Unit: Technical Assessment Unit

Public assessment report for biological products

(Rabies vero cell)

Administrative information:

Trade name of the medicinal product:	Rabies vaccine for Human use (vero cell) freeze dried
INN (or common name) of the active substance(s):	Purified and inactivated rabies whole virus existed in the form of purified bulk.
Manufacturer of the finished product	-Liaoning Cheng Da Biotechnology Co., Ltd, Shenyang, China - Egyptian Company for Production of Vaccines , Sera and Drugs (EGYVAC)- VACSERA, 51 Wezaret El Zeraa Street , Agouza , Giza , Egypt.
Marketing Authorization holder	In Country of origin : Liaoning Cheng Da Biotechnology Co., Ltd, Shenyang, China In Egypt : Egyptian Company for Production of Vaccines , Sera and Drugs (EGYVAC), 51 Wezaret El Zeraa Street , Agouza , Giza , Egypt.
Applied Indication(s):	The product can induce immunity against rabies virus in recipients following immunization ,it is used to prevent rabies in human.
Pharmaceutical form(s) and strength(s):	Lyophilized powder for reconstitution, Purified vero cell rabies antigen, inactivated ≥2.5IU/dose
Route of administration	IM injection
Type of registration (EMA/FDA – Local)	Local

List of abbreviations

MA file:Marketing authorization file
WHO :World health organization
CP: Chinese pharmacopeia

Ab	Antibody
CDBIO	Cheng Da Biotechnology Co., Ltd.
CVS	Challenge Virus Standard
D	Day
GCP	Good Clinical Practice
GMT	geometric mean antibody titer
IU	International unit
IM	Intramuscular(ly)
ID	Intradermal(ly)
IV	Intravenous(ly)
NIH method	A method in which a known, calibrated standard reference serum used in a standardized immunological assay to measure the potency of Abs
PCE	Polychromatic Erythrocytes
RVNA	rabies virus-neutralizing antibodies
SC	Subcutaneous(ly)
MA file:	Marketing authorization file
WHO	World health organization
CP	Chinese pharmacopeia
RNP	ribonucleoprotein
RNA	Ribonucleic acid

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

Rabies virus belongs to the order Mononegavirales, viruses with anonsegmented, negative-stranded RNA genomes. Within this group, viruses with a distinct "bullet" shape are classified in the Rhabdoviridae family, Rhabdoviruses are approximately 180 nm long and 75 nm wide. The rabies genome encodes five proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and polymerase (L). All rhabdoviruses have two major structural components: a helical ribonucleoprotein core (RNP) and a surrounding envelop. In the RNP, genomic RNA is tightly encased by the nucleoprotein. Two other viral proteins, the phosphoprotein and the large protein (L-protein or polymerase) are associated with the RNP. The glycoprotein forms approximately 400 trimeric spikes which are tightly arranged on the surface of the virus.
Rabies vaccine for human use (vero cell) Freeze dried looks like a white crisp cake. The reconstituted vaccine is a clear liquid, free of foreign matters, The vaccine is filled in the sterilized injection vial (neutral borosilicate glass), which is stoppered with brominated butyl rubber closure and sealed with aluminium-plastic multi-cap. All of containers and closures are pharmaceutical grade.

2. Quality aspects:

2.1.Introduction

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2.2.Drug Substance (Active ingredient)

- **General information**

- Nomenclature

-INN: Purified and inactivated rabies whole virus existed in the form of purified bulk

-Structure

-Rabies virus belongs to the order Mononegavirales, viruses with a nonsegmented, negative-stranded RNA genomes. Within this group, viruses with a distinct "bullet" shape are classified in the Rhabdo viridae family

- General Properties

- The general properties for (Purified and inactivated rabies whole virus existed in the form of purified bulk, CDBIO) are listed in the MA file .

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

- Description of Manufacturing Process and Process Controls.

