



Target product profiles

for animal plasma-derived antivenoms

Antivenoms for treatment of snakebite
envenoming in south Asia



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The Irula Snake Catcher's Industrial Co-operative Society use clay pots to house snakes used for venom production. They are the main source of venoms for all of India's antivenom producers. © David J. Williams/WHO

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TPP Development Process

These target product profiles (TPPs) were developed in line with the procedure defined in the WHO Target Product Profiles: Generic Methodology (Harmonized guidance document dated 25 January 2019).

Management of Conflicts of Interest

All TSAG members acted independently and in a personal capacity. Declarations of Interest were submitted by all members, and these were reviewed by two members of the technical unit. Potential conflicts of interest were further assessed with the technical unit team leader. Where there was a possibility of potential or perceived conflict of interest, advice was obtained from the WHO Office of Compliance, Risk Management and Ethics (CRE) and the WHO Legal Department (LEG). Nominations were approved by the Assistant Director General, Universal Health Coverage/Communicable and Noncommunicable Diseases.

Glossary of key terms and abbreviations

This glossary provides brief definitions of terms and abbreviations used in this document; they may have different meanings in other contexts.

20WBCT	20-minute whole blood clotting test
Active pharmaceutical ingredient (API)	The specific drug substance defined by the manufacturer according to its physical and chemical composition.
AKI	Acute kidney injury
Antivenom efficacy	The efficacy of an antivenom is a preclinical measure of the <i>in vivo</i> or <i>in vitro</i> neutralizing potency against a specific activity of a venom or venoms. Preclinical efficacy data is valuable for developing hypotheses that are subsequently tested in clinical trials, and for quality control of antivenom batches, where the activity of each batch lot is compared to an established minimum specification to determine the acceptability of the batch for release by the manufacturer or regulator.
CFR	case fatality rate
Clinical effectiveness	The effectiveness of an antivenom is a measure of its ability to produce a clinically effective outcome when used to treat snakebite envenoming. Antivenom effectiveness should be established through well-designed and managed clinical trials of antivenom in the treatment of real cases of envenoming.
CTD	Common Technical Document (CTD) format: a specific format for product dossier preparation recommended by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).
DALY	disability-adjusted life year. A measure of overall disease burden, expressed as the number of years lost due to ill health, disability or early death; used to compare overall health and life expectancy in different countries. DALYs for a disease or health condition are calculated as the sum of the years of life lost due to premature mortality in the population and the years lost due to disability resulting from the health condition or its consequences.
DNDi	Drugs for Neglected Diseases <i>initiative</i>
ED ₅₀	Median effective dose (or 50% effective dose): the quantity of antivenom that protects 50% of test animals injected by a particular route (e.g., subcutaneously, intravenously, or intraperitoneally), with a dose of venom (e.g., typically 5xLD ₅₀) from death after an established period (usually 24–48 hours).
Envenoming	Injection of venom by an organism (e.g., a venomous snake) into another organism, leading to pathological manifestations (also called envenomation).
Fab	An antigen binding fragment of an immunoglobulin comprising a heavy chain and a light chain that each have a single constant domain and a single variable domain. Fab fragments typically result from the proteolytic digestion of IgG by papain at the amino terminal side of the disulfide bonded hinge region and have an approximate molecular weight of 50 kDa. Sometimes referred to as F(ab).
F(ab') ₂	An antigen binding immunoglobulin fragment comprising a pair of Fab fragments connected by a protein hinge and produced by proteolytic digestion of IgG with pepsin to cleave away the Fc fragment on the carboxyl terminal side of the disulfide bonded hinge region. The approximate molecular weight is 110 kDa.

