Arab Republic of Egypt
Egyptian Drug Authority
Central Administration of Biologicals, Innovative Products and Clinical Studies
G.A. of biological products

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الحيوية والمبتكرة والدراسات الإكلينيكية
إ.ع. المستحضرات الحيوية

Unit: Technical Assessment Unit

Public assessment report for biological products

Hexaxim

Administrative information:

Trade name of the medicinal product:	Hexaxim
INN (or common name) of the active substance(s):	Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed).
Manufacturer of the finished product	Sanofi Winthrop Industrie, France.
Marketing Authorization holder	Sanofi Winthrop Industrie, France.
Applied Indication(s):	Hexaxim (DTaP-IPV-HB-Hib) is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b (Hib).
Pharmaceutical form(s) and strength(s):	Suspension for injection in pre-filled syringe. One dose (0.5 mL) contains: -Diphtheria Toxoid: 30 Lf (≥ 20 IU†§) -Tetanus Toxoid: 10 Lf (≥ 40 IU‡§) -Bordetella pertussis antigens; Pertussis Toxoid 25 micrograms Filamentous Haemagglutinin 25 micrograms -Poliovirus (Inactivated) ; Type 1 (Mahoney) 29 DU†† Type 2 (MEF-1) 7 DU†† Type 3 (Saukett) 26 DU†† -Hepatitis B surface antigen 10 micrograms -*Haemophilus influenzae* type b polysaccharide 12 micrograms (Polyribosylribitol Phosphate) conjugated to Tetanus protein 22-36 micrograms † As lower confidence limit (p = 0.95) and not less than 30 IU as mean value ‡ As lower confidence limit (p = 0.95)

	§ Or equivalent activity determined by an immunogenicity evaluation. †† These D-antigen quantities expressed by using optimized parallel line method are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method (sigmoid method).
Route of administration	Intramuscular (IM) injection
Type of registration (EMA/FDA – Local)	Imported

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List of abbreviations

Ag	Antigen
acP	acellular Pertussis
AE(s)	Adverse event(s)
BCG	Bacille-Calmette-Guérin
DTaP	Diphtheria, Tetanus, acellular Pertussis
DU	D antigen unit which measures the amount of inactivated polio virus antigen in each 0.5 mL dose
EMA	European Medicines Agency
FHA	Purified Filamentous Hemagglutinin
GCP	Good Clinical Practice
GMT	Geometric mean of Ab titer
HBsAg	Hepatitis B surface antigen
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
HHE	hypotonic hyporesponsive episode

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IgG	Immunoglobulin G
IU	International unit
IM	Intramuscular
OPV	Oral Poliovirus Vaccine
IPV	Inactivated Vero Trivalent Poliovaccine
PRP-T	Polyribosyl Ribitol Phosphate conjugated to the tetanus protein
rDNA	recombinant Deoxyribonucleic acid
SAEs	serious adverse events
TRS	Technical report series
WHO	World Health Organization
wP	Whole-cell pertussis

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

HEXAXIM is a combined hexavalent vaccine indicated for the active immunization of infants and young children from 6 weeks of age. It provides protection against six serious infectious diseases: diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib). By combining multiple antigens into a single vaccine, Hexacima helps reduce the number of injections while ensuring broad immunological protection as part of routine childhood vaccination programs.

2. **Quality aspects:**

2.2 Introduction

As mentioned in the aforementioned section.

2.3 Drug Substance (Active ingredient)

- **General information**

Hexaxim vaccine is a preservative free liquid formulation for intramuscular administration which combines aluminum hydroxide as adjuvant and six Drug Substances as follows:
• Purified Diphtheria Toxoid (PDT);
• Purified Tetanus Toxoid (PTT);
• 2-component acellular pertussis (purified pertussis toxoid and purified filamentous haemagglutinin);
• Inactivated poliomyelitis trivalent concentrate;
• Hepatitis B surface antigen;
• *Haemophilus influenzae* type b polysaccharide conjugated to tetanus protein.
The vaccine is presented in single-dose type I glass vials or syringes without needle.

