EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Healive

Date: October 2024

Unit: Technical Assessment Unit

Assessment report

Healive

Administrative information:

Invented name of the medicinal product:	Hepatitis A Vaccine (human Diploid Cell), inactivated, injection; Healive.
INN (or common name) of the active substance(s):	Inactivated hepatitis A virus (HAV) antigen
Marketing Authorization holder	Sinovac Biotech Co., Ltd., No. 39 Shangdi Xi Road, Haidian District, Beijing-China
Applied Indication(s):	Healive 1.0 ml dose is indicated for active immunization against infection caused by hepatitis A virus in susceptible adults and adolescents of 16 years of age and above, and 0.5 ml dose in children over 1 but below 16 years old
Pharmaceutical form(s) and strength(s):	- Single Adult dose vial of 1 ml suspension - Single Pediatric dose of 0.5 ml suspension
Route of administration	Suspension for intramuscular injection
Approved pack(s)	**Adult:** One box containing 1 vial tubing made of neutral borosilicate glass with chlorobutyl rubber stopper and sealed with aluminum cap & insert leaflet **Pediatric:** One box containing 1 vial tubing made of neutral borosilicate glass with chlorobutyl rubber stopper and sealed with aluminum cap & insert leaflet

List of abbreviations

ALT	Alanine aminotransferase
HAV	Hepatitis A Virus
IgM	Immuno-globulin M
GMC	Geometric Mean Concentration
mIU/mL	milli-international units per milliliter
SD rats	Sprague Dawley rats
CTD	Common technical document
SOP	Standard operating procedures
WHO	World Health Organization
NIBSC	National Institute for Biological Standards and Control
AI	Active ingredients
QC	Quality control
MOA	Method of analysis
UV	Ultra violet
COA	Certificate of analysis
TSE	Transmissible Spongiform Encephalopathies
BSE	Bovine spongiform encephalopathy
UV	Ultraviolet
HPLC	High performance (pressure) liquid chromatography
SDS-PAGE	Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis
ELISA	Enzyme Linked Immunosorbent Assay
ICH	International Council for Harmonisation
MA	Marketing Authorization

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 21.9.2020 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

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

Hepatitis A Vaccine (Human Diploid Cell), Inactivated is a viral vaccine with ATC code of J07BC02. For the production drug substance, hepatitis A virus (HAV), TZ84 strain, is grown in human diploid cell (2BS strain) cultures. After cultivation and harvest, the virus suspension is purified and inactivated. After inactivation, the qualified virus bulk shall be diluted to an antigen concentration of 500 u/ml after the adsorption of aluminum hydroxide, and then it shall be defined as the final bulk. For the filling of final bulk, it can be divided into 2 kinds: pre-filled syringe and vial. After filling and packaging, it comes to the final product. 1.0 ml dose is indicated for active immunization against infection caused by hepatitis A virus in susceptible adults and adolescents of 16 years of age and above, and 0.5 ml dose in children over 1 but below 16 years old. It should be administered by intramuscular injection in the deltoid region. In order to provide long-term protection, a second dose (booster) should be given. The second dose is preferably given 6-12 months after the first dose (WHO position paper on hepatitis A vaccines – June 2012). Healive vaccine® was launched in China in 2002 and is exported to a number of countries in Southeast Asia (Ex. China, Mongolia, Bangladesh) and Central and South America (Ex. Chile). Healive vaccine® (Adult & pediatric) is a prequalified vaccine by WHO, effective 22/12/2017.

2. Quality aspects:

2.2.1 Introduction

Healive vaccine® is a viral vaccine indicated for active immunization against infection caused by hepatitis A virus in susceptible adults and adolescents of 16 years of age and above (1 ml dose), and in children over 1 but below 16 years old (0.5 ml dose).

2.2.2 Drug Substance (Active ingredient)

- **General information**

Inactivated HAV antigen bulk is a colorless transparent liquid. The active substance is the inactivated HAV antigen. Under Direct electron microscope and immunoelectron microscope : Viral particles of 27-30 nm in diameter are detected, solid or hollow, with the typical morphology of hepatitis A virus

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

Manufacturer:

Manufacturer: Sinovac Biotech Co., Ltd. Address: No.39 Shangdi Xi Rd., Haidian District, Beijing-100085, P.R. China Responsibility: Production of bulk, testing of relevant in-process products and materials.

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

- For the production drug substance, hepatitis A virus (HAV) is grown in human diploid cell (2BS strain) cultures. After cultivation and harvest, the virus suspension is purified and inactivated, which is defined as the vaccine bulk
- All process steps and materials controls are well described.