Fc	An immunoglobulin fragment without antigen binding capacity that contains paired CH ₂ and CH ₃ domains and the C-terminal halves of the two heavy chains connected by disulfide bonds. Approximate molecular size is 40 kDa.
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Commission on Harmonization
IgG	Immunoglobulin G: a polypeptide antibody secreted by B cells that has an approximate molecular weight of 150 kDa comprised of two heavy chains of approximately 50 kDa and two light chains of approximately 25 kDa each.
LD ₅₀	Median lethal dose (or 50% lethal dose): the quantity of snake venom, injected by a particular route (e.g., subcutaneously, intravenously, or intraperitoneally), that leads to the death of 50% of the animals in a group after an established period (usually 24–48 hours).
Monovalent antivenom	Antivenoms that are raised from venom of a single species and are marketed for use in treating envenoming by that species or by closely related species (typically from the same genus). The term “monospecific” is often used and has the same meaning.
NTD	neglected tropical disease
POC	point of care
Polyvalent antivenom	Antivenoms that are raised from the venoms of multiple species and are marketed for use in treating envenoming by those species or by closely related species (typically from the same genus). The term “polyspecific” is often used and has the same meaning.
Potency [P]	Potency [P] is the amount of venom completely neutralized per millilitre of antivenom (e.g., resulting in 100% survival of test animals). Potency is a mathematically derived parameter calculated from <i>in vivo</i> antivenom ED ₅₀ and corresponding venom LD ₅₀ data using the equation $P = n - 1 \text{ LD}_{50} / \text{ED}_{50}$ where n = number of LD ₅₀ in the challenge dose.
QALY	Quality-adjusted life year. A measure of overall disease burden, similar to DALY, that includes both the quality and quantity of life lived and used to compare overall health and life expectancy in different countries.
RCT	randomized controlled trial
Total Protein	The mass of all the protein material in an antivenom solution, including but not limited to intact or fragmented immunoglobulins, non-immunoglobulin donor animal proteins, and extraneous protein material, determined by any conventional protein-specific quantification assay (e.g., colorimetric, fluorometric, spectrophotometric, chemical) and expressed in terms of mg protein per millilitre of reconstituted antivenom solution, or mg protein per gram of lyophilized antivenom solids.
TPP	target product profile
TSAG	Technical and Scientific Advisory Group on TPPs for Snake Antivenoms and Other Treatments
WFI	water for injection
WHO	World Health Organization





Executive summary

We describe here WHO public-benefit Target Product Profiles (TPPs) for antivenoms intended to be used for treatment of snakebite envenoming in South Asia, the region of the world that harbours arguably the greatest burden of morbidity and mortality from snakebites. Four TPPs are described. The first is for products that are intended for widespread use throughout south Asia, for treatment of envenoming irrespective of the species of snake causing a bite. This would include products minimally targeted to treat the ‘big four’ species that dominate the landscape of snakebites in the south Asian sub-continent. The second is for products where the snakebite causes predominantly neurotoxic effects. The third is for snakebites where the effects are largely haemorrhagic or procoagulant. The fourth is for treatment of envenoming for a single species or genus of snake. These TPPs are intended to provide guidance to manufacturers, regulators, procurement agencies, clinicians, and researchers, to improve antivenoms and thus treatment of snakebite envenomation.

Introduction

Snakebites are responsible for considerable mortality and morbidity throughout much of the world. The World Health Organization (WHO) has convened a Technical and Scientific Advisory Group (TSAG) to generate public-sector Target Product Profiles (TPPs) for treatment of snakebite envenoming. The overall goal of this program is to ensure access to safe, effective, affordable, and accessible treatments for all patients in need.

Heterologous animal plasma-derived immunoglobulin preparations (“antivenoms”) have been the mainstay of treatment for snakebite envenoming for nearly 130 years (1) and are the most effective drugs currently available for treatment of snakebite envenoming. They are typically produced by immunizing donor animals such as horses or sheep with small amounts of snake venoms and then purifying antibody fractions from the hyperimmune plasma for intravenous administration to snakebite envenoming victims. The quality, safety, and effectiveness of antivenoms is highly dependent upon the investment of producers in research and development, application of Good Manufacturing Practices (GMP) and rigorous quality control (1).

This set of four TPPs focuses on animal plasma-derived antivenoms for south Asia. They provide guidance on conventional broad-spectrum polyvalent antivenoms, including those products directed to treatment of the 'big four' venomous snakes – Indian cobra, common krait, Russell's and saw-scaled vipers. They also accommodate expanded polyvalent coverage through inclusion of additional immunizing venoms (e.g., *Hypnale hypnale* for Sri Lanka and south India), provide guidance on monovalent products and two important new product classes; south Asian polyvalent antivenoms for treatment of envenoming dominated by neurotoxic effects, and south Asian polyvalent antivenoms for treatment of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

Unmet medical need/problem

WHO estimates that 5.4 million people worldwide are bitten each year, with 2.7 million envenomings. Snakebites are responsible for some 83,000-138,000 deaths per annum (2). An additional 400,000 people per year suffer from disabilities such as amputations, scarring leading to impaired limb function and post-traumatic stress disorder. As much as 70% of this burden occurs in south Asia (3). In India alone there were an estimated 1.11-1.77 million snake bites resulting in 0.77-1.24 million cases of snakebite envenoming based on 2015 data, and the mean mortality from 2001-2014 was 57,671 (95% CI: 55,872-59,471) (4). Poor national level data in Pakistan, Nepal and Bhutan undermines efforts to reliably estimate regional mortality but based on available data from Sri Lanka (>400) and Bangladesh (>6000), deaths across south Asia due to snakebite envenoming are likely to exceed 66,000 cases per annum (5-7). Victims are from some of the least-empowered, poorest, and most-marginalized communities; often agricultural workers, rural villagers, working children; in poorly constructed housing with very limited access to education and health care.