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

Manufacturer of Drug Substance: Sanofi Winthrop Industrie 1541 avenue Marcel Mérieux, 69280 Marcy L'Etoile - France.
Sanofi Health Argentina, Calle 8, N◦ 703 (esquina 5), Parque Industrial Pilar - (1629), Provincia de Buenos Aires - Argentina.
Sanofi Winthrop Industrie, Voie de l'Institut Parc Industriel d'Incarville BP 101, 27100 Val de Reuil - France.

Description of Manufacturing Process and Process Controls.

Purified Tetanus Toxoid; The drug substance is the Purified Tetanus Toxoid (PTT), a detoxified protein obtained from Clostridium tetani Harvard 49205 strain.

Conjugated *Haemophilus* b Polysaccharide Bulk; The drug substance is the Conjugated *Haemophilus* b Polysaccharide bulk (PRP-T), covalently bound to a carrier protein, the tetanus protein. These two components are produced, extracted and purified separately using their own seed lot systems and manufacturing processes.

Inactivated Vero Trivalent Poliovaccine Bulk; The cell substrate used for poliomyelitis virus growth at the production stage is the Vero continuous cell line. The virus seed, virus Working Seed Lot (WSL), is inoculated into Vero cells which have been amplified to a suitable volume, to permit active virus propagation.

The Hepatitis B Surface Antigen (HBsAg); is produced by recombinant (DNA) technology. The main stages of the production process of HBsAg are cell culture and harvest (stage 1), purification (stage 2) and maturation (stage 3).

Purified Diphtheria Toxoid; The drug substance is the Purified Diphtheria Toxoid (PDT), a detoxified protein obtained from Corynebacterium diphtheriae. The manufacture of the Purified Diphtheria Toxoid is divided in 3 major manufacturing process stages: fermentation including pre-cultures and industrial culture, harvest, treatment and Detoxification, purification.

Component Acellular Pertussis (FHA-PTxd); The drug substance is composed of two antigenic proteins, the adsorbed purified Pertussis Toxoid (PTxd) and the adsorbed purified Filamentous Haemagglutinin (FHA). These proteins are obtained from Bordetella pertussis.
The manufacture of the 2-component acellular Pertussis is divided into 5 major manufacturing process stages: 1- Fermentation including pre-cultures and industrial culture. 2- Separation of the two antigenic proteins by adsorption chromatography 3- Purification of the two antigenic proteins 4- Detoxification of purified Pertussis Toxin 5- Adsorption on aluminum hydroxide for each purified protein.

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 & Supplier's Certificate of Analysis with reference to internal specifications. IPCs applied during production of pre master, master, working seed bank and their validation are included in details.

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Controls of Critical Steps and Intermediates.
Critical steps and their associated controls throughout the DS manufacturing process have been identified. The submitted information describes the quality control of the intermediates, including the applicable tests, process parameters, and their corresponding acceptance criteria
Process Validation
The DS manufacturing process has been adequately validated based on the submitted process validation data. The identified critical process parameters and applicable quality attributes were evaluated against the predefined acceptance criteria.

- **Control of drug substance:**
  Specification
  The release specification for the DS comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes. The specification has been prepared in line with the requirements of pharmacopeial, WHO and ICH guidelines.
  Analytical Procedures
  The analytical procedures were appropriately referenced. Pharmacopeial procedures were referenced to the applicable Ph. Eur. requirements, while in-house analytical procedures were described. The analytical procedures requiring validation are clearly identified and adequately described.
- **Container closure system**
  Primary closure system is described together with its specification. Suitability of the container closure system has been demonstrated by stability studies.
- **Stability of drug substance**
  - **Approved Shelf-Life:**

