worst-case conditions. No microbial growth was observed after 14 days of incubation.

- Compatibility.

Compatibility with the supplied sterile Water for Injection was demonstrated by post-reconstitution in-use stability studies. The reconstituted vaccine maintained its quality attributes under the evaluated storage conditions.

- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities.

The drug product manufacturing and filling operations are performed at the Fill and Finish facility (Plant-5/SVP2) of **Zydus Lifesciences Limited, Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, 49 & 50, Sarkhej-Bavla N.H. No. 8A, Opp. Ramdev Masala, Village-Changodar, Tal: Sanand, Dist.-Ahmedabad-382213, Gujarat State, India**. Three consecutive process validation batches were manufactured.

The manufacturing process includes formulation with Stabilizer 176 and Medium 199, aseptic filling into the specified Type I amber glass vials and lyophilization, followed by sealing and secondary packaging.

- Control of critical steps and intermediates

Critical process parameters and CQAs have been identified for the MMR drug product. Controls include parameters associated with formulation, filling and lyophilization, with monitoring of viral concentration, sterility, pH, moisture and appearance.

- Process validation and / or evaluation.

Process validation was supported by three consecutive process validation batches. The validation strategy included aseptic process simulation, process performance qualification and evaluation of critical process parameters and CQAs.

The submitted validation data support the consistency and robustness of the commercial manufacturing process.

- **Product specification:**

The drug product specification is established with reference to the **Indian Pharmacopoeia, British Pharmacopoeia, WHO requirements and applicable in-house methods**. The specifications include appearance, pH, reconstitution time and volume, moisture content, identification, viral titre, thermal stability, abnormal toxicity, BSA, ovalbumin, sterility and mycoplasma.

The specification is intended to ensure the identity, purity, safety, potency and quality of the finished vaccine. The specification is aligned with the relevant pharmacopeial and WHO requirements.

The analytical procedures were based on pharmacopeial, WHO and validated in-house methods and were demonstrated to be suitable for their intended purpose.

Batch analysis of the finished product demonstrated compliance of the tested batches with the established specifications, confirming the consistency and quality of the drug product.

The formulation contains **Stabilizer 176**, comprising gelatin, D-sorbitol, lactose monohydrate, lactalbumin hydrolysate, calcium gluconate, L-alanine, L-histidine and tricine, with sodium hydroxide for pH adjustment and Diluent Medium 199.

Human diploid **MRC-5 cells** as the propagation substrate for measles and rubella and **CEF cells derived from SPF eggs** for mumps. Thus, materials of biological origin are used in the manufacture of the viral components.

Relevant process-related impurities include bovine serum albumin and ovalbumin, which are controlled by specified analytical methods. The BSA limit for the viral bulk was justified to ensure compliance of the formulated bulk with NMT 50 ng per dose.

No novel excipient is identified in the submitted formulation.

- **Reference Standards or Materials.**

Reference standards and materials used for finished-product testing are controlled in accordance with the applicable pharmacopoeial and in-house analytical procedures. The analytical methods used for release and stability testing are defined in the relevant Standard Testing Procedure.

- **Container closure system.**

The primary packaging consists of a **5 mL USP Type I amber glass vial**, a **13 mm grey bromobutyl rubber stopper**, and an aluminum flip-off seal. The vial contains the 10-dose lyophilized vaccine. A 5 mL glass ampoule containing sterile Water for Injection is supplied as the diluent.

The container closure system has been qualified for suitability, container closure integrity and compatibility with the vaccine, including extractables and leachables assessment.

- **Stability of the drug product.**

Approved Shelf Life:
Finished product: 24 Months

Diluent (WFI): 60 Months.

Approved Storage Conditions:
Finished product:
-Before and after reconstitution: store at (2- 8°C).
-Do not freeze after reconstitution
-Keep the vial in the outer carton in order to protect from light
- After reconstitution: use within 6 hours

Diluent:

Store at (30±2°C/65%±5%RH)

The diluent should not be frozen but should be kept cool.