WHO has identified access to safe, effective, affordable, and accessible antivenoms as a key priority for addressing snakebite morbidity and mortality (1). Defining TPPs for antivenoms in this market is an essential early step towards improving the current manufacturing environment. It will help to end a vicious cycle dominated by poorly designed, ineffective, and weakly regulated products, and provide regulators, manufacturers, procurement agencies and medical professionals with essential characteristics that define well-designed, quality-assured alternatives. Thus, it represents an opportunity to change the product landscape, drive innovation and development of improved antivenom products, and result in better treatment, and outcomes for the victims of this neglected tropical disease.

Rationale

Snakebite envenoming can be a complex disease to manage effectively. There are approximately 70 venomous snake species in south Asia, but not all are medically important. Many of these species have very small geographical ranges and/or a low risk of human contact. Some of them have venom that is not considered dangerous to humans. Venoms are complex mixtures of multiple toxins and, depending on the type of toxins present in a venom, the physiological and pharmacological effects may vary considerably among and even within species. Fortunately, many of the toxins share broad immunological homogeneity such that neutralizing antibodies raised against one snake species are often effective against other species too.

To make the snakebite problems more manageable, some important intellectual and practical simplifications need to be considered.

For the purposes of this document, we consider south Asia to comprise of Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka. This group of countries is defined by the distributions of major venomous snake species and needs for similar antivenoms, rather than mapping precisely to WHO regions.

WHO considers 13 species from two main families (Viperidae and Elapidae) to be of highest (Category 1) medical importance in south Asia and the major targets for antivenom products in the region (8). These are the venomous snakes that are most often encountered and pose the greatest potential threat to human life and wellbeing. A further 10 species are of secondary (Category 2) medical importance, either because they are known to be highly venomous, but are either less frequently associated with serious snakebites, or have little epidemiological data available. The list of these species and their distributions have been published by WHO (8).

The clinical syndromes of envenoming in south Asia are well-defined and the syndromic grouping of species is potentially useful in the management of snakebites. WHO guidelines define four clinical syndromes (9):

1. Local swelling with altered bleeding/clotting: typically caused by bites from vipers.
2. Local swelling with altered bleeding/clotting, shock or acute kidney injury caused by bites from Russell's vipers.
3. Local swelling with progressive paralysis (neurotoxicity): due to cobra bites.
4. Paralysis with minimal evidence of local swelling at a bite site, most commonly when sleeping on the ground: due to kraits.

Administration of an appropriate antivenom requires the correct early diagnosis of symptoms and signs of snakebite envenoming. Syndromic assessment of patients can inform both the diagnosis and the selection of the right antivenom from those available. It also enables health workers to identify the type of snake that may be involved by distinguishing between neurotoxic, haemorrhagic, cytotoxic, or procoagulant effects (9, 10). At present most of the antivenoms available in south Asia are broad-spectrum, polyvalent products that are designed to be used for bites by the 'big four' species – Russell's and Saw-scaled vipers *Daboia russelii* and *Echis carinatus*), spectacled cobra (*Naja naja*) and common krait (*Bungarus caeruleus*). These antivenoms negate the need for species level identification of the biting snake and can be effective in the geographical areas where those snakes occur. Polyvalent products sometimes have considerable paraspecific cross-neutralizing activity against venom from other species. One key problem however is that antivenoms designed for large numbers of species (and especially those that produce large volumes of venom) may lack specific potency for some of those species. This can result in a need for administration of very large doses of antivenom, and if this is not possible, the performance of the product may be poor. Reducing the number of venoms and taking a syndromic approach to antivenom design coupled to deeper understanding of the proteomic and pharmacological profiles of each venom used can lead to products of greater specificity and potency that are highly effective, safe, and more affordable.

Monovalent products are appropriate where one species or genus causes either most of the snakebite cases in a defined geographical range or where the venom has specific activities that are not neutralized by available polyvalent antivenoms. Outside south Asia, monovalent antivenom products are currently manufactured to treat envenoming by, for example, monocellate cobra (*Naja kaouthia*) and Russell's vipers (*Daboia siamensis*).