Manufacturer: M/s. Liaoning Cheng Da Biotechnology Co., Ltd No. 1, Xinfang Street, Hunnan New District, Shenyang City, China

- The detailed manufacturing process is mentioned in the MA file along with flow diagram

- **Control of Materials.**
- List of starting materials used in the manufacturing process is provided along with quality control testing .

-- information regarding the used cell line & cell banking is mentioned in detail in the MA file.

- -- Biologically-sourced materials (their suitability for intended use including clearance or control of adventitious agents), Their specific use in the process and TSE/BSE risk evaluation are described in the dossier
- **Controls of Critical Steps and Intermediates**.

- Critical process steps and critical process parameters are mentioned in the manufacturing process .-The process controls selected for each critical manufacturing step and the acceptance criteria are provided in the MA file .
- **Process Validation**
- The process validation activities were carried out at various stages of the bulk manufacture and were submitted in the CTD
- Manufacturing Process Development.
- The developmental history of the manufacturing process is sufficiently described in the MA file .

- **Characterization.**

-Characterization tests are described in the MA file.
-The manufacturer presented clearance data for several identified impurities.
-The applied methods for detection of impurities have been described and specifications have been presented in the dossier

- **Specification**

The tests performed on the drug substance comply with the requirements of ICH Q6B guideline, USP, Ph. Eur, and In-house practices

- **Reference Standards or Materials.**

- National Standard for Bacterial Endotoxin and National Standard for Protein were manufactured by National Institute for the Control of Pharmaceutical and Biological Products (NICPBP).
- Certificate of analysis & instructions of use for reference standards are presented.
- Reference materials used in the QC testing together with supportive information on their stability is provided.

- **Container closure system**

-The drug substance is filled into the pre-sterilized purification tank before further processing, which is suitable for the storage of sterile product.
-The purification tank is stainless steel tank.

- **Stability of drug substance**

- Store at 2-8 °C for 30days

2.2.3 Drug product:

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

The freeze-dried vaccine looks like a white crisp cake, The reconstituted vaccine is a clear liquid, free of foreign matters
The accompanying reconstitution diluent is sterile water for injection.
Composition Each single dose 0.5 ml
Purified Rabies Virus Antigen ≥ 2.5 IU
Human Serum Albumin ≥ 5.0 mg

(Rabies verocell/*≥2.5IU/dose*)

Dextran 40	18.0 mg
PBS q.s	
Sodium Dihydrogen Phosphate di hydrate	0.15mg
Disodium Hydrogen Phosphate Dodecahydrate	0.54mg
Sodium Chloride.	4.25 mg

- Pharmaceutical Development:

-The drug substance is presented as purified and inactivated rabies whole virus existed in the form of purified bulk, The final concentration of human serum albumin in the Drug product is more than 5.0 mg/dose, which is as stabilizer to maintain the potency of Drug product
The product development has been adequately described in the MA file .

- Physicochemical and Biological Properties

The product properties have been adequately described in the MA file

- Container closure system and their compatibility.

The packaging materials are of pharmaceutical grade and are widely used in the pharmaceutical industry.

-it is concluded that the packaging method and packaging materials are suitable for the storage, transportation and usage.

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- Compatibility.

- The compatibility of drug substance with excipients and the compatibility of drug product and the accompanied diluent for reconstitution was adequately described in the MA file.

- **Manufacture of the drug product:**

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

-Manufacturer: M/s. Liaoning Cheng Da Biotechnology Co., Ltd No. 1, Xinfang Street, Hunnan New District, Shenyang City, China

- Egyptian company for production of vaccines , sera and drugs, 51 Wezarat el zeraa street, Agoza, Giza, Egypt

-A flow chart of the manufacturing process is presented, including all the steps in the process. The points at which the material enters the process, the critical steps and control points in the process are presented. Intermediate products, final product, the in-process controls, and the critical points are identified

- Control of critical steps and intermediates

- All critical steps are carried out under validated conditions, and monitored according to Good Manufacturing Practice (GMP) standards. Process parameters and controls are established to ensure consistent product quality throughout the manufacturing cycle.

