ETHIOPIAN FOOD AND DRUG AUTHORITY

GUIDELINE FOR REGISTRATION OF SNAKE ANTIVENOM PRODUCTS

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Contents

Abbreviations and Acronyms

CoA	Certificate of Analysis
CTD	Common Technical Document
EFDA	Ethiopian Food and Drug Authority
ELISA	Enzyme-Linked Immunosorbent Assay
eRIS	Electronic Regulatory Information System
GMP	Good Manufacturing Practice
ICH	International Council for Harmonization
MA	Marketing Authorization
NRA	National Regulatory Authority
QC	Quality Control
MEMA	Medicine Evaluation and Market Authorization
RMP	Risk Management Plan
SDS-PAGE	Sodium Dodecyle Sulfate Polyacrylamide Gel Electrophoresis
WHO	World Health Organization

1. Introduction

Snake antivenom immunoglobulins (antivenoms), also known as antivenin or anti-snake venom (ASV), are purified immunoglobulins or fragments derived from animal plasma (e.g., equine or ovine) immunized against specific snake venoms. As the sole treatment for snakebite envenoming, antivenoms address a critical public health issue in Sub-Saharan Africa, including Ethiopia, where 22 of 98 snake species are venomous, notably Echis pyramidum in Eritrea, Ethiopia, and Kenya. Underreporting, as victims often avoid government facilities, obscures Ethiopia's snakebite burden, contributing to an estimated 3,500–32,100 annual deaths regionally.

The Ethiopian Food and Drug Authority (EFDA), mandated by Proclamation No. 1112/2019, regulates medicines and biological products, including antivenoms to ensure safety, efficacy, and quality. EFDA's responsibilities include evaluating product dossiers, conducting Good Manufacturing Practice (GMP) inspections, issuing market authorizations, and enforcing pharmacovigilance to monitor adverse events. EFDA collaborates with manufacturers, healthcare providers, and international organizations to enhance access to essential medicines, set technical standards, and address Ethiopia's epidemiological needs, particularly in rural areas with high snakebite incidence.

This guideline is developed to align with World Health Organization (WHO) Technical Report Series, No. 1004, 2017, Annex 5, and International Council for Harmonization (ICH) Guidelines for Biological Products, standardizes snake antivenom registration to reduce morbidity and mortality through stakeholder collaboration.

This guideline is prepared to ensure antivenoms meet rigorous safety, efficacy, and quality standards, addressing Ethiopia's snakebite burden.

2. Scope

This guideline is applicable to registration and market authorization of snake antivenom products derived from animal plasma for human use in treating snakebite envenoming in Ethiopia.

3. Dossier organization for Submission of Application

Applicants shall submit the required registration document in Common Technical Document (CTD) format through the electronic regulatory information system (eRIS) of EFDA:

a. Module 1: Administrative/legal information, including GMP compliance.

- Cover Letter to the Medicine Evaluation and Market Authorization Lead Executive Office (MEMA LEO) regarding express of interest to register the product.
- Completed, signed, stamped, and dated application form (use the application form annexed to the guideline for the registration of medicines).
- Valid GMP compliance certificate issued from the National Regulatory Authority (NRA) of country-of-origin
- Screening and registration fees per Regulation No. 370/2015.
- Ethiopia-specific Risk Management Plan (RMP) and pharmacovigilance contact.
- Agency agreement between MAH and local agent
- Product and Labeling information as indicated in 4.8 section of this guideline.

b. Module 2: Quality, safety, and efficacy summaries.

c. Module 3: Chemistry, Manufacturing, and Controls.

- Applicants are advising to consider the issued discussed under section 4.1 to 4.4, 4.7 and 4.8 of this guideline.

d. Module 4: Non-clinical data (safety and efficacy).

- Applicants are advising to consider the safety data requirements discussed under section 4.5.1 and efficacy data requirements under section 4.6.1of this guideline.

e. Module 5: Clinical data (safety and efficacy).

- Applicants are advising to consider the safety data requirements discussed under section 4.5.2 and efficacy data requirements under section 4.6.2 of these documents.