We have also very specifically considered the extent to which this current TPP should be similar to, or vary from, the TPP recently published for antivenoms to be used in sub-Saharan Africa (10). The snake faunas are different on the two continents and there are quantitative differences in the frequency of presentation with different clinical syndromes in that neurotoxic envenoming is more frequently observed in South Asia. But the unmet needs are largely the same and there is an important issue of equity and so the use case scenarios, scope, and details of the two TPPs have been kept as similar as possible.

Use-case scenarios

Taken collectively, these considerations have led us to propose four potential use-case scenarios:

1. Snakebite envenoming by an unidentified species of WHO category 1 or 2 south Asian snake.
2. Snakebite envenoming by a known species of WHO category 1 or 2 south Asian snake.
3. Snakebite envenoming by an unidentified species of WHO category 1 or 2 south Asian snakes that produces a clinical syndrome of envenoming dominated by neurotoxic effects.
4. Snakebite envenoming by an unidentified species of WHO category 1 or 2 south Asian snakes that produces a clinical syndrome of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

These in turn lead to four potential classes of antivenom products:

- A. Broad-spectrum polyvalent antivenoms
- B. Monovalent antivenoms for specific use cases
- C. Syndromic south Asian polyvalent antivenoms for neurotoxic envenoming
- D. Syndromic south Asian polyvalent antivenoms for non-neurotoxic envenoming

Scope of TPPs

For every characteristic of these TPPs, we define both ideal and minimal criteria; the former as targets to which all should aspire and the latter as currently acceptable criteria, based on knowledge of products currently available.

Almost all the people living in the countries within the south Asian region are potentially at risk of snakebite envenoming because indigenous populations of venomous terrestrial snakes are so widespread. Antivenoms are used to treat snakebites in men, women (including pregnant women), and children of all ages. While patients will ultimately be the recipients of antivenoms, procurement agencies and health care professionals are the major "end-users" rather than patients themselves.

Antivenom is a time-critical emergency biotherapeutic drug and should ideally be available as close to the communities in which people are at risk of snakebite envenoming as is possible. Products defined by this TPP should have safety profiles that make them amenable to being deployed to primary health care facilities that have health

workers who have been trained in the diagnosis and emergency treatment of snakebite envenoming. While it is minimally preferable that antivenom will be administered under the direct supervision of an appropriately qualified and experienced medical doctor, the use of antivenom under indirect (e.g., following telephone consultation, radio communication or other “telemedicine” engagement with the medical doctor) supervision should be encouraged as the optimal case for expanding accessibility to safe, effective antivenoms for most of the population. Minimal clinical skills for health workers administering antivenoms should include the ability to detect criteria for antivenom treatment (e.g., clinical signs of envenoming, perform and interpret bedside tests such as 20WBCT), gain intravenous access, and detect signs of anaphylaxis and treat with adrenaline/epinephrine.

Several studies have reported on the low efficacy and high prevalence of adverse reactions of antivenom products in several south Asian countries (11, 12). This contrasts with the situation in some other parts of the world where antivenoms have been reported as being both safe and effective with mortality less than 2% (13, 14). Improved or new products, manufactured with characteristics set out in these TPPs, should maintain as a minimum the best standards achievable globally and optimally exceed them. These TPPs also propose optimally and minimally acceptable effectiveness characteristics for clinical consequences of snakebite envenoming (e.g., coagulopathy, amputation, tissue injury, etc.) that are pragmatically based on the performance of existing good quality products.

Indications and contraindications

Current south Asian polyvalent products are designed primarily for treating bites by the ‘big four’ species – *Bungarus caeruleus*, *Daboia russellii*, *Echis carinatus* and *Naja naja*. The optimal TPP characteristics for a polyvalent antivenom to treat envenoming by unidentified species broadens this to include the possibility of also including immunizing venoms from other species that may be common causes of envenoming locally, for example *Hypnale hypnale* in southern India and Sri Lanka.

In general terms, monovalent antivenoms are only appropriate for species that fulfil one or more of the following conditions:

- Very common and dominating snakebite epidemiology in at least parts of their range.
- Rare but potentially lethal, with venoms that are difficult to source in large amounts and cannot be neutralized by other antivenoms.

Elsewhere in Asia monovalent products have been designed for treating bites by Monocellate cobra (*Naja kaouthia*) and Russell’s viper (*Daboia samiensis*), but these may not be geographically suitable for transposition into south Asian markets. The use of monovalent antivenoms in settings where accurate identification of the biting species is not available is not recommended. Including additional venoms in the immunizing mixtures used to manufacture polyvalent antivenoms is a safer and more cost-effective approach. There may be a rationale for raising monovalent antivenoms for some rare species such as *Gloydius himalayanus* or for species that produce unique clinical profiles that support accurate diagnosis.