- Process validation and / or evaluation.

--The process validation rabies vaccine have been demonstrated
-The demonstration of process consistency for at least 3 consecutive batches that show compliance with the pre-established quality specifications.

- **Product specification:**
  - Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.

  -The specifications for the routine release are described in the file
  - -Excipients are mentioned in the dossier along with their specifications, and their references.
  - Excipients are all pharmacopoeial excipients.
  - drug product align with CP and WHO .
  - **Reference Standards or Materials.**

    The National reference standards used in the testing of ***(Rabies Vaccine for Human Use (Vero cell), Freeze-dried, CDBIO)*** final containers are listed in the submitted file. along with their instructions of use.
    - **Stability of the drug product.**

    The approved shelf life of the drug product is 36 months in the country of origin and 2years in Egypt when stored at 2-8°C.

1. **Non –clinical aspect:**

➢ SPEEDA is an inactivated Rabies vaccine (Vero cells) freeze-dried. The vaccine is a preparation of rabies fixed virus produced on Vero cells, after the virus suspension is harvested followed by concentration, inactivation, purification and lyophilization. The vaccine is formulated by adding human serum albumin and dextran. Within the period of validity, the potency of one dose is not less than 2.5 IU. It can induce immunity against rabies virus in recipients following immunization and is used to protect against rabies. This product was granted approval by the Chinese State Food and Drug Administration in 2004.

➢ **Pharmacology:** As far as vaccine product is concerned, pharmacological studies usually focus on antigenicity and immunogenicity of this kind of pharmaceutical. Antigenicity test: NIH method was used for testing the immunogenicity on the vaccine product. The qualified immune potency should be not less than 2.5 IU/dose. After test, the immune potency of 3 consecutive batches of Rabies vaccine produced by CDBIO is higher than 2.5 IU/dose (4.6, 4.5 & 4.8 IU/dose), which indicated that the immunogenicity of the vaccine has reached the national standard. Immunogenicity Test*:* 0.5 ml of Rabies vaccine was inoculated IP into each of 40 mice with on D 0 and D 7, respectively. A positive control group is needed. Challenge the mice of the test group as well as the control group with a certain amount of Challenge Virus Standard (CVS) on D 14 after the first inoculation. The protective index should be above 100. After test, the protective index of the vaccinated mice is 1584, which showed that the protection of the vaccine was satisfactory and also complied with the official regulations.

(Rabies verocell/*≥2.5IU/dose*)

➢ **Pharmacokinetics:** The pharmacokinetic studies are normally not needed for vaccines as per *Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines.*

➢ **Toxicology:** For the vaccine products for which the national standards have already been established as for SPEEDA, it is unnecessary to conduct each of these test items for toxicity study (acute & long-term toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other special toxicity). According to related test results on the vaccine product, the potency, antigenicity as well as immunogenicity of the vaccine product has reached or superior to related national standards. As a result, it is feasible to conduct local tolerance test, allergenicity test and genotoxicity test as the main test items for toxicity study on the vaccine product. •The acute toxicity of rabies vaccine was observed in mice by IV & SC administration under the dosage of 750 IU/kg (as much as 20,833 times for human clinical use through the administration route of IM injection) for 2 injections at an interval of 6 hours. The result showed that no obvious acute toxicity was observed. All mice survived the observation period with an average of 11-14 g's body weight increasing. As the dosage and immunization regimen can be compendially reference, the repeat dose toxicity study had not been conducted. The genetic toxicity of rabies vaccine was tested in mice by Micronucleus Test of Mice Bone Marrow Polychromatic Erythrocytes (PCE). The result showed that there was no increase of the Micronucleus Rate under the dosage of 375 IU/kg of rabies vaccine following the SC administration in mice, which indicated that the probability of chromosome abnormality was small within the tested dosage range. •Local tolerance: Two sound rabbits, a male and a female, were injected with the vaccine product at one side of quadriceps femoris muscle, 0.5ml per rabbit. Meanwhile, the same volume of water for injection was injected to the other side, 48 hours later, these rabbits were killed, and the injection sites and nearby tissues were evaluated. The results showed that there was no muscle stimulation pathological change found on the injected sites. •Allergenicity: 0.5 ml of positive control, negative control, test vaccine and reference vaccine were inoculated SC into each of four Guinea pigs for each group at one-week intervals, totally for three inoculations. The allergenic reaction on the animals for 30 minutes was observed as follows: strongly positive with positive control and negative with negative control, test vaccine and reference vaccine.