4. Registration Requirements

The registration requirements for suppliers of snake antivenom biological products in Ethiopia aim to ensure that submissions for market authorization align with local needs through thorough and well-prepared documentation.

4.1.Manufacturer Responsibilities

Manufacturers shall submit a CTD dossier, including:

1) Product composition, formulation, and venom sources.
2) Immunization protocols, plasma collection, and purification processes.
3) Quality control measures, preclinical, and clinical data.
4) Ethiopia-specific RMP and qualified person for pharmacovigilance in Ethiopia.

4.2. Venom Selection

1. Antivenoms must target Ethiopia's medically relevant snake species, accounting for venom variability:
   a. **Category 1** (Highest Priority): Elapidae: Dendroaspis polylepis, Naja ashei (south-east), Naja haje, Naja nigricollis; Viperidae: Bitis arietans, Echis pyramidum.
   b. **Category 2**: Atracta spididae: Atractaspis fallax, Atractaspis irregularis (Mt Bizen); Colubridae: Dispholidus typus; Elapidae: Naja melanoleuca, Naja pallida; Viperidae: Bitis parviocula, Bitis harenna.

2. Manufacturers must provide:

   a. Venom characterization and cross-reactivity studies.
   b. Venom yield data, pooling strategies, and geographic/seasonal variability.
   c. **Cross**-neutralization documentation for non-immunized venoms, validated by preclinical (ED50) and clinical studies.

3. Polyvalent formulations may include Category 1 and 2 species. In vitro cross-reactivity alone is insufficient for therapeutic claims beyond production venoms.

4. Monovalent Antivenoms: Applications for monovalent antivenoms targeting a single species (e.g., Echis pyramidum) or related species with cross-neutralization may be acceptable if its use in Ethiopia is justified by:

    a. Regional species prevalence.
    b. Validated clinical algorithms for species identification.
    c. Reliable, affordable immunodiagnostic or blood tests.
    d. epidemiological and clinical justification due to Ethiopia's diverse snake fauna.

4.3. Manufacturing Process

The applicant should submit relevant documentation related to animal immunization, plasma collection, and purification and formulation. These includes:

a. Evidence for using healthy animals (e.g., horses, sheep) under ethical conditions, with documented schedules and venom doses.
b. Assurance animal welfare procedure was followed, including regular health monitoring and humane treatment.
c. Aseptic plasma collection process, with traceability of donor animals.
d. Test for infectious agents (e.g., equine infectious anemia, brucellosis) as per WHO standards.
e. validated methods (e.g., pepsin digestion, caprylic acid precipitation) used to isolate F(ab')2 or Fab fragments.
f. Information/data on stability, sterility, and minimal residual toxins in lyophilized products.

4.4.Quality Control

The applicant should submit Module 3 (Chemistry, Manufacturing, and Controls) in accordance with WHO Technical Report Series, No. 1004, 2017, Annex 5, and ICH Q6B. This quality control shall ensure antivenoms meet stringent standards for consistency, purity, and stability. Detailed requirements include:

4.4.1. Raw Materials

The raw materials used in the manufacturing of antivenom shall meet the following minimum requirements regarding venom sourcing, plasma, and excipients.

a. Venoms must be sourced from certified suppliers, with records of snake species, geographic origin, and extraction methods. Each venom batch requires a Certificate of Analysis (CoA) confirming toxin profile via HPLC or mass spectrometry.
b. Plasma donor animals must be screened for health status and infectious agents. Plasma must comply with pharmacopeial standards (e.g., European Pharmacopoeia for equine plasma).
c. Excipients such as **s**tabilizers (e.g., sorbitol, glycine) and preservatives used for manufacturing of the antivenom products must be pharmaceutical-grade. Supporting specifications for purity and compatibility should be submitted.

4.4.2. In-Process Controls

In-process controls should, at a minimum, include the quantification of anti-venom immunoglobulins, impurity levels, and tests for intermediate products. The required tests, along with their recommended methods and test parameters, are:

a. Monitoring immunization to ensure consistent antibody titers, using Enzyme-Linked Immunosorbent Assay (ELISA) to quantify anti-venom immunoglobulins.
b. Validating purification steps (e.g., ammonium sulfate precipitation, ion-exchange chromatography) to remove impurities (e.g., albumin, non-specific IgG).
c. Testing intermediate products for protein content, pH, and osmolarity to ensure batch-to-batch consistency.