Additional TPPs aimed at encouraging production of polyvalent antivenoms for use in the syndromic treatment of snakebites are intended to facilitate products with broader species coverage but with a narrower range of toxin targets such that the products achieve greater neutralizing potency against the respective venoms. One such type of product would target neurotoxic venoms that can potentially cause rapid death through paralysis of airway and breathing muscles. A second type of syndromic product is described for treatment of envenoming by species whose clinical effects are predominantly cytotoxic, procoagulant or haemorrhagic resulting in spontaneous bleeding and haemorrhage and tissue necrosis.

There are no absolute contraindications to treatment of snakebite envenoming with antivenom. The choice as to which type of antivenom should be used – polyvalent, monovalent, or syndrome-specific - will be guided by availability of products and clinical judgement.

Manufacturing considerations

Animal plasma-derived antivenoms are described in several key pharmacopeia’s, including those in the United States, United Kingdom, Europe, and India. Considering the biological nature of the product and its manufacture, stating explicitly a few principles that would be regarded as implicit for other types of drugs, is useful. Antivenom products should be manufactured and subjected to routine quality controls following GMP standards. Pre-clinical testing and any additional assays should follow Good Laboratory Practice (GLP) to meet minimum standards for study conduct, personnel, facilities, equipment, quality assurance, and protocols, processes, and reports. Such requirements encompass the preparation of immunizing venoms from snakes and the immunization and collection of hyperimmune plasma from host animals (1).

Active pharmaceutical ingredient

Antivenoms are currently available as intact (whole) immunoglobulins (IgG), or as $F(ab')_2$ fragments. Antivenom manufacturers broadly define the active pharmaceutical ingredient (API) in animal plasma-derived antivenoms as the specific antibody component that is produced through their production process. This definition typically describes the type of antibody (e.g., IgG or a fragment that has been derived from it), the molecular weight range, physical characteristics, and tertiary structure. It refers to all the antibodies present that meet this description, not just the specific neutralizing antibodies, which typically comprise only 3-30% of the total antibodies present. Hence the definition of API adopted by the TSAG for these TPPs refers to the specific drug substance defined by the manufacturer according to its physical and chemical composition.

Antivenom preparations of $F(ab')_2$ are considered minimally acceptable whilst preparations of intact immunoglobulins (IgG) are optimal because they are:

- Higher in yield compared to $F(ab')_2$ fragments (1).
- Consistently of higher purity and with lower non-API content compared to $F(ab')_2$ products (1).
- Benefit from the robust contribution of caprylic acid treatment to the inactivation of lipid-enveloped viruses (15, 16).
- Have favourable pharmacokinetic profiles including longer half-lives (17).
- Demonstrate comparable safety and tolerability profiles with evidence that retention of the Fc region does not induce increased adverse drug reactions (18).
- Clinical studies have provided evidence that intact immunoglobulins produced under GMP are safe, well tolerated, effective in neutralizing various types of venoms and with good clinical effectiveness (13).

Finished product form

Both lyophilized and liquid preparations have advantages and limitations. Current liquid preparations dispensed in the final container under GMP-compliant conditions are easier to use clinically but require the guarantee of storage and transportation under conditions maintaining a cold chain (typically 2-8°C). Lyophilized formulations may usually be transported and stored at a temperature not exceeding 25°C and are of interest for distribution to areas where the cold chain cannot be guaranteed, such as in many tropical regions of the world. However, lyophilization is an expensive and complex manufacturing operation that should be carefully validated and operated to maintain the quality of the product. Faulty lyophilization can result in denatured protein that is difficult to solubilize. The TSAG also recognized that a thermal tolerance upper limit of 25°C potentially limits the use of lyophilized antivenoms since daily ambient temperatures in many parts of south Asia exceed this throughout the year. Many countries in south Asia have climates that range from ICH climatic zone III (>22°C and <15 hPa) to IVb (>22°C and >27 hPa) where ambient temperature frequently exceeds 25°C. For this reason, specifications related to lyophilized product characteristics were aligned to ICH climatic zone IVb thermal tolerance range and manufacturers should demonstrate that their products comply with this specification.

Protein and immunoglobulin content

Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Broad-spectrum and syndrome-directed polyvalent antivenoms must be capable of neutralizing large quantities of venom from several species for which the average adult venom yield of some species may differ by more than ten-fold from that of others. WHO has found that products with very low total protein content simply cannot contain adequate API at the minimum specifications to effectively neutralize large amounts of venom. In line with the recommendation for products intended for sub-Saharan Africa, the TSAG recommended that specifications of at least 5.0% w/v (minimal model) and 7.5% w/v (optimal model) be introduced for the lower limits of acceptable protein content. Maximum protein content should be in accordance with requirements of regulatory agencies and the relevant pharmacopeia.