    - **Purified Tetanus Toxoid:** 36 months.
    - **Inactivated Vero Trivalent Poliovaccine Bulk:** 24 months
    - **2-Component Acellular Pertussis (FHA-PTxd):** 48 months
    - **Conjugated *Haemophilus* b Polysaccharide Bulk:** 36 months
    - **Purified Diphtheria Toxoid:** 36 months
    - **Hepatitis B surface Antigen:** Stored at +5°C ± 3°C for a maximum of 30

    Approved Storage Conditions:

    - **Purified Tetanus Toxoid:** (2°C - 8°C).
    - **Inactivated Vero Trivalent Poliovaccine Bulk:** (2°C - 8°C).
    - **2-Component Acellular Pertussis (FHA-PTxd):** (2°C - 8°C).
    - **Conjugated Haemophilus b Polysaccharide Bulk:** Storage at ≤ -35°C.
    - **Purified Diphtheria Toxoid:** (2°C - 8°C).

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- **Hepatitis B surface Antigen:** (2°C - 8°C).

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  The six Drug Substances consist of the following: Purified Diphtheria Toxoid (PDT), Purified Tetanus Toxoid (PTT), 2-component acellular pertussis (purified Pertussis Toxoid (PTxd) and purified Filamentous Haemagglutinin (FHA)), Inactivated Poliomyelitis Virus (IPV), Hepatitis B surface Antigen (HBsAg) and *Haemophilus influenzae* type b polysaccharide conjugated to Tetanus protein (PRP-T). The excipients of the Drug Product are aluminum hydroxide (as adjuvant), phosphate buffer (composed of disodium hydrogen phosphate, potassium dihydrogen phosphate, essential amino acids, trometamol and saccharose),and water for injection.

- **Pharmaceutical Development**
  Formulation Development
  The Final Bulk Product is prepared by sequential addition of Drug Substances and excipients in a specific order to achieve a homogeneous and consistent formulation.
  Manufacturing Process Development.
  The selection and optimization of the manufacturing process of Hexaxim Drug Product are clearly presented in MA file, for the Final Bulk Product (FBP) and the Final Product (FP) stages as well as the comparability study between the initial and the optimized formulation.
  Container closure system.
  Hexaxim vaccine is presented in single-dose glass vials or syringes without needle.
- **Manufacture of the drug product:**
  Component Preparation, Final Bulk Product Formulation, Final Bulk Product Storage (Before Filling) and filling into vials or syringes are the main manufacturing stages. The critical steps are monitored by process parameters applied to ensure that all quality attributes of manufactured vaccine met the acceptance criteria. All results obtained with the optimized formulation batches meet these acceptance criteria.
- **Product specification:**
  The specifications and justifications used to control the Final Bulk Product (FBP) and the Filled Product (FP) are clearly illustrated in MA file.
- **Container closure system.**
  Glass container (vials and syringes) in type I grade; Elastomeric closures: synthetic isoprene-bromobutyl tip cap and, bromobutyl plunger stopper for syringes; and bromobutyl stopper for vials.

- **Stability of the drug product.**
  Based on available stability data,
  Approved Storage Conditions:

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- Refrigerator (2°C - 8°C)
- Do not freeze.
- Shake the pre-filled syringe so that the contents become homogenous.
- Protect From Light.

Approved Shelf-Life: 48 months.

3. Non –clinical aspect:

- HEXAXIM (DTaP-IPV-HB-Hib) is a fully liquid pediatric vaccine. It is adjuvanted with aluminium hydroxide and contains six antigens [Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed)]. HEXAXIM is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b. It offers a practical solution to the increasing complexity of paediatric immunization schedules by reducing the number of injections and minimizing administrations errors. HEXAXIM received initial European marketing authorization approval in April 2013, backed by EMA.