4.4.3. Final Product Testing

Final product testing should, at a minimum, include assessments of potency, purity, safety, and stability. Details of each test shall be described as mentioned below:

a. Potency of the snake antivenom contained in the formulation should be expressed in Milligram (mg) of venom neutralized per **millilitre** of snake antivenom using ED50 assays in murine models in accordance with the WHO requirements.
b. Potency tests must cover all targeted snake species (e.g., Echis pyramidum, Naja nigricollis).
c. Purity test should be conducted by Sodium Dodecyle Sulfate - Polyacrylamide Gel Electrophoresis (SDS-PAGE) or size-exclusion chromatography and the content of the active immunoglobulin shall be ≥ 90%. Limits for aggregates (<5%) and contaminants (e.g., endotoxins <0.5 EU/mL) should be specified.
d. Safety tests should be confirmed by sterility (no bacterial/fungal growth), non-pyrogenicity (by rabbit pyrogen test or LAL assay), and absence of residual toxins via in vitro assays.
e. Real-time (2–8°C) and accelerated (25°C, 40°C) stability studies should be conducted for lyophilized and reconstituted products, assessing potency, pH, and clarity over 24–36 months. Data must support shelf-life claims under Ethiopia's climatic conditions (Zone IVb). Applicant need to consult Annex 5-Guidelines for the production, control and regulation of snake antivenom immunoglobulins, WHO TRS 1004, 2017 for details of stability requirements and conditions on snake antivenom products.

4.4.4. Batch Release

a. Potency, purity, and safety of each batch of antivenom shall be tested by an ISO/IEC 17025 accredited or a designated WHO-prequalified laboratory.
b. The applicant should submit CoAs detailing test methods, acceptance criteria, and results, in accordance with ICH Q6B.

4.5.Safety

Module 4: (Non-Clinical and Module 5: Clinical Safety) Safety assessments, should be submitted in accordance with the Annex 5-Guidelines for the production, control and regulation of snake antivenom immunoglobulins, WHO TRS 1004, 2017 and ICH S6(R1), ensure antivenoms pose minimal risk to humans, addressing Ethiopia's high-risk rural populations.

4.5.1. Non-Clinical Safety (Module 4)

The non-clinical safety section should contain

a. Acute Toxicity: single-dose studies conducted in rodents to identify adverse effects (e.g., anaphylactoid reactions, organ toxicity) by using doses 5–10 times the human equivalent.
b. Repeat-Dose Toxicity: 14–28-day studies performed in two species (e.g., rats, rabbits) to assess cumulative effects, focusing on immunogenicity and renal/hepatic function.
c. Local Tolerance: Evaluate injection site reactions (e.g., edema, necrosis) evaluated in rabbits to ensure intramuscular/subcutaneous administration safety.
d. Pyrogenicity and Endotoxin Testing: Confirmed absence of pyrogenic contaminants using LAL assays and rabbit pyrogen tests, critical for Ethiopia's limited healthcare settings where adverse reactions complicate treatment.
e. Residual Venom: Verify no residual venom activity via in vitro hemolytic or enzymatic assays, preventing envenoming-like effects.

4.5.2. Clinical Safety (Module 5)

a. **Phase I Trials**: Safety assessed in 20–50 healthy volunteers, monitoring for early adverse events (e.g., anaphylaxis, fever) within 24–48 hours post-administration. Use escalating doses to establish a safe range.
b. **Phase II/III Trials**: Safety evaluated in 100–500 snakebite patients, focusing on:
    - Early anaphylactic reactions (within 1 hour), occurring in 5–20% of patients, requiring pre-treatment protocols (e.g., antihistamines, adrenaline readiness).
    - Serum sickness (5–14 days post-treatment), characterized by fever, rash, and arthralgia, reported in 10–30% of cases.
    - Neurological or hematological adverse events linked to venom-antivenom interactions.
c. **Pharmacovigilance Plan**: Include Ethiopia-specific monitoring for adverse events in rural clinics, with training for healthcare workers on recognizing and managing anaphylaxis. The plan should also mention reporting of Report serious adverse events to EFDA within 15 days, in accordance with EFDA requirements/WHO pharmacovigilance standards.

d. **Special Populations**: Safety assessed in children, pregnant women, and elderly patients, common in Ethiopia's snakebite demographics, using subgroup analyses.