3. Non –clinical aspect:

Measles is caused by a paramyxovirus of the genus Morbillivirus and is transmitted from person to person via aerosolized or large respiratory infectious droplets. The clinical presentation consists of prodromal fever, conjunctivitis, coryza, and cough. In some cases, Koplik spots (an erythema with white spots in the buccal mucosa) can be observed. Subsequently, a maculopapular rash usually appears, spreads from the head to the entire body, and fades within 4 to 7 days. Measles can result in otitis media, pneumonia, encephalitis and death. Mumps is caused by a paramyxovirus of the genus Rubulavirus and is spread by direct contact via the respiratory route. The clinical presentation is characterized by swelling of one or more salivary glands (usually the parotid glands) and may be preceded by several days of non-specific symptoms, including fever, lymphadenopathy, headache, malaise, myalgias, and anorexia. Mumps can result in deafness, orchitis, pancreatitis, meningitis, encephalitis and death.

Rubella is caused by a togavirus of the genus Rubivirus and is spread via infectious droplets shed from the respiratory secretions of infected persons to susceptible individuals. The clinical presentation is characterized by nonspecific signs and symptoms, including transient erythematous and sometimes pruritic rash, postauricular or suboccipital lymphadenopathy, and low-grade fever. The most important consequences of rubella are miscarriages, stillbirths, fetal anomalies, and therapeutic abortions, associated with Congenital Rubella Syndrome (CRS) that result when rubella infection occurs during early pregnancy. Anomalies associated with CRS include sensorineural deafness, cataracts, glaucoma, and other ophthalmic disorders, cardiac defects, microcephaly, meningoencephalitis and mental retardation.

Measles, Mumps and Rubella Vaccine (Live) is a freeze-dried combination pediatric vaccine produced in cell culture using well-established attenuated vaccine strains recommended in WHO guidelines. It's a live attenuated viral vaccine which uses Edmonston Zagreb strain of Measles virus propagated in MRC-5 cells, RA27/3 strain of Rubella virus propagated in MRC-5 cells and Hoshino strain of Mumps virus propagated in Chicken embryo fibroblast cells.

The protective function of the active substances in Zyvac®MMR is associated with antigenic stimulation of the host's immune system to induce virus neutralizing antibodies (Abs) against Measles, Mumps and Rubella viruses.

ZyVac®MMR is indicated for prevention of Measles, Mumps and Rubella virus infections.

ZyVac®MMR Multi-dose Vial (5 ml – 10 dose) is formulated as a freeze-dried powder containing Live attenuated measles virus (Edmonston Zagreb strain) NLT 1000 $CCID_{50}$; live attenuated mumps virus (Hoshino strain) NLT 5000 $CCID_{50}$; Live attenuated rubella virus (RA 27/3 strain) NLT 1000 $CCID_{50}$ per single dose (0.5 ml).

Pharmacology

No nonclinical immunogenicity studies were submitted for ZyVac®MMR vaccine. Live virus vaccines require virus growth following vaccination in order to induce an immune response. Since measles, mumps, and rubella are the active pharmaceutical components, and since there is an obligate requirement, as biological agents, to replicate in order to induce immunity, direct pharmaco-dynamic assessment of the active components is not meaningful. For this reason, traditional pharmacology studies were not conducted with measles, mumps, and rubella (live) vaccine. This was considered acceptable also supported by the WHO TRS 927.

Experimental studies to demonstrate absorption, distribution, metabolism and excretion of the active ingredients in ZyVac®MMR have not been performed for any of the component viruses. This is in line with the WHO TRS 927.

Pharmacokinetics: Conventional pharmacokinetic studies were not conducted, consistent with WHO TRS 927, as they are not applicable to live attenuated viral vaccines.

Toxicology

In the acute toxicity study, it is evident that up to a maximum subcutaneous dose of 2.0 mL per animal of MMR vaccine (Live) which is 4X of the proposed single human dose (0.5 mL), has not revealed any toxicity in Swiss Albino mice.

In the acute toxicity study, it is evident that up to a maximum subcutaneous dose of 4.0 mL per animal of MMR vaccine (Live), which is 8X of the proposed single human dose (0.5 mL), did not show any toxicity in Wistar rats.

Repeated administration of MMR vaccine by SC route up to the dose of 2.0 mL per animal (4X of the absolute human dose) did not affect the survival of Wistar rats. Further, no adverse changes were noticed during detailed clinical, hematological, biochemical, organ weight estimations and histopathological examination in this study.

Repeated administration of MMR vaccine by SC route up to the dose of 4.0 mL per animal (8X of the absolute human dose) did not affect the survival of NZW rabbits. In addition, no adverse changes were noticed during detailed clinical, hematological, biochemical, organ weight estimations and histopathological examination.

