FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF SNAKE ANTIVENOMS

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Abbreviation

FDA	:	Food and Drugs Authority
WHO	:	World Health Organization
QPPV	:	Qualified Person for Pharmacovigilance
SmPC	:	Summary of Product Characteristics
RMP	:	Risk Management Plan
RMMs	:	Risk Mitigation Measures
HCPs	:	Health Care Professionals

INTRODUCTION

The Food and Drugs Authority (FDA) is mandated by the Public Health Act, 2012, Act 851 to regulate the registration and importation of drugs, including snake antivenoms. Snake antivenoms are the only therapeutic products for the treatment of snake-bite envenoming. The unavailability of effective snake antivenoms to treat specific types of snake envenomation encountered in different regions of the world has become a critical health issue at the global level. The crisis has reached its greatest intensity in Africa, particularly the Sub-Saharan Africa, where Ghana is no exception.

Puff adders, black-necked spitting cobra, mambas, saw-scaled vipers are the common species found in Ghana. The West African carpet viper (*Echis ocellatus*) is the cause of most snake bites/envenomation. Most bites occur among rural and farming populations who are exposed to the vipers during agricultural activities. Venoms of these species cause relatively high morbidity and mortality due to local tissue necrosis and systemic coagulopathies induced by their venom.

In March 2007, anti- snake venom immunoglobulins were included in the WHO Model List of Essential Medicines, acknowledging their role in a primary health care system.

Objective

This policy is to provide guidance to applicants, manufacturers and importers on the specific requirements for the registrations of snake antivenom in Ghana.

Scope

The policy guideline shall be applicable to the registration of snake antivenom in Ghana. Please note that these guidelines are to be read in conjunction with FDA's Guidelines for Registration of Vaccines.

Snake Venoms Selection

An accurate selection of snake venoms is critical for the production of snake antivenoms that have the capacity to cover the majority of cases of envenomation. The composition of snake venoms is very complex and a high inter-species and intra-species variation can pose a challenge to the product development design. As a result, the design of the antigenic mixture to be used in snake antivenom production is a critical task, and the selection of the most appropriate snake venoms for the production of an anti-venom should be carefully though through, and manufacturers should ensure that the product satisfy the underlisted requirements:

A. Only medically most relevant snakes from the geographical region where the snake antivenom would be used are selected, considering the variability of venom composition within the region of distribution of the snake species;

B. Information on cross-neutralization of snake antivenoms against the venoms of species not included in the mixture of venoms used to immunize animals for the snake antivenom formulation is available and made known in documentations;
C. Information and data on the average venom yields of each snake species used in the snake antivenom formulation is made available in the product documentation;
D. Polyvalent formulations which are intended for registration in Ghana should contain the following species;

1) Puff adder (*Bitis arietans*)
2) West African carpet viper (*Echis ocellatus*)
3) Western green mamba (*Dendroaspis viridis*)
4) Black-necked spitting cobra (*Naja nigricollis*)
5) Senegalese cobra (*Naja senegalensis*)
6) Gaboon viper *(Bitis gabonica)*
7) Rhinoceros viper *(Bitis nasicornis)*
8) Roman's saw-scaled viper *(Echis leucogaster)*
9) Saw-scaled viper *(Echis carinatus)*
10) Egyptian cobra *(Naja Haje)*
11) Forest cobra *(Naja melanoleuca)*
12) The black mamba *(Dendroaspis Polylepis)*
13) Jameson's mamba *(Dendroaspis Jamesoni)*
14) Green mamba *(Dendroaspis Angusticeps)*

Polyvalent formulation must also reflect any updates in the serpentine species, as new scientific understanding evolves. Additionally, for any species, the venom which is included in the formulation must be justified according to incidence of snake bite and geographical endemism, relevant to Ghana.

The following species are a priority and shall be included in any venom formulations to be imported into or manufactured in Ghana;

1) Puff adder (*Bitis arietans*)
2) West African carpet viper (*Echis ocellatus*)
3) Western green mamba (*Dendroaspis viridis*)
4) Black-necked spitting cobra (*Naja nigricollis*)
5) Senegalese cobra (*Naja senegalensis*)

There are variations in venom composition and antigenicity within the range of a single taxonomic species as well as other causes of intra-species variation (such as changes according to the age of the specimens). Therefore, pooled representative samples of venoms should be prepared from snakes of different ages.

Cross-neutralization of venoms outside the range of venoms used for immunization may extend the range of therapeutic applications of some snake antivenom. Results of preclinical potency testing may be used to identify a potential cross-neutralization capacity of antivenoms, which should subsequently be confirmed by clinical testing in envenomed patients.

In vitro immunological cross-reactivity should not be used as the single basis for recommending therapeutic use of snake antivenom outside the range of venoms used in its production.

MONOVALENT SNAKE ANTIVENOM

Monovalent snake antivenoms are limited in use to a single species of venomous snake or to a few closely related species whose venoms show clinically effective cross-neutralization. These conditions apply in areas where:

1) There is only one medically important species (e.g. *Vipera berus* in the United Kingdom and Scandinavia);
2) A simple blood test, suitable for use even in peripheral health care centres, can define the biting species (e.g. detection of incoagulable blood by the 20-minute whole blood clotting test in the northern third of Africa where only *Echis spp*. cause coagulopathy);
3) A simple algorithmic approach allows the species to be inferred from the pattern of clinical and biological features;
4) There is a reliable and affordable rapid immunodiagnostic test readily available allowing the toxins to be identified unambiguously.

Ghana is inhabited by several species of snakes, where there may be no distinctive clinical symptoms to direct the use of a monovalent snake antivenom. As a result, applications for market authorization for a monovalent snake antivenoms will not be processed.

DOSAGE FORMS

The Food and Drugs Authority (FDA) requires that snake antivenom applications are submitted for lyophilized products only, since the available infrastructure and logistics favours a lyophilized product.

Further, the concentrations/potency of all the snake antivenom contained in the formulation should be expressed in Milligrams (**mg**) of venom neutralized per Millilitre of snake antivenom, instead of the current practice of Lethal Dose (**LD_{50}**).

REGISTRATION REQUIREMENTS

An applicant intending to register a snake antivenom shall prepare and submit the underlisted product registration requirements;

1) An application letter addressed to the Chief Executive Officer (CEO) expressing your intention to submit for registration a particular snake antivenom product.
2) Pay the appropriate registration and Good Manufacturing Practice inspection fee (please refer to the FDA website at https://fdaghana.gov.gh)
3) Completed (signed/stamped and dated) registration application form for biological products. Forms can be obtained by visiting the FDA website at https://fdaghana.gov.gh
4) Product representative samples and reference standards.
5) Full product development dossier (CTD Module 1 to 5):
    a) Module 1 – Administrative/ legal information
    b) Module 2. Summaries/overviews
    c) Module 3 Quality information (Chemistry, Manufacture and Control)
    d) Module 4 Non clinical information
    e) Module 5 Clinical information

    This shall include the Ghana specific Risk Management Plan (RMP) and the identity of the Qualified Person for Pharmacovigilance (QPPV) in Ghana.
6) Commitment to training health care professionals on the correct dosing regimen.
7) Commitment to providing information and poster for training health care professionals on the correct dosing of patients.
8) Commitment for monitoring the effectiveness of the Risk Mitigation Methods (RMMs)