Unit: Technical Assessment Unit

Public assessment report for biological products

Gardasil 4

Administrative information:

Trade name of the medicinal product:	Gardasil Vaccine (Quadrivalent Human Papillomavirus Recombinant Vaccine)
INN (or common name) of the active substance(s):	Type 6 L1 Protein. Type 11 L1 Protein. Type 16 L1 Protein. Type 18 L1 Protein.
Manufacturer of the finished product	Merck Sharp and Dohme Corp
Marketing Authorization holder	Merck Sharp and Dohme Corp
Applied Indication(s):	The vaccine is indicated for the prevention of cancer, precancerous or dysplastic lesions, genital warts, and infection caused by the HPV types targeted by the vaccine.
Pharmaceutical form(s) and strength(s):	- Vial for Injection - Quadrivalent Human Papilloma virus Each 0.5ml Vial contain: Type 6 L1 Protein 20mcg Type 11 L1 Protein 40mcg Type 16 L1 Protein 40mcg Type 18 L1 Protein 20mcg
Route of administration	IM injection
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

MBAP - Monovalent Bulk Adsorbed Products.
VLPs - Virus-like particles

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1. Introduction:

Human papillomavirus (HPV) infection is the most common sexually transmitted disease worldwide. The quadrivalent HPV vaccine was developed based on that a systemic neutralizing anti-HPV response by vaccination with type-specific HPV L1 VLPs result in protective immunity against type-specific HPV infection and disease. The vaccine also elicits cell-mediated responses as detected by in vitro stimulation of PBMCs, Th1 and Th2 cytokines and immunoglobulin subclasses It is believed that the vaccine provides protection by inducing type-specific antibodies that interfere with transmission by binding to and neutralizing contaminating HPV prior to entry into basal cells.
Gardasil is a vaccine for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

2. Quality aspects:

Introduction

As mentioned in the previous section.

Drug Substance (Active ingredient)

General information

The drug substance consists of the four monovalent bulk adsorbed products (MBAPs), one for each of the four human papillomavirus (HPV) types included in GARDASIL™ (Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine. The active components in each MBAP are the highly purified virus-like particles (VLPs) made up of the recombinant major capsid (L1) protein for that HPV type. L1 is the major structural protein of the human papillomavirus viral capsid.

Manufacture, process controls and characterization:

The drug substance is manufactured & controlled

- Merck Sharp & Dohme Corp. Sumneytown Pike P.O. Box 4 West Point, Pennsylvania 19486-0004 USA.
- Merck Sharp & Dohme Corp. 2778 South East Side Highway Elkton, Virginia 22827 USA.

The sites comply with the GMP requirements.

- The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.

Control of Materials:

List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided.
Information regarding the used strain & cell substrate is mentioned in detail in the MA file.

Process Validation

The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.
Validation protocols and reports are attached to the MA file illustrating the details of the batches used.

Manufacturing Process Development
In the development process of the viral strain, there were changes to the manufacturing process. The quality equivalence was verified by analyzing the release test, characterization, and stability test results to evaluate equivalence depending on the changes of each manufacturing process.
Detailed description for each step development is mentioned in the MA file.

Specification
The tests performed on the drug substance comply with the requirements of United States Pharmacopeia (USP) & European Pharmacopeia (Ph. Eur).
Detailed SOPs are provided with their validation report.
The purity, potency, physicochemical properties & sterility of the MBAP: Monovalent Bulk Adsorbed Product

Analytical Procedures.
A summary of each assay procedure used for release testing is provided including descriptions of the method, standards, and controls.

Reference Standards or Materials.
The information on the tests using the reference material among the bulk release testing, as well as information on the reference material used were described.

Container closure system
Monovalent Bulk Adsorbed Product (MBAP) is stored in 45L glass bottles for up to 36 months at 2-8 °C. In order to increase production flexibility worldwide, MBAP will also be stored in 18L and 20L glass bottles. The materials of construction, product contact surface finish, and container closure system of the 18L and 20L glass bottles are identical to that of the 45L glass bottle. Since the only change is the size of the bottle, use of the new containers is supported by existing media challenge and stability data. Further details are provided below.