Local tolerance: In accordance with the WHO, the evaluation of local tolerance for ZyVac®MMR is based on the findings in the acute and repeat-dose toxicity studies.

In the “Acute Toxicity Studies, at the end of study period, injection sites were examined for local reactions such as erythema, edema, if any. There were no visible signs of local reactions noticed at the site of injection in control as well as treated animals in both sexes at the end of the study period.

In the “Repeated Dose Toxicity Studies, Tolerance was determined by the occurrence of erythema, edema, both visually and microscopically, at injection sites. There were no test item related adverse reactions and gross lesions at the site of injection in both male and female rats and rabbits were observed in the study. Microscopic examination of skin or the site of injection did not reveal any adverse histopathological changes.

4. **Clinical aspect:**

➢ **Clinical Overview**

The clinical development program of ZyVac® MMR consisted of **four clinical studies:**

- **Phase I**: two safety studies of both the single dose and multi dose formulations of the vaccine were established in adults.
- **Phase II:** randomized open label, multicentric, non- comparative study was conducted in pediatric population of 15 to 18 months age to evaluate the immunogenicity and safety of the two vaccine formulation (single-dose and multi-dose).
- **Phase III**: prospective, randomized, single blind, comparative, non-inferiority study in healthy pediatric subjects aged 15-18 months to compare the safety and immunogenicity of the two formulations with MMR vaccine of M/s Serum Institute of India.

All studies were conducted in accordance with Good Clinical Practice (GCP), ensuring compliance with ethical principles, informed consent, and regulatory requirements consistent with ICH E6(R2) and WHO guidelines.

The program was designed to evaluate the safety and immunogenicity of Measles, Mumps and Rubella (MMR) vaccine (Live) (Freeze-dried) of M/s Zydus Lifesciences Ltd. (formerly known as Cadila Healthcare Ltd.) compared with licensed comparator vaccines administered according to standard immunization schedule.

➢ **Clinical Efficacy:**

- **The Phase II study** demonstrated that both single dose and multi dose formulations of ZyVac®MMR induced robust immune responses against Measles, Mumps and Rubella following single dose vaccination.
  - Immunogenicity was assessed 42 days after vaccination.
- **The pivotal Phase III study**
  - Seroconversion and seropositivity rates were comparable between study groups
  - The primary non-inferiority objectives were achieved overall, with comparable immunogenicity demonstrated between ZyVac®MMR and the comparator vaccine.
  - Geometric mean titres supported comparable immune responses across all vaccine components

Overall: ZyVac®MMR demonstrated non-inferior immunogenicity compared with the MMR vaccine (Live) (Freeze-dried) of M/s Serum Institute of India Limited, confirming adequate primary immune protection.

➢ **Clinical Safety:**

Across the submitted clinical studies, ZyVac®MMR demonstrated an acceptable safety profile:

- Most adverse events were mild to moderate and transient.
- No vaccine-related serious adverse events or deaths were reported.

- ZyVac®MMR treated subjects were rated to have an "Excellent" tolerability.
- Safety findings were comparable between ZyVac®MMR and comparator vaccine.
  Overall: no new or unexpected safety concerns were identified as claimed by the applicant.

➢ **Clinical Immunogenicity:**

- ZyVac®MMR induced robust antibody responses against measles, mumps and rubella that were comparable to those of the licensed comparator vaccine.
- The vaccine met all predefined Non-inferiority or comparability criteria for seropositivity, seroconversion and antibody magnitude.
- The submitted studies demonstrated robust immune responses following a single study vaccination; however, vaccination should follow the recommended national immunization schedule.

➢ **Benefit-Risk:**

The overall benefit-risk balance of ZyVac®MMR is considered favorable for active immunization of children.

Key benefits include:

- Strong and consistent immunogenicity
- Non-inferiority to licensed comparator vaccines
- Well-characterized and acceptable safety profile

➢ **Conclusion:**

Based on the totality of clinical evidence, ZyVac® MMR (Measles, Mumps and Rubella vaccine) is:

- Safe, Immunogenic and non-inferior to comparator vaccine.
- Suitable for use in single dose in children
  The vaccine provides a clinically relevant public health benefit by reducing the number of injections required and supporting improved vaccination compliance.

5. General Conclusion and Recommendations if any:

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