Unit: Technical Assessment Unit

Public assessment report for biological products

Varicella Vaccine, Live

Administrative information:

Trade name of the medicinal product:	Varicella Vaccine, Live
INN (or common name) of the active substance(s):	Live varicella-herpes zoster virus
Manufacturer of the finished product	Sinovac (Dalian) Vaccine Technology Co., Ltd.No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, Liaoning Province, P.R - CHINA
Marketing Authorization holder	Sinovac (Dalian) Vaccine Technology Co., Ltd.,No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, Liaoning Province, P.R - CHINA
Applied Indication(s):	Active immunization for the prevention of varicella in individuals aged 1 year (12 months) and above
Pharmaceutical form(s) and strength(s):	Lyophilized Powder for Injection (≥ 3.3 Ig PFU)
Route of administration	S.C injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

BDS	bulk drug substance
BW	Body weight
CD	Cluster of differentiation
CNS	Central nervous system
CVS	Cardiovascular system
GMT	Geometric Mean titer
ICR	Institute of Cancer Research
IgG	Immunoglobulin
NOAEL	the no-observed-adverse-effect level
PFU	plaque-forming units

S.C.	Subcutaneous
SD	Sprague Dawley
SV-1	self-established human diploid cell
TRS	Technical Report Series
VZV	varicella-zoster virus
WHO	World Health Organization

Table of contents

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

Varicella Vaccine, Live is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted using the accompanying 0.5 mL sterile diluent (WFI). The presentation is 0.5 mL/vial after reconstitution (≥ 3.3 Ig PFU). This vaccine should be stored at 2°C - 8°C and cannot be frozen. 0.5 mL dose is indicated for active immunization for the prevention of varicella in individuals aged 1 year (12 months) and above. The vaccine shall be administrated by subcutaneous injection into the deltoid muscle.

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

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- International non-proprietary Name (INN): Live attenuated Varicella-Herpes Zoster Virus (VZV), Oka Strain
- The live attenuated VZV belongs to the subfamily of Alpha Herpesviridae in the Herpesviridae family.
- VZV DNA is composed of about 124,884 base pairs, has a molecular mass of about 80 MDa, and an average GC content of 46%.
- The live attenuated VZV exists as the drug substance in the Varicella Vaccine bulk. The Vaccine Bulk is an opalescent aqueous suspension that can be stratified due to precipitation and can be dispersed by shaking. No clumps shall be found upon shaking**.**

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

➢ **Manufacturer**

Sinovac (Dalian) Vaccine Technology Co., Ltd. No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, China

➢ **Description of Manufacturing Process and Process Controls**

- The manufacturing process steps include cell culture and harvest, virus pool, ultrasonic filtration and clarification.
- The bulk manufacturing process steps including the critical process parameters/control tests and specifications are provided in the MA file.

➢ **Control of Materials**

The starting materials for Varicella Vaccine, Live are human diploid cell SV-1 Strain and live attenuated VZV (Oka Strain). The control tests on the Master Cell Bank, Working Cell Bank and End-of-production Cell are performed by the National Institutes for Food and Drug Control and Sinovac (Dalian).

- **Controls of Critical Steps and Intermediates**

- The starting materials for Varicella Vaccine, Live are human diploid cell SV-1 Strain and live attenuated VZV (Oka Strain). The control tests on the Master Cell Bank, Working Cell Bank and End-of-production Cell are performed by the National Institutes for Food and Drug Control and Sinovac (Dalian).
- All the materials of non-biological origin are commercial and supplied by qualified suppliers. The quality of these materials follows the current edition of Pharmacopoeia of the People's Republic of China (Chinese Pharmacopoeia, ChP) or other international common standards.
- The test methods and specifications for intermediates are provided in the MA file.

- **Process Validation**

- Facilities and equipment, production operators, related documents of Varicella Vaccine, Live are applicable for continuous production, stable product quality and yield, qualified to specification.
- Cell culture, virus amplification, virus harvest, bulk preparation processes, final bulk preparation, filling, lyophilization, capping, visual inspection, labeling and packaging processes of the manufacturing process of Varicella Vaccine, Live are included.

- **Manufacturing Process Development**

- According to the biological characteristics of VZV as the critical control point throughout the whole production process development, the production process and corresponding critical process parameters were preliminarily determined based on the research results of cell culture, virus inoculation, virus amplification, virus release, virus harvest, bulk, and stabilizer and storage conditions.
- The procedures of the manufacturing process development are provided in the MA file.

- **Characterization**

- The active substance is the live attenuated VZV, Oka strain. The description and evaluation of the characteristics, comprehensive analysis has been performed. The results demonstrate that the morphology, biological activity, and physicochemical properties of live attenuated VZV are indistinguishable from those in bibliographical

information, and the molecular biological characteristics and genetic characteristics are stable, maintain attenuated.
- The impurities are verified to be removed in the process validation reports, and the residuals shall be controlled in process.

