Unit: Technical Assessment Unit

Public assessment report for biological products

(Stamaril)

Administrative information:

Trade name of the medicinal product:	Stamaril
INN (or common name) of the active substance(s):	After reconstitution, each 1 dose 0.5 ml contains: Yellow fever virus strain 17D-204 (live, attenuated) at least 1000 IU per dose
Manufacturer of the finished product	Sanofi Winthrop Industrie, Parc Industriel d'Incarville, Voie de l'Institut, B.P 101, Val de Reuil,27100-France
Marketing Authorization holder	Sanofi Winthrop Industrie,82 Avenue Raspail,94250 Gentilly-France.
Applied Indication(s):	Protection against a serious infectious disease called yellow fever
Pharmaceutical form(s) and strength(s):	Powder and solvent in PFS
Route of administration	Subcutaneous or intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

Abbreviation	
GMT	Geometric Mean Titer
TT	Tetanus Toxoid
Td	Tetanus and Reduced Diphtheria Toxoid
DTP	Diphtheria, Tetanus, and Pertussis Vaccine
U/ml	Units per Milliliter

Abbreviation

hr	Hour
min	Minute
p	Probability Value
WHO	World Health Organization
YF	yellow fever
SAGE	Safety Advisory Group of Experts
CDC	Centers for Disease Control
RMP	Risk Management Plan
IHR	International Health Regulations

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Stamaril is a stabilized attenuated live yellow fever virus vaccine.
   Each 0.5-mL dose of reconstituted vaccine contains not less than 1000 IU of 17D strain yellow fever virus, propagated in specified pathogen-free chick embryos (SPF). The excipients constitute the stabilizing medium, the composition of which is patented and has been defined to have a protective effect on the infectious titre (virus concentration) of the attenuated live yellow fever virus and obtain a thermostable vaccine.

The vaccine is administrated by intramuscular or subcutaneously.
The single-dose presentation corresponds to a freeze-dried vaccine packaged in a type-1 glass vial containing 1 dose. The corresponding reconstituted diluent, a 0.4% sodium chloride solution is packaged in a type-I glass syringe with an attached needle.

2. **<u>Quality aspects:</u>**

2.2.1 Introduction

As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

Nomenclature:

- International Nonproprietary Name (INN): Yellow Fever vaccine (live)
- Compendial Name (Eu.Ph.): Yellow Fever vaccine (live) (Vaccinum febris flavae vivum)
- World Health Organization Name: Stamaril

The structure:

Yellow Fever vaccine (live) consists of a freeze-dried preparation of live, attenuated Yellow Fever virus.
The Yellow Fever vaccine satisfies all the requirements of the WHO (TRS 872) and European Pharmacopoeia Monograph (537) and is produced according to their recommendations by multiplication of the Yellow Fever virus strain 17D on chick embryos free from avian leucosis.
The Yellow Fever vaccine is a member of the Flaviridae. It is a small (35 - 45 nm) virus and consists of a core containing single-stranded RNA surrounded by a lipoprotein envelope. It is a positive sense single-stranded, encapsulated RNA virus. The virus enters cells by receptor-mediated entocytosis.

Manufacture, process controls and characterization:

Manufacturer:

Sanofi Winthrop Industrie, Parc Industriel d'Incarville, Voie de l'Institut, B.P/101 Val de Reuil,27100-France (Manufacture from Cell culture to DS)

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

The manufacture of Concentrated Bulk is divided into 2 major manufacturing process stages:
• Cell Culture and Harvest and
• Filling, Storage and Transportation

- **Characterization.**

The virus concentration is the biological activity test that describes the specific ability or capacity of the harvest to achieve a defined biological effect. In order to determine the appropriate dilution for the preparation of the final bulk, the virus concentration test is performed in the harvest.

The impurities can be linked to the fact that the multiplication support for the Yellow Fever virus is fertilized hen eggs. The routine tests for residual protein nitrogen content is performed on each final bulk product, while residual ovalbumin content and bacterial endotoxin are carried out on each final product batch.

* IPCs for the intermediates of the DS include tests with specified acceptance criteria and tests to monitor the process. All IPCs applied are in compliance with the international pharmacopeias, and with WHO guidelines.
* IPCs during the production process are well defined in the process schemes

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.

-Materials used in the manufacture of DS are tested internally and accepted on the basis of relevant pharmacopeia testing methods.