Regarding immunoglobulin content, the purity of antivenom is intrinsically linked to product safety and tolerability and reducing the proportions of non-immunoglobulin proteins in antivenoms will improve safety. Most manufacturers currently specify that products contain not less than 85% API (e.g., whole IgG or $F(ab')_2$ molecules). Several products assessed by WHO fell short of this specification in independent laboratory assessments. For this reason, 85% was considered by the TSAG to be the absolute minimum acceptable specification for specific API whether it be $F(ab')_2$ or intact (whole) IgG. Smaller fragments such as $F(ab')$, Fab or Fc should not be included in the measurement of this specification. Optimally, higher purity is desirable with 90% being recommended. The amount of total protein, the amount of API and the specific amounts of any other vial contents (e.g., aggregates, non-API immunoglobulins, other proteins, etc.) should be included on vial labels and other packaging.

Preclinical efficacy studies

Antivenom should be comprehensively evaluated in a preclinical laboratory environment prior to marketing authorization or licensing. WHO Guidelines set out a suite of quality control, viral safety, stability, and efficacy tests that should be used to evaluate products (1). Establishing preclinical efficacy using biologically relevant toxin activity neutralization bioassays is fundamentally important for ensuring products that do not meet specifications are not marketed. At a minimum, the assessment of an antivenom's ability to neutralize venom-induced lethality is required. This establishes a volume range of antivenom that is required to neutralize venom lethality as determined by the antivenom median effective dose (ED_{50}) bioassay in laboratory animals. ED_{50} data should be converted to Potency (P), to estimate efficacy based on the amount of antivenom required to provide complete neutralization of a given quantity of venom (19). This is more relevant than the ED_{50} , since P estimates the dose for complete neutralization of lethality (and protection of all the test animals) rather than just protection of 50% of the test animals. In addition to estimating the dose required to prevent lethality, antivenoms that meet the optimal TPP specifications will also be robustly evaluated for their ability to neutralize specific toxin activities (e.g., necrotic, haemorrhagic, myotoxic, defibrinogenating or coagulant activities) through various toxin-specific activity bioassays (1).

It is also important that preclinical efficacy data should demonstrate the potential of the antivenom to neutralize *in vivo* a biologically relevant amount of venom. Many products currently express efficacy in terms of the ability of antivenom to neutralize a specified number of murine median lethal doses (LD_{50}). This is disingenuous because depending on the LD_{50} of the species concerned the mass of venom neutralized using this metric can vary substantially (19). In the absence of empirical data on the mass of venom injected by various species during defensive strikes, TSAG considered that the approach adopted elsewhere (e.g., Seqirus antivenoms in Australia), using neutralization of the average adult venom yield for each immunizing species by the recommended dose of antivenom, should be applied to preclinical efficacy testing of antivenoms in sub-Saharan Africa.

Antivenoms should not be marketed based on preclinical efficacy studies alone, however the use of robust preclinical data in the development of hypotheses that are subsequently tested through well-designed and managed clinical trials is appropriate. All antivenoms should be subject to clinical evaluation to validate the proposed dosage and its safety profile before the product is marketed. WHO Guidelines recommend that national regulatory authorities should expect antivenom manufacturers to either provide data confirming the clinical effectiveness and safety of products against envenoming by local snake species, or to support in-country clinical testing of the products to validate the preclinical efficacy and proposed dosages (1). Such studies must incorporate robust methodologies for reliable identification of the biting species as an essential component of all clinical trials and other clinical studies of antivenoms.

Clinical considerations

Venomous snakes do not meter the dose of injected venom according to the size or weight of bitten persons, and it is currently not possible to quantitatively measure the concentration of injected venom in patients at the bedside to inform dosing decisions routinely. Hence all patients, irrespective of body size, need to receive the same, standardized initial dose of antivenom, one which is adequate to neutralize the potential mass of injected venom.

Current dose recommendations on package inserts of available products are rarely based on results of well-designed clinical dose-finding studies or clinical trials yet this should be a fundamental minimum requirement for all antivenom products seeking registration and marketing approval (1).