- **Specification**

The specifications of all intermediates including single virus harvest, virus pool and bulk are provided in the MA file.

- **Batch analysis**

3 consecutive batches of bulk were tested as per Chinese Pharmacopoeia and WHO Technical Report Series 848, and their certificates of analysis are provided in file.

- **Reference Standards or Materials**

The reference standards and their uses are provided in the MA file.

- **Container closure system**

Stainless steel bottle formed by the stainless steel pipe and plate are used for bulk storage.

- **Stability of drug substance**

Based on available stability data:
Approved Shelf Life: 6 months
Approved Storage Conditions: Below -60ºC

2.2.3 Drug product:

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

- Varicella Vaccine, Live is a single-dose glass vial of lyophilized vaccine, accompanying the sterile diluent (sterile WFI). After reconstitution, the suspension for injection (approximately 0.5 mL/dose) is a transparent and slightly opalescent liquid free of foreign matter.
- The sterile water for injection is a clear, colorless and odorless liquid. It is used as the solvent of the diluent for Varicella Vaccine, Live.
- Type of container and closure used for the dosage form: vial for the lyophilized vaccine, ampoule for diluent.

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

- Active Ingredient: Live attenuated VZV

- **Excipients:** Phosphate buffer salts (potassium dihydrogen phosphate and disodium hydrogen phosphate dodecahydrate) in harvest solution A and the stabilizer components, which include potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate dodecahydrate, sodium glutamate, and sucrose
- **Diluent:** Sterile water for injection

➢ **Physicochemical and Biological Properties**

The quality attributes and their compendia specification are provided in the MA file.

➢ **Container closure system and their compatibility**

- The container closure system for final bulk vaccine (ready to fill) is disposal system called AllegroTM Single Use System including Flexel® Bag for Magnetic Mixer (50L), all components of this system are sterile and single used and manufactured in a controlled environment under a Quality Management System certified to ISO 9001 Quality Systems Standard.
- The materials used for final product inner package are injection vial made of neutral borosilicate glass tubing, brominated butyl rubber stopper for sterile lyophilized powder for injection and caps made of aluminium-plastics combinations for antibiotics vials.
- The properties as moisture-proof, light-proof, compatibility between structural material and formulation (including the adsorption and leaching of container), the safety and performance comply with the National Standards for Pharmaceutical Packaging Containers of National Medical Products Administration (NMPA).
- The container closure system for sterile water for injection is ampoules made of low borosilicate glass tubing.

➢ **Microbiological Attributes**

- The sterility and mycoplasma are tested for both final bulk and final product.
- No preservative is used in the Vaccine.
- Regarding to the container closure, it is sufficient in regards to prevention of microbial contamination.
- The diluent is filled and sealed into the ampoule by Type AGF ampoule filling and sealing machine. Leaking test is performed before release to use, by applying dye tracer liquid into the sterilizing cabinet and run the leaking test procedure.

➢ **Compatibility**

- The compatibility study of Varicella Vaccine, Live after reconstitution with Sterile Water for Injection was conducted. The test results proved that the compatibility of Varicella Vaccine, Live and the primary package materials are good.

- The compatibility studies of the diluent are provided in the MA file.

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities

➢ **Manufacturer(s):**
Sinovac (Dalian) Vaccine Technology Co., Ltd.No. 36, 2nd Life Road, DD Port, Economic and Technical Development Zone, Dalian, China
Manufacturer of Diluent: Jiangsu Desano Pharmaceutical Co., Ltd,No.3, Kanganroad, Economic and Technology Development District, LiyangCity, Jiangsu Province, China
- The manufacturing process steps and the in process controls for the final bulk and the diluent are provided in the MA file.

➢ **Control of critical steps and intermediates**
- The controls of the final bulk are mentioned in the MA file.
- An intermediate of sterile water for injection is manufactured during the whole process. The in-house criteria is stated in the MA file.

➢ **Process validation and / or evaluation**
- The manufacturing process validation of Varicella Vaccine, Live final bulk and final product have been studied in 2017 and details are provided in the MA file.
- Regarding the diluent, the validation successfully demonstrated that the WFI process is reproducible and compliant with quality standards.

- **Product specification:**
  - Excipients comply with the Chinese Pharmacopoeia.
  - No excipients of human or animal origin are used in the production of drug product.
  - No excipient used for the first time in a drug product or by a new route of administration is used in the production of drug product.
  - The product and diluent specifications comply with the Chinese Pharmacopoeia.
  - The test items for the finished product and related SOPs are listed and the analytical procedures of the methods for the finished product and the diluent are described in the MA file.

