Unit: Technical Assessment Unit

Public assessment report for biological products

Menactra

Administrative information:

Trade name of the medicinal product:	Menactra
INN (or common name) of the active substance(s):	Each 0.5 ml contain Meningococcal (Serogroup A) polysaccharide (monovalent conjugate) 4µg Meningococcal (Serogroup C) polysaccharide (monovalent conjugate) 4µg Meningococcal (Seogroup Y) polysaccharide (monovalent conjugate) 4µg Meningococcal (Seogroup W135) polysaccharide (monovalent conjugate) 4µg Diptheria Toxoid protein 48µg
Manufacturer of the finished product	Sanofi Pasteur Inc., building 57, Discovery Drive, Swiftwater, PA 18370- USA
Marketing Authorization holder	Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370- USA
Applied Indication(s):	Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W135, for use in individuals 9 months through 55 years of age.
Pharmaceutical form(s) and strength(s):	Solution for Intramuscular Injection
Route of administration	Intramuscular
Approved Pack	Carton box containing 5 vials (borosilicate type I glass) each of 0.5 ml solution for injection closed with grey butyl stopper (latex free) and sealed with flip off seal, with insert leaflet.
Registration track	**Normal Pathway**
Type of registration (EMA/FDA – Local)	**FDA**

List of abbreviations:

DS	Drug Substance
IPCs	In-Process Controls
CQA	Critical Quality Attributes
DP	Drug Product
IM	Intramuscular

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Dossier initial submission and evaluation process:

The file evaluated according to normal track pathway & the company submitted data which are the Quality module-3 from the CTD file.

1. Introduction

Menactra, meningococcal (Groups A,C,Y,W-135) polysaccharide diphtheria toxoid conjugate vaccine, is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A,C,Y and W135. Menactra is used for individuals 9 months through 55 years of age.

Menactra vaccine is a clear to slightly turbid solution enclosed in single dose vial. It is administered as a single 0.5ml dose intramuscularly.

- **Quality aspects:**

- General information:

Serogroup A,C,W135,Y polysaccharide diphtheria toxoid conjugate concentrates are sterile colorless to light amber solutions that are devoid of foreign matter. Also, are consist of capsular polyssacharide purified Serogroup A,C,W135,Y Neisseria meningitidis.

Manufacture, process controls and characterization:

- **Manufacturer:** Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370- USA.
- **Description of Manufacturing Process and Process Controls**

- production of drug substance (DS) begins with biosynthesis of a polysaccharide and a protein. The N. meningitidis capsular polysaccharide is released into fermentation medium and collected precipitation with an anionic detergent.

- depolymerization and derivatization of the polysaccharide purified bulk powder intermediate gives the polysaccharide intermediate.

- diphtheria toxin is released by C. Diphtheriae into fermentation medium, denatured with formaldehyde to diphtheria toxoid.

- the two intermediates are covalently linked by chemical reaction to give DS.

- the process consists of four stages: Fermentation, Inactivation, Purification and Drying.

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.
-The master and working seed banks were prepared without the use of biologically derived material
-Materials used in the manufacture of DS are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.
- IPCs applied during production of bacterial pre master, master, working seed bank and its validation are included in details.

- **Controls of Critical Steps and Intermediates**

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all critical quality attributes (CQA) were achieved.
- Test results of critical quality attributes and results for critical parameter attributes in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and showed production process consistency.

- **Manufacturing Process Development.**

- After the original approval by a regulatory authorities, several changes were made. They are classified as follows:
1- Changes that occurred after the final manufacturing process
2- Changes that occurred before the final manufacturing process
3- Changes that occurred before phase 3, 2 and phase 1
Comparability studies were performed supporting the changes that occurred and critical process parameters were maintained and all critical attributes were achieved.
- All the changes are illustrated in detail with justification and their impact on quality.
- tests used to assess impact of manufacturing changes are described well.

- **Characterization**

- tests used to characterize *N.meningitidis* polysaccharide purified bulk powder are mentioned together with tests done to assure purity. Additionally, these tests may be used for release and stability assessment. The release specifications and the results from three process batches showed consistency.
- results from analytical tests performed at various stages during the manufacture process are used to characterize the diphtheria toxoid, purified preservative free protein. Additionally, these tests may be used for release and stability assessment.
- results for tests done for characterization of *N.meningitidis* polysaccharide diphtheria toxoid conjugate concentrate is submitted and showed consistency

- **Impurities:**

Process related impurities are formed during manufacturing process of DS are mentioned with tests performed to check their level. The process validation demonstrated that these impurities are consistently removed so that their levels are below the limits of detection or below levels of potential toxicity during the manufacture process.

- **Control of Drug substance:**

Specification

The release specification for the DS comprises tests for physical characteristics, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes. The specification has been prepared in line with the requirements of USP and ICH guidelines.

Analytical Procedures

All analytical procedures either pharmacopeia or in house developed were described.