- **Pharmacology:** Non clinical immunogenicity should address interference between antigens according to WHO guidelines on nonclinical evaluation of vaccines. Within the HEXAXIM formulation, HBsAg and PRP-T Haemophilus influenzae type b antigen were the two antigens identified as the most susceptible to antigenic interference based on literature review. A study, looked at how well the two important vaccine ingredients (HBsAg and PRP-T) work when combined in a single vaccine called HEXAXIM, was carried out. This study was conducted in mice. The results indicated that no significant negative interferences on immunogenicity were observed between HBsAg and PRP-T, formulated without or with the other antigens of the hexavalent combination, in the presence or absence of aluminium hydroxide. On the contrary some benefits of mixing these antigens were observed for both PRP-T and HBsAg specific immune responses. The aluminium hydroxide helped boost the response to HB, but did not have much effect on the response to Hib. After 3 immunizations, specific IgG antibodies against both antigens were induced and remained high (HBsAg) or significant (PRP-T) for at least 16 weeks.

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

- **Toxicology:** In a repeated dose toxicity study in New Zealand White Rabbits, five IM injections of HEXAXIM at 2-week intervals did not result in toxicologically relevant changes in mortality, clinical observations, body weights, body weight gains, food consumption, or organ weights. Treatment did result in a slightly increased level of Draize observations following the last injection, variations in some clinical pathology parameters probably linked to the inflammatory

and immune reactions induced by a vaccine which are generally reversible, and gross pathology findings at the injection sites associated with histopathology findings of inflammation still observed at the end of a two-week treatment-free period.

- In a repeated dose toxicity & local tolerance study, five IM injections of HEXAXIM vaccine at 2-week intervals were clinically well tolerated in rabbits. Toxicological findings were restricted to a persistent inflammatory reaction at the injection sites associated with a transient increase in neutrophil counts & stimulation of the lymphoid tissues. These observations are consistent with the results typically recorded after the administration of an aluminum hydroxide adjuvanted vaccine.
- In a local tolerance study, four IM injections of three batches of the vaccine at 2-week intervals were clinically well tolerated in the female rabbits. Toxicological findings were confined to inflammatory reactions at the injection sites with an increase in neutrophil counts noted one day after the last injection. There was no sign of reversibility 30 days after treatment, and the inflammatory reactions were slighlty less severe with one batch than with the two other batches.

- **Overall conclusion:** The nonclinical profile of HEXAXIM vaccine suggests that the vaccine can safely and effectively combine these ingredients without weakening the body's protection against either disease.

4. Clinical aspect:

➢ **Clinical Overview**

Hexaxim has been investigated in **12 main studies** conducted in **four continents**, involving children of various ethnicities aged between **six weeks** and **two years**. The children received either Hexaxim or a comparator vaccine, with **3,424** children receiving **three doses** of **Hexaxim** and **1,511** of them receiving a **booster dose**. The **two-dose** vaccination schedule was investigated in an additional **main study** involving **554** children who either received **Hexaxim** or a **comparator** vaccine, when given as a **two doses** schedule followed by **a booster 6 months** later.

The studies compared levels of **protective** antibodies produced following vaccination with **Hexaxim** with the **levels** produced following vaccination with **comparator** vaccines.

➢ **Clinical Efficacy**

Clinical studies demonstrated that Hexaxim induced protective immune responses against all six vaccine antigens following primary vaccination and booster immunization.
Across all studies:

- Seroprotection rates exceeded 93% for diphtheria, tetanus, hepatitis B, poliovirus types 1–3, and Hib following completion of the primary vaccination series.
- Booster vaccination induced strong anamnestic immune responses, demonstrating effective immune priming.
- Although geometric mean antibody titres (GMTs) for some antigens were numerically lower than those observed with certain comparator vaccines, seroprotection thresholds recommended by WHO were consistently achieved, and these differences were not considered clinically relevant.
- The vaccine induced immune responses comparable to licensed combination vaccines across different vaccination schedules and populations.

The clinical evidence supports the effectiveness of Hexaxim for primary and booster immunization against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Hib disease.

➢ **Clinical Immunogenicity**

Hexaxim demonstrated robust immunogenicity against all six vaccine antigens following both primary and booster vaccination.

High seroprotection or seroconversion rates were achieved for diphtheria, tetanus, hepatitis B, poliovirus types 1–3, and Hib across all clinical studies. For pertussis, immune responses were comparable with licensed acellular pertussis-containing combination vaccines.