➢ **Overall conclusion:** The studies and evaluations presented constitute sufficient and adequate non-clinical evidence for SPEEDA, and the non-clinical data reveal no special hazard for humans based on the studies of safety pharmacology, toxicity and local tolerance.

2. Clinical aspect:

Clinical Overview

The clinical development and post-marketing experience of Rabies Vaccine for Human Use (Vero Cell), Freeze-dried, manufactured by Liaoning Cheng Da Biotechnology Co., Ltd. (CDBIO), provide extensive evidence supporting its immunogenicity, effectiveness, and safety for rabies prevention. The vaccine is produced using the Pasteur PV2061 rabies virus strain adapted to Vero cells and manufactured in accordance with World Health Organization (WHO) recommendations for cell culture-

derived rabies vaccines. The manufacturing process includes chromatographic purification and lyophilization, resulting in a highly purified vaccine formulation.
Clinical evidence supporting the vaccine includes published studies conducted internationally in China, India, Thailand, Vietnam, and the Philippines, as well as a pivotal Phase III randomized, blinded, controlled clinical trial performed under Good Clinical Practice (GCP) standards and approved by the Chinese regulatory authority. The clinical program evaluated immunogenicity, effectiveness, and safety in healthy individuals and in populations receiving post-exposure prophylaxis.
In addition, extensive post-marketing experience has been accumulated through routine clinical use. Between March 2013 and March 2016 alone, approximately 12.8 million individuals received the vaccine for pre-exposure or post-exposure prophylaxis, providing substantial real-world evidence supporting its continued safety and effectiveness.

Clinical Efficacy

The clinical efficacy of the vaccine was primarily evaluated through the induction of rabies virus-neutralizing antibodies (RVNA), a recognized surrogate marker for protection against rabies infection.
In the pivotal Phase III randomized comparative study involving 621 healthy volunteers aged 10–60 years, the vaccine was administered according to the WHO-recommended post-exposure vaccination schedule (Days 0, 3, 7, 14, and 28) and compared with a licensed purified Vero cell rabies vaccine.
All evaluable subjects achieved seroconversion by Day 14 following initiation of vaccination, corresponding to a seroconversion rate of 100%. Protective antibody responses remained present in all evaluated subjects through Day 45. No statistically significant differences were observed between the CDBIO vaccine and the licensed comparator vaccine regarding seroconversion rates or antibody responses.
These findings are consistent with published international studies demonstrating that purified Vero cell rabies vaccines provide highly effective protection against rabies when administered according to recommended vaccination schedules. Furthermore, post-marketing surveillance covering millions of vaccine recipients has not identified any confirmed vaccine failures following completion of the recommended vaccination regimen.
Collectively, the available evidence supports the effectiveness of the vaccine for both pre-exposure and post-exposure rabies prophylaxis.

Clinical Immunogenicity

The immunogenicity of the vaccine was assessed through measurement of rabies virus-neutralizing antibody concentrations using validated neutralization assays.
In the Phase III comparative study, all subjects were seronegative prior to vaccination. By Day 14 after the first vaccine dose, seroconversion rates reached 100% in both the CDBIO vaccine group and the comparator group, exceeding the WHO-recommended protective threshold of 0.5 IU/mL.
Among subjects evaluated for antibody responses:

* The geometric mean antibody titer (GMT) in the CDBIO vaccine group increased from ≤0.2 IU/mL at baseline to 4.5 IU/mL on Day 14 and 8.9 IU/mL on Day 45.
* In the comparator group, GMTs increased to 5.6 IU/mL on Day 14 and 9.8 IU/mL on Day 45.
* No statistically significant differences were observed between groups with respect to antibody titers or seroconversion rates.