- **Control of Materials**

-Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

-Specifications and supplier / manufacturer details are provided for all raw materials used in the production of inactivated HAV bulk. In addition, methods of analysis (MOA) for materials were mentioned. CoAs for materials were provided as well. TSE/BSE Freedom statements are provided for materials of animal origin

- **Controls of Critical Steps and Intermediates**

-Quality-control (QC) release tests performed on the intermediates isolated during the manufacturing process of the drug substance as well as the specifications employed and the Methods of analysis (MOA) were described in detail. In addition, CoAs of virus harvest are provided.

- **Process Validation**

Process Validation on Inactivated Hepatitis A Vaccine Bulk was attached.

- **Manufacturing Process Development.**

- The hepatitis A vaccine production mainly includes the virus replication, purification and inactivation. Passage 10-30 of TZ84 virus is capable for the production of hepatitis A vaccine and the yield of antigen is 5000-6000 u/ml, and the cultivation period is around 14 days
- The virus can be purified through different normal methods, including chemical and physical methods, such as chemical precipitation, ultra-centrifugation, ion exchange, gel-filtration and ultrafiltration. PEG6000 precipitation, chloroform exaction were employed for the primary purification and gel-filtration (S-400) and ultra-filtration were co-employed for the further purification process
- Regarding the inactivation process, different concentrations of formaldehyde and different inactivation time have been studied during the process development process. The further purified hepatitis A virus could be completely inactivated. Following the inactivation, ultra-filtration was employed to remove the formaldehyde and then the bulk of vaccine is obtained

- **Characterization**
- **Elucidation of structure and other characteristics**

The characterization Hepatitis A antigen comprised the following aspects:
Characterisation of Purified harvest by: - Direct electron microscope and Immunoelectron microscope - UV absorption - HPLC - SDS-PAGE 2. Characterization of Inactivated Harvest / Bulk by: - Lowry method - ELISA for antigen content and validation of virus inactivation - ELISA for determination of residual bovine serum albumin

- **Impurities**

The impurities are verified to be removed in the process validation reports, and the residuals controlled in process.

- **Specification**

The release specification for the active substance comprises tests for purity and impurities, potency, quantity, microbiological attributes and general attributes.
The specification has been prepared in line with the requirements of requirements of ICH guideline Q6B. The specification takes into account the critical quality attributes (CQAs) of the active substance that can affect the safety and efficacy of the product, and defines the acceptable range for the physicochemical and biological characteristics of the active substance within the context of the wider control strategy.

- **Analytical Procedures**

Fully detailed analytical procedures for the tests performed on vaccine bulk are provided.

- **Batch analysis**

Commercial batches representing process validation analyses data were submitted and their results comply with specification sheet and defined acceptance criteria.

- **Reference Standards or Materials**

- WHO International Standard, Hepatitis A Vaccine Inactivated 1st International Standard 1999, NIBSC Code: 95/500, Specification: 1.0 g, the labeled amount: 100 IU/ml and manufacturer: National Institute for Biological Standards and Control (NIBSC). Report for preparation and standardization of in house HAV antigen reference standard used for inactivated harvest testing was attached.

- **Container closure system**

AllegroTM 10 L single use containers are applied for the storage of vaccine bulk.

- **Stability of drug substance**

Based on available stability data

✓ Approved Shelf Life: 9 months
✓ Approved Storage Conditions: 2-8°C

2.2.3 Drug product:

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

Hepatitis A Vaccine (Human Diploid Cell), Inactivated is a sterile suspension for intramuscular injection with two dosages: 1.0 ml dose for adult use and 0.5 ml dose for pediatric use.

- Each 1.0 ml of Hepatitis A Vaccine (Human Diploid Cell), Inactivated in vial contains components as follows:

Name of Ingredient	Amount	Function	Criteria
Active Substance			
Inactivated HAV antigen	500 u	Active ingredient	
Other Ingredients			
Aluminum hydroxide	1.25 mg	Adjuvant	*Chinese Pharmacopoeia*
Disodium hydrogen phosphate	q.s.(1)	Buffering agent	
Sodium chloride	9 mg	Buffering agent	
Sodium dihydrogen phosphate	q.s.(2)	Buffering agent	
Water for injection	1.0 ml	Diluent	

- Each 0.5 ml of Hepatitis A Vaccine (Human Diploid Cell), Inactivated in vial contains components as follows:

Name of Ingredient	Amount	Function	Criteria
Active Substance			
Inactivated HAV antigen	250 u	Active ingredient	
Other Ingredients			
Aluminum hydroxide	0.625 mg	Adjuvant	*Chinese Pharmacopoeia*
Disodium hydrogen phosphate	q.s.(1)	Buffering agent	
Sodium chloride	4.5 mg	Buffering agent	
Sodium dihydrogen phosphate	q.s.(2)	Buffering agent	
Water for injection	0.5 ml	Diluent	

- **Pharmaceutical Development**
  - **Components of drug product**

-The drug substance of hepatitis A vaccine is inactivated hepatitis A virus,
-The excipients of hepatitis A vaccine are aluminum hydroxide as adjuvant, sodium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate and water for injection.