- IPCs applied during production of pre master, master, working seed bank are complying WHO, TRS 323, 1966, Annex 1, WHO, TRS 872 and European Pharmacopoeia.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.

- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

- **Control of Drug substance:**

- **Specification**

The release specification for the DS comprises tests for sterility test, Test for cultivable mycoplasma, Test for mycobacteria, Identity and Virus concentration. The specification has been prepared in line with the requirements of pharmacopeias and WHO TRS 872 & 873.

- **Analytical Procedures.**

All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.

- **Reference Standards or Materials.**

All reference standards used during manufacturing are well described in the MA file

- **Container closure system**

The DS is filled into storage bag which is a flexible container composed of an S71 film and an assembly tubing aseptic connection. The container closure system is sterilized by gamma irradiation.

- **Stability of drug substance**

- The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Stamaril is a stabilized attenuated live yellow fever virus vaccine. to be administered by the intramuscular or subcutaneous route.
  Each 0.5-mL dose of reconstituted vaccine contains not less than 1000 IU of 17D strain yellow fever virus, propagated in specified pathogen-free chick embryos (SPF). The excipients constitute the stabilizing medium, the composition of which is patented and has been defined to have a protective effect on the infectious titre (virus concentration) of the attenuated live yellow fever virus and obtain a thermostable vaccine.
  Each dose of freeze-dried vaccine is reconstituted using a sterile solution of 0.4% sodium chloride to provide a single dose of 0.5 mL.
  - Container closure system and their compatibility.
  The Freeze-Dried Product is presented in a Type I glass vial (3ml) with a grey chlorobutyl stopper and a cap.
  The product is accompanied with diluent 0.4% sodium chloride in 1-mL syringe with attached needle.
- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Sanofi Winthrop Industrie, Parc Industriel d'Incarville, Voie de l'Institut, B.P 101, Val de Reuil,27100-France

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

  - The Final Bulk Product (FBP) is a sterile solution. Sterility is achieved by blending aseptically an appropriate number of sterile yellow fever harvest sub-lots, active substance stabilizing medium and Water for injections in appropriate volumes. The FBP is stirred for homogenization at +5°C ± 3°C for at least 15 min ± 5 min. The FBP is stored at +5°C ± 3°C in a sterile bank.
  - The FBP is filled under environmentally controlled conditions which have been checked to guarantee aseptic filling of sterile products. The aseptic filling is followed by the freeze-drying stage, which observes the specific parameters of the defined cycle adapted to the product.

  - **Control of critical steps and intermediates**

  There are no intermediate in the DP manufacturing process.
  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 and / or evaluation**

- Aspetic process, Blending, Fillling and Freeze drying: carried out in three manufacturing consistency batches and the study reports enclosed

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned.
- All excipients are controlled according to the European Pharmacopoeia (Ph. Eur.).
- these is no excipient from human origin used.

- **Control of drug product**

-The specifications include physical characters, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at the release and during stability studies are provided.
- the analytical procedures, principles and validity criteria used for control testing of the vaccine were provided.

- **Container closure system.**
  - The product is filled in type I glass vials (3ml) stoppered with chlorobutyl rubber stopper and sealed with flip off aluminium seals. The product supplied 0.5ml solvent in PFS type I glass with a plunger stopper attached with needle and needle shield.
  - Identity of materials of construction together with their specifications are described
- **Stability of the drug product.**
  -Approved shelf life for the Finished product: 36 months when stored at 2-8°C
  -Approved Storage Conditions:
  - Store at temperature 2-8ºC. Don't freeze. Keep away from light.
  - after reconstitution, use immediately after opening.

3. **Clinical aspect:**

➢ **Clinical Overview**

Stamaril is a stabilized live attenuated yellow fever (YF) vaccine developed by Sanofi Pasteur. It is indicated for active immunization of children aged 9 months and older, adolescents, and adults for the prevention of yellow fever infection. Protective immunity is achieved from Day 10 following primary vaccination (single dose) and may provide long-term, potentially lifelong, protection.

To support the clinical development of Stamaril, Sanofi Pasteur conducted Five clinical studies between 2005 to 2014; 16 between 1983 to 1997 evaluating the vaccine's immunogenicity and safety. According to the applicant, all studies were conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Clinical Efficacy and Clinical Immunogenicity:

- Over the past 75 years, yellow fever vaccines have represented the most effective means of preventing yellow fever disease. Stamaril demonstrated a high level of immunogenicity

during early clinical development, and this profile has been consistently confirmed in subsequent clinical studies.