Well-designed, pragmatic, and transparently managed clinical trials of antivenom are essential, and these TPPs recommend that antivenoms be carefully evaluated in both preclinical laboratory studies and in clinical trials prior to marketing authorization or licensing. Clinical trials need to adhere to the principles of Good Clinical Practice (GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Stakeholders including the World Health Organization have developed the International Council for Harmonization (ICH) GCP Guideline (20) to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

To define minimal parameters for clinical effectiveness the TSAG considered available data from WHO risk-benefit assessment data of the performance of antivenoms manufactured by Bharat, VINS, Premium Serums, Haffkine, Biological E, and the National Institute of Health (Pakistan). Characteristics for optimal performance were then defined with the aim of aspiring to an improvement over and above what is currently best-in-market performance of at least

50%, based on adoption of these TPPs in the design and manufacturing of new or improved products. The effectiveness parameters assume that patients will receive treatment within an acceptable time frame after the bite (i.e.: optimally within not more than 4-6 hrs; minimally within not more than 6-8 hrs), and that antivenom will be given in an appropriate initial dose, optimally based on results of independent pre-clinical testing by a competent laboratory and preliminary dose-finding clinical trials, and which has been accepted and is recommended by national regulators, or in national/regional guidelines. Prima facie evidence of effectiveness should first be established for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species). Clinical effectiveness against other species for which there is preclinical data supporting a hypothesis of paraspecific neutralization should also be established based on the same assumptions.

Frequency and route of administration

Snakebite is a time-critical emergency, and the sooner that a fully effective dose of an appropriate antivenom is administered, the better the chance that the patient will have a good outcome with minimal sequelae. This is best achieved by ensuring that every patient who has clinical signs and symptoms sufficient to warrant administration of antivenom receives a primary (initial) dose that can neutralize all the injected venom. Since data is lacking on the masses of venom injected in real cases of snakebite envenoming, the most appropriate available proxy (and one that is used elsewhere in the world) is average adult mass by weight of venom collected from specimens of each species during manual venom extraction. WHO plans to coordinate collection of data on average adult venom yields and include these data in its Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins (1).

Intravenous infusion and intravenous injection are the two available methods for delivery of antivenom. Each has advantages and disadvantages. Infusion of antivenom diluted in isotonic fluid is safe, easy, and convenient, but equipment and consumables add additional cost in resource-poor settings. One advantage is that venous access can be maintained for administration of other drugs or for ongoing fluid management. Potential risks include (1) that patients may be left unattended during administration at a time when there is a risk of evolution of adverse drug reactions, (2) unobserved and uncontrolled infusion rate may lead to fluid overload, and (3) that antivenom will be incorrectly diluted in a large quantity of intravenous fluid (e.g., 1 L) and wrongly given over a protracted time at a maintenance rate.

Intravenous slow-push injection requires the attending health worker to remain at the bedside and uses minimal equipment. It may however be uncomfortable for patients, and poor technique can lead to local trauma and infiltration into tissue rather than the circulation. If not undertaken carefully with aseptic technique, there is a risk of introducing contaminants with either technique. Dilution of antivenom with isotonic fluid prior to administration can potentially lead to contamination of sterile products, dosing errors, or administration errors so care and vigilance are essential.

Stability, storage, presentation, and packaging

As previously mentioned, much of south Asia is classified as falling between ICH climatic zones III, IVa or IVb. Temperature tolerance of at least $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$, and relative humidity of up to $75\% \pm 5\%$ is required for long term stability of products deployed in these environments. Longer shelf lives are preferred. Both real-time and accelerated stability studies should be considered to establish the thermal tolerances of antivenoms.

The presentation of antivenoms in vials or ampoules that do not contain a complete therapeutic dose contributes to the systematic under-dosing of patients in many settings, but especially in cases where out-of-pocket spending remains the main source of funding for antivenom treatment. To ensure that all patients receive an effective therapeutic dose of antivenom as early as possible, presenting the antivenom as a single effective therapeutic dose (e.g., in single 50-100 ml vials or sterile infusion bags) is recommended. Another alternative is to package several smaller vials (e.g., 10-20 ml) together in a single outer container or carton that clearly indicates that all the contents should be administered to deliver an effective initial dose. All outer packaging should clearly indicate that the product is intended for single use/single dose. Solutions provided for reconstitution of lyophilized antivenoms must be produced in competent GMP environments, be sterile, appropriately packaged and correctly labelled.

Vial labels and packaging should also include the amount of total protein (e.g., mg protein/vial), the proportion (e.g., not less than 85%) that is comprised by the API and indicate the presence of other potential vial contents (e.g., aggregates, non-API immunoglobulins, other proteins, preservatives, stabilizers).