- **Reference Standards or Materials**
The reference standards and their uses are provided in the MA file.

- **Container closure system**
  - 50 L disposable sterile stirring bags are applied for the storage of final bulk.

- Study reports on compatibility of packaging materials and compatibility of leachable from packaging materials were submitted.
- The container closure system for sterile water for injection is ampoules.

- **Stability of the drug product**
  Based on available stability data:
  Approved shelf life
  Finished product: 24 months
  Diluent: 48 months
  Approved Storage Conditions
  Diluent: Store at (2-30ºC)
  Vaccine and Diluent Package: Stored and transported between +2ºC to +8ºC, protect from light. Do not freeze.

3. Non –clinical aspect:

- Varicella Vaccine Live is a lyophilized live virus vaccine containing as the active ingredient the attenuated VZV Oka strain.
- Oka strain has been around for decades. The initial approvals (e.g., US in 1995) were initially obtained from a child with wild-type varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus for varicella vaccine was conducted in self-established human diploid cell (SV-1).
-This vaccine induces both humoral and cell-mediated immune responses. It produces an IgG humoral immune response in individuals, and the cell-mediated immune response is by varicella-zoster-specific activation of both $CD4^+$ T-helper and $CD8^+$ T-lymphocyte cells.

- **Pharmacodynamics**

-From immunogenicity study performed on macaca fascicularis, it was found that the GMT of Abs in the high-dose sample group was higher than that in the low-dose sample group, and not lower than that in the commercial vaccine control group.

-In addition, the immunogenicity of Varicella Vaccine, Live was be evaluated on SD rats, in this experiment, antibodies were detected from all animals in the low-dose group, with a seroconversion rate of 100% and an antibody GMT of 1:73.5, and antibodies were also detected from all animals in the high-dose group, with a seroconversion rate of 100% and an antibody GMT of 1:111.4. Therefore, Low-dose and high-dose vaccination of Varicella Vaccine, Live could induce a good immune effect for SD rats and macaca fascicularis.

- Safety pharmacology endpoints regarding CVS were integrated in the repeated dose toxicity study performed on macaca fascicularis, statistically significant changes ($P \leq 0.05$) were observed in Q-T and P-R intervals; however, these changes were not considered to be toxicological as it still within the reference range, and no dose-response relationship was observed. In addition, the impact of the candidate vaccine on the CNS was evaluated in a separate study conducted on rhesus monkeys. All the rhesus monkeys showed good general status, including neurobehavior, motor function, food intake, and body temperature.

- **Pharmacokinetics:**

Specific non-clinical studies on absorption, distribution, metabolism, excretion, or drug interactions were not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).

- **Toxicology:**

- Acute toxicity: No significant toxicity was observed in ICR mice injected subcutaneously with 0.5 mL of reconstituted BDS of Varicella Vaccine, Live, and the NOAEL was greater than 25 mL/kg BW. When the body weight of clinical trials subjects was calculated as 10 kg of infants and young children, clinical dosage was 0.05 mL/kg BW, and the NOAEL was greater than 25 mL/kg BW, which was 500 times of the clinical dose.
- Repeated dose toxicity: No significant toxicity was observed upon repeated administration of the candidate vaccine in SD rats. The safe dose was determined to be 5 doses/animal, which was 5 times the intended clinical dose (4.1 lgPFU/dose/time/person).
In the repeated toxicity study on macaca fascicularis received repeated subcutaneous injections of Varicella Vaccine, Live, and no sample-related toxicity was observed in all groups and the safe dose was determined to be 5 doses/animal, equivalent to 75 times the proposed clinical dose based on mg/kg body weight.
- No drug-induced irritative reactions were observed at the injection sites (i.e. quadriceps) in the rabbits intramuscularly injected once with 0.5 mL of reconstituted BDS of Varicella Vaccine, Live
- Regarding Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity:
No studies were conducted. This is consistent with the guidelines for vaccines (WHO, 2005 (TRS No.927).
- Toxicology conclusion: No potential toxicity risk was found from the long-term toxicity study on SD rats and macaca fascicularis.

4. Clinical aspect:

The clinical development program included **9 trials**: 3 pre-licensure studies and 6 post-marketing studies, evaluating safety, immunogenicity, booster immunization, and efficacy across different age groups. The pivotal Phase III study (PRO-VZV-3001) enrolled **5,997**

healthy children aged 1–12 years, with additional studies assessing immune persistence, concomitant administration with Hepatitis A vaccine, and a two-dose schedule in individuals aged ≥13 years. All studies were conducted per **Good Clinical Practice (GCP)** and Chinese regulatory standards.