Booster vaccination produced marked increases in antibody concentrations, confirming effective immune priming after the primary vaccination series.

Although antibody geometric mean titres for some antigens were lower than those observed with certain comparator vaccines, established protective thresholds were consistently achieved and no clinically relevant differences in protection were identified.

➢ **Clinical Safety**

The safety profile of Hexaxim was evaluated in **12 clinical studies** involving more than **3,400 infants and toddlers**, supported by an integrated safety analysis of 11 studies. Overall, Hexaxim demonstrated an acceptable and well-characterized safety profile consistent with that of licensed combination pediatric vaccines.

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The most frequently reported adverse reactions were expected local and systemic reactions following vaccination, including **injection-site pain, redness, swelling, irritability, crying, and pyrexia**. Compared with some licensed comparator vaccines, Hexaxim showed **slightly higher reactogenicity** for solicited local and systemic adverse reactions compared with Pentaxim + Engerix and Infanrix hexa, particularly with respect to injection-site reactions. A higher frequency of injection-site reactions and pyrexia was also observed when Hexaxim was co-administered with Prevenar compared with Infanrix hexa + Prevenar. Conversely, Hexaxim demonstrated **lower reactogenicity than Hexavac**. These differences were generally mild to moderate in severity, transient, and considered clinically acceptable.

Rare cases of **hypotonic hyporesponsive episode (HHE)** and **extensive limb swelling (ELS)** were reported, including one HHE occurring 7 hours after the first Hexaxim dose and two cases of ELS. These events are recognized risks associated with combination pediatric vaccines and were consistent with the established safety profile of vaccines containing similar antigens.

No anaphylaxis meeting the **Brighton Collaboration** case definition was identified. A total of **15 related hypersensitivity events** were reported in 14 subjects, primarily consisting of mild injection-site allergic reactions (e.g., rash, pruritus, urticaria, dermatitis, and vesicles) and mild systemic skin reactions. Most events occurred within three days of vaccination, resolved within eight days, and were predominantly Grade 1 in severity. The frequency of hypersensitivity reactions was **3.6 per 1,000 subjects (12.4 per 10,000 doses)**, with no clinically meaningful differences observed between males and females.

Although **11 deaths** occurred among subjects who received Hexaxim during the clinical development program, **none were considered related to vaccination**. The clinical safety database included fewer than 4,000 subjects and therefore was considered adequate to characterize very common, common, and uncommon adverse events, while continued post-marketing surveillance remains important for detecting rare and very rare adverse events. Furthermore, limited data are available in certain populations, including premature infants, immunocompromised individuals, and children with significant chronic medical conditions.

Overall, the available clinical evidence indicates that **Hexaxim is well tolerated and has a favorable safety profile**, with no unexpected safety concerns identified and an acceptable balance between reactogenicity and clinical benefit.

- **Benefit-Risk Assessment**

The submitted clinical evidence demonstrates that Hexaxim provides robust immune responses against all six vaccine antigens while maintaining an acceptable and well-characterized safety

profile. Although slightly higher reactogenicity was observed for some local and systemic reactions compared with certain comparator vaccines, these events were predominantly mild to moderate and consistent with the known safety profile of combination pediatric vaccines.
Overall, the demonstrated clinical benefits of protection against six serious childhood infectious diseases outweigh the identified risks, resulting in a favorable benefit–risk balance.

- **Overall Conclusion**

The submitted clinical data demonstrate that Hexaxim is immunogenic, effective, and well tolerated for primary and booster immunization of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive *Haemophilus influenzae* type b disease.
Protective immune responses were consistently achieved for all vaccine antigens, booster vaccination induced strong immune memory, and the overall safety profile was consistent with that of licensed combination pediatric vaccines. Based on the available evidence, the overall benefit–risk balance of Hexaxim is considered favorable for the approved indication.

5. General Conclusion and Recommendations if any:

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