  - **Formulation Development**

Detailed description of formulation process, drug product component, active ingredient and excipient is provided. During the formulation process, the major production step is to employ the adjuvant involved in final formula of vaccine.

  - **Physicochemical and Biological Properties**

In Healive, antigen is the active substance and the adjuvant enhances immune response, meanwhile, antigen is adsorbed on the adjuvant, therefore, key factor is pH adjustment during the mixing process, which adjusts the formation of aluminium hydroxide.

  - **Manufacturing Process Development**

Detailed description of manufacturing process development was submitted.

  - **Microbiological Attributes**

The manufacturing process of adsorption and formulation is conducted in sterilized close system including formulation tank and single-use bag. Meanwhile, studies on media fills are conducted to validate the aseptic status. The integrity of closure system for final lot are tested (sealing test) before being released to use.

  - **Compatibility**

The compatibility study of the drug product was conducted via simulated test and interactions; Simulated test results complied with the requirements. Results of the influence of container to product quality complied with the requirements and no influence was made to the product quality by the container. Results of the influence of product to the container showed that no influence was made to the container by the product

- **Manufacture of the drug product:**

  - **Description of manufacturing process and process controls along with manufacturers and responsibilities.**

- **Manufacturer**:

Manufacturer:	Sinovac Biotech Co., Ltd.
Address:	No.15, Zhi Tong Road, Changping Science Park, Changping District, Beijing

-The manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.
- The qualified virus bulk shall be diluted to an antigen concentration of 500 u/ml after the adsorption of aluminum hydroxide, and then it shall be defined as the final bulk. After filling and packaging of the final bulk, it comes to the final product of Hepatitis a Vaccine (Human Diploid Cell), Inactivated.

- **Control of critical steps and intermediates**

Adsorption and Formulation Tests carried out as per the monograph of Hepatitis A Vaccine (Human Diploid Cell), Inactivated in current Chinese Pharmacopoeia. Control on final bulk and Methods of analysis (MoA) for the final bulk are provided. In addition, CoAs for final bulk are attached.

- **Process validation and / or evaluation**

Validation reports on final bulk production and filling into final product are provided.

- **Product specification:**

The specifications for the routine Quality control release of Hepatitis A virus (HAV) vaccine, at final bulk and final container levels, are described

- Materials applied as excipients in the formulation of final bulk include aluminum potassium sulfate, sodium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate and sodium chloride. These are compendial excipients and comply with the Chinese Pharmacopoeia

-These components are controlled and tested to the standards appropriate for their intended use and function.
- Process-related impurities arising during the manufacturing process of HAV vaccine are clearly described in the MA file. The impurities are verified to be removed in the process validation reports, and the residuals shall be controlled in process. The analytical procedures currently used in testing for impurities are illustrated

- **Reference Standards or Materials.**

The reference standard is qualified to serve for release and stability assays for both drug substance and drug product.

- **Container closure system**
  100 L and 200 L single use containers are applied for the storage of vaccine final bulk. Specification and analytical methods (MoA) are mentioned. - 2 packaging forms are available for Hepatitis A Vaccine (Human Diploid Cell), Inactivated. - Primary packaging components are: Assemblages for Prefilled Syringe with Stainless Steel Needle, Injection Vial and Stopper for Injection - The non-functional secondary packaging components are: Cap, Label, Package Insert and Inner Box.

- **Stability of the drug product**

-Based on available stability data,

- ✓ Approved Shelf Life: 42 months
- ✓ Approved Storage Conditions: Store and ship between 2°C -8°C, (protected from light. Do not freeze).

3. Non –clinical aspect:

1. Non –clinical aspect:

Hepatitis A Vaccine (Human Diploid Cell), Inactivated is a viral vaccine produced from hepatitis A virus (HAV), TZ84 strain that was grown in human diploid cell cultures. After cultivation and harvest, the virus suspension is purified and inactivated. After inactivation, the qualified virus bulk shall be diluted to an antigen concentration of 500 U/ml after the adsorption of aluminum hydroxide adjuvant.