- In line with recommendations issued by the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO), a single dose of Stamaril may provide long-term protection against yellow fever and may confer lifelong protective immunity in immunocompetent individuals.

Clinical Safety:

- The safety profile of Stamaril has been evaluated through clinical studies, post-marketing case reports, and ongoing safety surveillance activities. No serious adverse reactions or deaths were reported during the clinical studies.
- The principal identified risks associated with yellow fever vaccination are yellow fever vaccine-associated neurotropic disease (YEL-AND), with a reporting rate of approximately 0.15 cases per 100,000 doses administered, and yellow fever vaccine-associated viscerotropic disease (YEL-AVD), with a reporting rate of approximately 0.08 cases per 100,000 doses administered. Both events are considered very rare and are defined according to criteria established by the CDC Yellow Fever Working Group and the Brighton Collaboration.
- These risks are continuously monitored and assessed through routine pharmacovigilance activities, including Periodic Benefit-Risk Evaluation Reports (PBRERs). They are also incorporated into the Stamaril Risk Management Plan (RMP), with ongoing efforts to improve their detection and characterization across vaccinated populations.
- For travelers, vaccination decisions should be based on an individual benefit-risk assessment, taking into account destination-specific yellow fever risk, official contraindications, and relevant warnings.
- Administration of Stamaril should be undertaken in accordance with local regulations, with particular consideration given to immunocompromised individuals, pregnant or lactating women, and elderly persons.

Benefit/ Risk discussion:

- The recommendation for yellow fever vaccine booster doses every 10 years has been included in the International Health Regulations (IHR) since 1965 and was originally established based on limited available evidence.
- Available data indicate that most vaccine recipients develop protective antibody titers against yellow fever virus within 28 days following vaccination and maintain protective immunity for several decades, and potentially throughout life.
- Children younger than 2 years of age have demonstrated lower seroconversion rates following a single vaccine dose compared with older populations.

- Reports of primary vaccine failure are very rare, and no cases of secondary vaccine failure attributable to waning immunity over time have been documented.
- Emerging evidence suggests that, in addition to neutralizing antibodies, innate and cell-mediated immune responses contribute to both the initial immune response and the maintenance of long-term protection against yellow fever virus.
- No dedicated clinical studies were conducted in certain special populations, including pregnant women, lactating women, and immunocompromised individuals, as these populations are generally included among the contraindications for live attenuated vaccines.
- The total clinical development program included 4,896 subjects. While this sample size provided a 95% probability of detecting adverse events with a true incidence of approximately 0.06%, it was not sufficient to identify very rare adverse events occurring at frequencies below 0.01%.
- Yellow fever remains a significant public health concern in endemic regions of Africa and South America, where periodic outbreaks continue to occur. Consequently, vaccination remains a key preventive public health measure endorsed by international health authorities and national immunization programs.
- In endemic areas, routine immunization programs and preventive mass vaccination campaigns are recognized as effective strategies for disease control. Outbreak-response vaccination campaigns have also demonstrated effectiveness when required. Stamaril is available in both single-dose and multidose presentations and has been prequalified by the WHO for use in endemic countries.
- Unvaccinated travelers remain at risk when visiting endemic regions. Vaccination should therefore be considered following an assessment of travel itinerary and exposure risk, while also taking into account the potential risk of rare vaccine-associated adverse events, including YEL-AVD and YEL-AND.
- Recent clinical studies have confirmed high rates of seroprotection following a single dose of Stamaril in both adult and pediatric populations, together with a favorable safety profile.
- The WHO Expert Group has concluded that a single dose of any yellow fever vaccine is likely sufficient to provide lifelong protection in immunocompetent individuals. As Stamaril is among the most widely used yellow fever vaccines globally, the available evidence supports alignment with this recommendation.

Overall Conclusion:
Based on the available clinical efficacy, immunogenicity, and safety data, Stamaril demonstrates a favorable benefit-risk profile when used in accordance with the approved prescribing information and current public health recommendations. The vaccine provides robust and sustained protection against yellow fever, while its identified risks remain rare and are subject to continuous pharmacovigilance monitoring and risk minimization measures.

4. General Conclusion and Recommendations if any:

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