4.6.Efficacy

The applicant should submit Module 4: (Non-Clinical and Module 5: Clinical Efficacy) as per WHO Technical Report Series, No. 1004, 2017, Annex 5. The applicant should ensure that antivenoms neutralize target venoms effectively, tailored to Ethiopia's snake species.

4.6.1. Non-Clinical Efficacy (Module 4)

a. Neutralization Studies: Conduct ED50 assays in mice to quantify antivenom's ability to neutralize lethal, hemorrhagic, or neurotoxic effects of target venoms (e.g., Bitis arietans, Naja haje). Test cross-neutralization for Category 2 species (e.g., Naja pallida).
b. Dose-Response: Establish dose-response curves to determine minimum effective doses, ensuring potency against variable venom yields (e.g., 0.5–2 mg/mL for Echis pyramidum).
c. In Vitro Assays: Use ELISA or Western blot to confirm binding affinity to venom components, supporting cross-reactivity claims, though clinical confirmation is mandatory.
d. Animal Models: Validate efficacy in alternative models (e.g., guinea pigs) to mimic human envenoming, focusing on symptom reversal (e.g., coagulopathy, paralysis).

4.6.2. Clinical Efficacy (Module 5)

a. Phase II Trials: In 50–100 snakebite patients, demonstrate reversal of envenoming symptoms (e.g., bleeding, neurotoxicity) within 6–24 hours. Use standardized endpoints (e.g., 20-minute whole blood clotting test for viper bites).
b. Phase III Trials: In 200–500 patients, confirm efficacy across Ethiopia's diverse regions, comparing antivenom to supportive care. Primary endpoints include:
c. Restoration of hemostasis (viper bites) within 6 hours.
d. Resolution of neurotoxic symptoms (elapid bites) within 24 hours.
e. Reduced mortality/hospitalization time.

f. Ethiopia-Specific Data: Incorporate epidemiological data (e.g., snakebite incidence in Oromia, Amhara) to design trials reflecting local venom profiles and patient demographics.
g. Cross-Neutralization: Clinically validate cross-neutralization claims (e.g., for Atractaspis fallax) in patients, using case series or observational studies if randomized trials are infeasible.

4.7.Dosage Form

The Food and Drugs Authority of Ethiopia (EFDA) requires that snake antivenom applications are submitted for lyophilized products only, since the available infrastructure and logistics favors a lyophilized product. Furthermore, the concentrations/potency of all the snake antivenom contained in the formulation should be expressed in Milligrams (mg) of venom neutralized per Milliliter(ml) of snake antivenom, instead of the current practice of Lethal Dose (LD_{50}).

4.8.Labeling and Packaging

4.8.1. Labeling Requirements Labels must specify:

a. Antivenom specificity (snake species).
b. Dosage/administration instructions.
c. Storage conditions, batch number, and expiry date.
d. Warnings for anaphylaxis/serum sickness.

4.8.2. Packaging

a. Ensure integrity during transport/storage.
b. Include clear instructions for low-resource settings.
c. Applicant are advised to refer Guideline for Medicine Product information (EFDA/GDL/032) for detail requirements on product information (SmPC, Patient information leaflet (PIL), immediate and outer carton label).

5. References

1. Annex 5-Guidelines for the production, control and regulation of snake antivenom immunoglobulins, WHO Technical Report Series, No. 1004, 2017
2. WHO Guidelines for Snake Antivenom Immunoglobulins (2016, updated 2018).
3. EFDA Guidelines for Registration of Vaccines.
4. ICH Guidelines for Biological Products (Q6B, S6(R1)).
5. Guideline on Registration of Snake Antivenom Serum, No. FDA/VBP/GDL-10/02, Technical Advisory Committee on Safety of Vaccines and Biological Products, 5th Sept, 2025, Ghana Food and Drug Authority.