The rapid development of protective antibody responses observed after vaccination supports the suitability of the vaccine for post-exposure prophylaxis, where timely induction of immunity is essential.

Published studies conducted in multiple countries have similarly demonstrated robust and consistent immunogenicity across different populations and vaccination schedules.

Overall, the available data confirm that Rabies Vaccine for Human Use (Vero Cell), Freeze-dried induces strong and reliable protective immune responses against rabies virus infection.

Clinical Safety

The safety profile of the vaccine has been evaluated in clinical trials and through extensive post-marketing surveillance involving millions of administered doses.

In the Phase III clinical study, adverse reactions were generally mild, transient, and self-limiting. The most frequently reported adverse events were local injection-site reactions, including:

* Pain, Redness, Swelling, Pruritus and Induration.

The overall incidence of local adverse reactions was low (2.5% of vaccinated subjects).

Systemic reactions were uncommon and mainly consisted of transient fever, nausea, or mild gastrointestinal symptoms. The incidence of systemic adverse reactions was less than 1%, and all events resolved without sequelae.

No severe vaccine-related adverse reactions were reported, and no clinically significant safety concerns were identified during the study. The incidence and nature of adverse events were comparable to those observed with the licensed comparator vaccine.

Post-marketing surveillance data covering approximately 12.8 million vaccinated individuals further support the favorable safety profile of the vaccine. Most reported adverse events following immunization were non-serious and consistent with the known safety profile of rabies vaccines.

Overall, the vaccine has demonstrated an acceptable and well-established safety profile consistent with internationally licensed cell culture-derived rabies vaccines.

Benefit-Risk Analysis

Rabies is an almost invariably fatal disease once clinical symptoms develop, making effective vaccination an essential public health intervention.

The submitted clinical and post-marketing data demonstrate that Rabies Vaccine for Human Use (Vero Cell), Freeze-dried:

* Induces rapid and robust rabies virus-neutralizing antibody responses.

* Achieves 100% seroconversion in evaluated subjects by Day 14 following vaccination.

* Demonstrates immunogenicity comparable to that of internationally licensed purified Vero cell rabies vaccines.

* Maintains a favorable safety profile characterized primarily by mild and transient local or systemic reactions.

* Has accumulated extensive real-world evidence from millions of administered doses without identified concerns regarding vaccine effectiveness.

Considering the severity of rabies infection, the demonstrated immunogenicity and effectiveness of the vaccine, and its favorable safety profile, the overall benefit-risk balance is considered highly favorable.

Overall Conclusion

The totality of clinical and post-marketing evidence supports the safety, immunogenicity, and effectiveness of Rabies Vaccine for Human Use (Vero Cell), Freeze-dried manufactured by Liaoning Cheng Da Biotechnology Co., Ltd.

The vaccine demonstrated rapid induction of protective rabies virus-neutralizing antibodies, achieving 100% seroconversion in the pivotal Phase III study and immunogenicity comparable to a licensed comparator vaccine. Clinical studies and published international experience consistently confirmed its ability to provide effective protection against rabies.

The vaccine was generally well tolerated, with adverse reactions predominantly mild, transient, and consistent with the established safety profile of purified Vero cell rabies vaccines. Extensive post-marketing experience involving more than 12 million vaccinated individuals further supports its favorable safety and effectiveness profile.

Based on the available evidence, Rabies Vaccine for Human Use (Vero Cell), Freeze-dried demonstrates a positive benefit-risk profile and represents an effective option for both pre-exposure and post-exposure prophylaxis against rabies.

3. General Conclusion and Recommendations if any:

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

(Rabies verocell/*≥2.5IU/dose*)