- **Pharmacology:**

- The immunogenicity and toxicity of Healive® have been investigated in a non-clinical study in macaca mulatts and common marmosets using two doses vaccination schedule (1000 u/dose). The immunogenicity of Healive® has been evaluated and the potential of the vaccine to protect the monkeys against challenge with wild hepatitis A virus was assessed.

Two weeks after one dose vaccination of Healive®, anti-HAV seroconversion was observed on both macaca mulattas and common marmosets. The antibody concentration was 625 to 2500 mIU/ml four weeks after single-dose vaccination. Regarding IgM antibody, the seroconversion occurred two weeks or three weeks after single dose vaccination, with the highest titer as 1:1000. The seroconversion of anti-HAV IgM lasted 5-10 weeks on common marmosets, and 1-3 weeks on macaca mulattas. Two weeks after the second dose vaccination, the anti-HAV antibody concentration reached 10000-40000 mIU/ml. There is no abnormal increase of ALT and pathological changes in the livers of both macaca mulattas and common marmosets observed during this test. Two weeks after challenging, there was no abnormal ALT increasing

and pathological changes on livers observed during this test. The HAV was not detected in the feces.

- **Toxicology:**

- The potential toxicity of Healive® was also investigated through a long-term toxicity study on SD rats. Inactivated Hepatitis A vaccine (HAV), was administrated by intramuscular injection to SD rats at a dose level of 500 U/rat four times (once per three weeks) with 3 weeks of recovery.

There is no animal died during this study. No abnormalities of clinical signs were observed in any treated animals or control animals during this study. No test article-rated significant body weight/temperature changes were observed. No change in food consumption was found in any of the animals during this study. No abnormalities were found from clinical laboratory studies (hematology, serum chemistry, immunity function, urinalysis, and bone marrow smear) from any of the animals. Inflammatory granuloma was observed in the injection site for some animals in vehicle and HAV groups. It was considered to be vehicle-relate. No other treatment-related changes were observed.

Overall conclusion: Due to the wide clinical experience and well-established safety and efficacy of inactivated hepatitis A vaccines. Healive®, with a similar production process and formula, shall have similar safety and immunogenicity profiles to the previously well-developed hepatitis A vaccine. Two doses vaccination schedule of Healive® could induce good protection for both macaca mulatts and common marmosets from the hepatitis A virus challenging. No potential toxicity risk was found in the long-term toxicity study on SD rats.

Thus, the non-clinical programme for Healive® ***is overall acceptable.***

2. Clinical aspect:

Clinical Efficacy

- The immunogenicity results have shown that 500u or 250u of this vaccine is highly immunogenic in healthy adults and children, conferring protective immunity against the disease 4 weeks after first administration.
- After full immunization with Healive®, the seroconversion rates of anti-HAV antibody were all 100% from 1-4 years. In the fifth year, the seroconversion rates were 97.3%-100.0% and GMC of anti-HAV antibody were high level among all groups.
- Comparing the immunogenicity of Healive® with imported inactivated hepatitis A vaccine, Havrix (720 EU, GlaxoSmithKline), the excellent and similar immunogenicity of the two vaccines has been demonstrated.
- Inactivated hepatitis A vaccine was applicable as booster for live attenuated hepatitis A vaccine and accepted immune response was induced at vaccination interval of 6-12 months.
- Vaccination can be accomplished using the same vaccine for both doses or a combination of vaccines may be administered.

Clinical safety:

- Data of clinical trials and post-marketing surveillance indicated that most adverse reactions of Healive® are mild and moderate. Serious adverse reactions are rarely and the causality with vaccination of some report cases can‘t be determined as well.
- Based on the cumulative global experience, the overall safety profile of all formaldehyde-inactivated hepatitis A vaccines administered to children (aged 1 to <15 years) and adults has been excellent, irrespective of schedule and manufacturer. No serious adverse events could be conclusively linked to hepatitis A vaccines. Inactivated hepatitis A vaccines were well tolerated in patients with mild to moderate chronic liver disease. Crossover immunization between inactivated vaccines appears to be well tolerated. The safety of hepatitis A vaccine during pregnancy has not been established but no evidence of risk has been documented either. Since the vaccine is prepared from inactivated virus the theoretical risk to the developing fetus is likely to be negligible.

Benefit/ Risk discussion:

In conclusion the overall benefit/risk assessment of Healive vaccine is favorable in the indication of active immunization against infection caused by hepatitis A virus in adults and children.