Stability of drug substance

MBAP may be stored in bulk storage containers for up to 36 months at 2-8°C.

Drug product:

Description and Composition of the Drug Product:

The Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (HPV VLP Vaccine) is a sterile liquid suspension prepared from the Type 6, Type 11, Type 16, and Type 18. Monovalent Bulk Adsorbed Products (MBAPs) combined with a buffer and a suspension of the adjuvant. It is filled into single-dose vials or syringes with a minimum recoverable volume of 0.5 mL.

Pharmaceutical Development

The processes are fully described in the MA. The finished product is manufactured by adding final bulk buffers. The verification test items for the manufacturer's certificate of analysis for quality control of each excipient, as well as the in-house acquisition test items are described.

Physicochemical and Biological Properties

The drug product is a sterile, white, cloudy liquid suspension of adjuvant-adsorbed VLPs at a target pH of 6.2. The particles settle during storage, requiring a mild shaking of the vials or syringes to regain full suspension before use.

Manufacturing Process Development.

Clinical supply manufacture has occurred exclusively at Merck Sharp & Dohme Corp. in West Point, Pennsylvania, USA. The most significant changes to the manufacturing process were changing the filling process from a manual process to an automated process using a filling machine and introducing the quadrivalent formulation. Only minor modifications were made upon transfer from the research pilot facilities to full manufacturing scale. they were fully described in the MA file. The company provided the required procedures.

Container closure system and their compatibility.

The vaccine is supplied in two images: vial and syringe. Suitability of the container closure systems is demonstrated by compendial testing of the components and also by drug product stability studies.

Microbiological Attributes.

Quadrivalent HPV VLP Vaccine is provided in single-dose vials and single-dose syringes with no preservative. The product is prepared from sterile drug substance bulks and sterile buffer components and is processed and filled using validated aseptic processing.

Compatibility.
This product does not require reconstitution. Suitability of the vial and syringe container closure systems is demonstrated by compendial testing of the components and drug product stability studies.

Manufacture of the drug product:
The Drug Product is manufactured by Merck Sharp & Dohme Corp.
Description of drug product manufacturing process that summarizes the following information was provided for the steps; formulation and filing.
Control of critical steps and intermediates
Detailed data for the identification, and control of critical steps involved in the manufacturing HPV vaccine and Filled Product was provided and found satisfactory. The Final Bulk Vaccine is considered as an intermediate in the manufacturing process of Drug Product. The specification applied for release of Final Bulk was provided.
Process validation and /or evaluation.
All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
All the analytical methods used during process validation shall be prior validated. Process validation batches shall also be subjected to stability studies to evaluate its impact on product quality over the period of time and to justify shelf life of the product.
The submitted Process validation study provided documented evidence, and high degree of assurance that the process stages were satisfactory.

- **Product specification:**
  Specifications proposed for release and stability testing of the finished product comply with USP ph. & Eu. Ph.
  Detailed SOPs validation protocols & reports are provided for the in-house methods
  The specifications include general characteristics, biological & general safety tests, potency & identity tests
  Excipients.
  The excipients are purchased in compliance to the pharmacopeial specifications. A test certificate accompanies each batch supplied to guarantee compliance with the specifications.
  The excipients enhance the stability during different manufacturing processes and during storage in addition to immunogenicity of vaccine.
  None of the excipients are of animal origin, and no animal-derived materials are used in the manufacture of any excipients.
  Impurities.

No impurities are introduced during the drug product manufacturing process. Impurities that are introduced during the manufacturing process are clearly discussed and illustrated in MA file.

- **Reference Standards or Materials.**
  List of reference materials used in the tests of the finished product were given together with their COAs as well as the assay kits.
- **Container closure system.**
  Primary Packaging is a glass vial; glass is compliant with European Pharmacopoeia and United States Pharmacopeia. The stoppers are compliant with the chemical test requirements for Type 1 closures, as described in Ph. Eur. They also meet the physicochemical test requirements as listed in USP Section. Secondary Packaging Labels are affixed to the filled and capped vials.

- **Stability of the drug product.**
  The proposed shelf-life for all final-container images is 36 months at 2–8 °C.

3. General Conclusion and Recommendations if any:

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

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/overview/gardasil-epar-summary-public_en.pdf