Batch analysis

The release data from three consistency batches for DS were submitted and their results comply with the specification sheet and defined acceptance criteria. □

- **Container Closure System**

Primary closure system is described together with its specification

- **Stability of DS**

- three batches of DS were placed on stability. All data met the acceptance criteria through the study and support the hold time of 24 months a the recommended storage temperature - 60 to - 80 ^{O}C

- **Drug product**
  - **Description and composition of DP**

    - The DP is presented as sterile, aqueous solution that contains group-specific polysaccharide antigens from *N.meningitidis* A, C, Y and W135 separately conjugated to diphtheria toxoid protein.
    - Each 0.5ml dose contains 4mcg of each meningococcal A, C, Y and W135 polysaccharides conjugated to a total of approximately 48 mcg of diphtheria toxoid protein carrier.
    - the product is supplied in a single dose vial (borosilicate type I glass) closed with grey butyl stopper (latex free) and sealed with flip off seal

  - **Manufacture of drug product**

    - The finished product is manufactured at Sanofi Pasteur Inc., building 57, Discovery Drive, Swiftwater, PA 18370- USA.
    - All manufacturing steps and release of DP is conducted at this site. The filling and packaging of DP final container vaccine is also done at the same Swiftwater, PA site but in a different building (Building 37).

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

  - manufacturing process is simply divided into two processes: formulation and filling of the unit-dose vials.
  - immediately after filling and stoppering, the vials exit immediately to copper room, and are then inspected or stored until inspection
  - after inspection, the vaccine vials are removed from storage, transported to the packaging area and labelled.

- **Control of critical steps and intermediates**

The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation (PV) and / or evaluation**

- PV consisted of the execution of aseptic process simulation and consistency lot validation for formulation process. Summary of process parameters results of validation lots were submitted. Summary of CQA and IPCs together with batch results were submitted.
- the process validation studies showed consistency of production. All IPCs and CQAs identified were achieved for all validation lots.

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned. All excipients comply with USP.
- no excipient of human or animal origin are used during DP manufacturing. No novel excipients were used

- **Control of drug product**

-The specifications include physical characteristics, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at release and during stability studies are provided.

- **Container closure system**

- primary packaging: Unit dose meets specification of EP.
- Identity of construction materials together with their specifications are described.

- **Stability**

-Approved shelf life for the Finished product: 24 months.
-Approved Storage Conditions: Store at temperature 2-8ºC, do not freeze. Frozen/ previously frozen product should not be used. Do not use after the expiration date.

- **<u>Non –Clinical aspect & Clinical aspect:</u>**

1. **Non –clinical aspect:**

➢ Menactra® is a tetravalent Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine, which belongs to the pharmacological class “anti-infective for systemic use – Vaccines group”. It is indicated, for active immunization of individuals 9 months through 55 years of age, to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135. . Menactra does not prevent N meningitidis serogroup B disease. Menactra is FDA-approved (first licensed in 2005) and prequalified by WHO (since 2014).

➢ **Pharmacology:** The immunogenicity studies were performed to assess the immune response, to determine the class of antibody elicited and prime-boost response to the Biological Product

in mice and rat models. The immune response was compared between the unconjugated free polysaccharide and adjuvanted formulations. The results demonstrated that the use of meningococcal conjugate vaccine for priming, boosting, or both, induced a robust memory response and therefore a significant increase in antibodies to all 4 meningococcal serogroup-specific polysaccharides. Similarly, priming with Diphtheria Toxoid resulted in a specific memory response induced by the meningococcal conjugate vaccine. The Biological Product elicited IgG1 and IgG2b antibodies subclass against each of the serogroup polysaccharides.

- **Pharmacokinetics:** PK studies are not required for vaccines according to the Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CHMP/SWP/465/95) and the WHO guidelines on nonclinical evaluation of vaccines (WHO TRS No.927 Annex 1).

- **Toxicology:** Three nonclinical toxicology studies were conducted to assess the safety of the Vaccine. The single/repeated dose toxicity study demonstrated that the candidate Product is well-tolerated and immunogenic in rats when administered IM, either single or two doses, at a level equivalent to one human dose. There were no mortality, and no treatment-related clinical signs observed in the study. The changes observed in WBC counts (mainly increased neutrophil counts) were considered as a pharmacological effect attributed to stimulation of immune system. No treatment-related changes were noted in all sampled organs including the injection sites. In a preliminary developmental toxicity study in rats, mouse and rabbits, the pre- and post-natal maternal antibody transport to fetus and pups was demonstrated in all species. In the pivotal reproductive and developmental toxicity study in mouse, IM administrations with the maximum feasible dose of the vaccine, before mating and during gestation, did not adversely influence the course and outcome of pregnancy or the post-natal development of the mouse offsprings.

- **Overall conclusion:** The nonclinical evaluations performed have shown that the Menactra® vaccine is safe and induce the appropriate immunological protection.

2. Clinical aspect:

The clinical development program has demonstrated that Menactra vaccine is safe, immunogenic, and non-inferior to Menomune vaccine with respect to hypothesis-driven comparisons.

The clinical safety profile of Menactra vaccine is similar to that of Menomune vaccine.

The benefits associated with receiving Menactra vaccine, which is capable of inducing an anamnestic immune response (in contrast to Menomune vaccine), outweighs the minimally elevated risk of experiencing predominantly local reactions of short (less than 3 days) duration at the injection site.

As meningococcal disease occurs across all age groups, substantial public health benefits may accrue from a product that fits within the current meningococcal vaccination recommendations made by several vaccination policy bodies and is anticipated to provide long-term primary protection, reduce carriage rates, and induce immunologic memory in targeted age groups.

In addition, Menactra vaccine has a recognized and well-established favorable safety profile based on approximately 20 years of post-marketing surveillance and more than 180 million doses distributed.

The benefit-risk profile of Menactra vaccine remains strongly favorable for use as indicated in this CTD application.

General Conclusion and Recommendations if any:
Based on the review of CTD modules and other supplementary documents, the product is approved.