- **Clinical Efficacy and Immunogenicity**

Pivotal Study: PRO-VZV-3001 (Phase III)
Design: Double-blind, randomized, placebo-controlled
Population: 5,997 children aged 1 - 12 years
Dose: Single subcutaneous dose, 0.5 mL
Follow-up: 6 months (monitoring period: Day 30 - 6 months post-vaccination)

Efficacy Results:

Laboratory-confirmed varicella cases: 6 in vaccine group vs 46 in placebo
Seroprotective rate:
Against all varicella: **87.1%** (95% CI: 69.7 - 94.5%)
Against breakthrough varicella (≥42 days post-vaccination): **89.2%** (95% CI: 72.9 - 95.7%)
Against moderate or more severe varicella: **100%** (95% CI: 83.53 - 100%)
Severity reduction: Fewer fevers and skin lesions in vaccine group; no severe varicella cases occurred.
Comparison with licensed vaccines: Comparable efficacy (VARIVAX 87%, VARILRIX 88%).
Immunogenicity Results (PRO-VZV-3001):

Seroconversion rates:
1:4 titer: 99.43%
1:8 titer: 96.28%
GMT: 46.48
Protective immune responses consistent across age subgroups (1–4, 5–8, 9–12 years).
Supportive Studies
PRO-VZV-1001 (Phase I) – Safety in adults, adolescents, children
Adverse reactions: 18.9% in vaccine group; mostly mild (fever, injection site redness)
No serious vaccine-related events
PRO-VZV-3002 (Phase III) – Lot-to-lot consistency in children 1–3 years
Seroconversion rates: 95.73–97.54% across commercial lots
GMTs: 24.47–25.88; equivalent across lots

Vaccine safety: Adverse reactions 15.48%, mostly Grade 1–2; 5 unrelated SAEs
PRO-VZV-3002-1 (Phase IV) – Booster immunization
Seropositive rates after initial dose: 97–99% (1:4)
Booster response 30 days post-booster: ≥99% seropositive (1:4, 1:8)
GMT increase after booster: 68–78
Safety: Adverse reactions 7.77%; mainly mild fever; no vaccine-related SAEs
PRO-VZV-4001 (Phase IV) – Concomitant administration with Hepatitis A vaccine
Immunogenicity: Non-inferior to separate administration; robust antibody responses
Safety: Well, tolerated; no serious vaccine-related events
PRO-VZV-4002 (Phase III) – Two-dose regimen in ≥13 years
Seroconversion rates: Comparable to licensed vaccine
GMTs increased markedly post-vaccination
Safety: Adverse reactions 13.45%; mostly mild to moderate; no vaccine-related deaths
PRO-VZV-4004 (Phase IV) – Long-term immune persistence (5–8 years)
Sustained antibody positivity in most participants
Booster responses restored high GMTs.

- **Clinical Safety**

Overall Safety Across Studies (Phase I–IV, N>20,000):

- **Most common local reactions:** Injection site redness, pain (<1%)
- **Most common systemic reactions:** Fever (10–14%), mild to moderate
- **Overall, AE incidence:**
  - Vaccine: 16.6%
  - Placebo: 17.6%
- **Serious adverse events (SAEs):** <1%; only one possibly vaccine-related (allergic purpura, resolved without sequelae)
- **No deaths or life-threatening events** related to vaccination
- **Safety across populations:** Consistent for infants, children, adolescents, and adults
- **Post-marketing data:** >7.9 million doses administered globally; AE incidence: 14.7 per 100,000; no new safety signals

- **Overall Conclusion**

The live attenuated varicella vaccine demonstrates **robust efficacy, strong immunogenicity, and an excellent safety profile** across multiple studies and populations. Specifically:

- **Efficacy:** Provides high protection (87–100%) against varicella infection, including moderate-to-severe cases.
- **Immunogenicity:** Consistently high seroconversion rates and GMTs after primary vaccination and boosters, with durable immune responses and confirmed lot-to-lot consistency.
- **Safety:** Generally mild to moderate adverse reactions; serious vaccine-related events are rare and resolve without sequelae.

➢ **Benefit–Risk Assessment:**

The vaccine offers a **favorable benefit-risk profile** for the prevention of varicella in children, adolescents, and adults, supporting its widespread use in routine immunization programs.

- **High efficacy:** Demonstrated 87–100% protection against varicella and severe disease in children, with robust responses in adolescents and adults.
- **Strong immunogenicity:** High seroconversion rates, durable immune responses, effective booster responses, and lot-to-lot consistency confirmed.
- **Favorable safety profile:** Predominantly mild to moderate AEs, predictable reactogenicity, no unexpected safety concerns.
- **Overall benefit-risk assessment:** The live attenuated varicella vaccine demonstrates a **favorable benefit-risk profile** for prevention of varicella in individuals aged 12 months and older.

5. General Conclusion and Recommendations if any:

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