Affordability and access

The TSAG have taken the view that the unit price of an antivenom is part of overall affordability which also includes considerations such as variations in clinical performance between products. It is apparent to WHO through its

risk-benefit assessment of antivenoms for the sub-Saharan African market that some manufacturers may base dose recommendations on marketing considerations rather than preclinical or clinical performance. Elsewhere pricing may be established by government panels, and in some cases these rates may fall below the manufacturing costs, threatening continued production and disincentivising innovation, modernization and GMP compliance by manufacturers. Procurement agencies and advisory panels or authorities should adopt policies that support the selection of antivenom products based on clinical effectiveness (e.g., cost per effective treatment), rather than cost per unit (e.g., vial, ampoule). Prices set by governments should balance the cost to buyers with fair return on investment for manufacturers so that sustainable production can be achieved and maintained. This has implications for cost-effectiveness evaluation of antivenoms since it shifts the criteria to base pricing on cost of an effective treatment, rather than a single arbitrarily formulated unit of product. Performance and cost-effectiveness data are not currently available across all relevant products, so it is not currently possible to define desired prices or costs in absolute numbers. Until such time as cost-effectiveness studies are completed, principles of 'fair pricing' should guide discussions between buyers and sellers, sometimes referred to as the lowest possible sustainable price. WHO considers that a "fair price" is one that is affordable for health systems and patients and at the same time provides sufficient market incentive for industry to invest in innovation and the production of medicines. In other words, fairness here implies positive incentives and/or benefits for all stakeholders.

Supportive/adjunctive therapy

The WHO guidelines for the management of snakebites in south-east Asia (and any relevant national protocols) should be followed (9). The items listed in those guidelines should be available for potential use with all patients who present with a suspected snakebite. They represent an essential list for any setting in which antivenom is being administered. Depending on individual case presentation some patients will need to be managed in facilities with substantially greater resources.

Training and education

There is a need for improved clinical training of health workers in the diagnosis, treatment, and management of patients with real or suspected snakebite envenoming. Medical schools, nursing, and health worker training colleges should be encouraged and supported to incorporate more detailed teaching on snakebite envenoming into curricula, countries should work with professional bodies and subject matter experts to develop standardized national or regional guidelines.

Animal plasma-derived antivenom TPP List

Target product profiles for South Asia^(a)

This document sets out four target product profiles (TPPs) for animal plasma-derived antivenoms intended for use against venoms from medically important snakes from South Asia:

TPP TITLE	USE CASE
Broad-spectrum South Asian polyvalent antivenoms	Snakebite envenoming by an unidentified species of WHO category 1 or 2 South Asian snake.
Monovalent antivenoms for specific use cases	Snakebite envenoming by a known species of WHO category 1 or 2 South Asian snake.
Syndromic South Asian polyvalent antivenoms for neurotoxic envenoming	Snakebite envenoming by an unidentified species of WHO category 1 or 2 South Asian snakes that produces a clinical syndrome of envenoming dominated by neurotoxic effects.
Syndromic South Asian polyvalent antivenoms for non-neurotoxic envenoming	Snakebite envenoming by an unidentified species of WHO category 1 or 2 South Asian snakes that produces a clinical syndrome of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

^a “South Asia” is defined as comprising the following Member States of the South Asian Association for Regional Cooperation (SAARC), which are Bangladesh, Bhutan, India, Nepal, Pakistan and Sri Lanka.



Common characteristics of TPPs



All South Asian, animal plasma-derived antivenoms

The following characteristics are common to the target product profiles of all animal plasma-derived antivenom products for use in South Asia. These should be read in conjunction with the specific TPP product characteristics of each of the four TPPs that are set out in the next section of this document.

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
1. Target population	All individuals and age groups with signs and symptoms of snakebite envenoming caused by a WHO Category 1 or Category 2 South Asian snake for which the antivenom was raised.	All individuals and age groups with signs and symptoms of snakebite envenoming caused by a WHO Category 1 South Asian snake for which the antivenom was raised.
2. Geographic working range	All South Asian countries: Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka.	
3. Level of implementation in the healthcare system	The product is capable of being deployed at all levels of the health system that meet minimal criteria for infrastructure and can be administered by trained health workers in accordance to recognized standards and existing national regulatory requirements.	The product is deployed to all levels of the health system that meet optimum criteria for infrastructure and can be administered by trained health workers in accordance to recognized standards and existing national regulatory requirements.
4. Intended end-users	End users include procurement agencies and health care professionals	
MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
5. Immunizing venoms	Immunizing venoms should meet the specifications of corresponding, geographically representative WHO reference venoms ^(b) for each species of snake included in the immunizing mixture for the product.	Immunizing venoms should be selected based on a detailed analysis of the composition of venoms from specimens across the broadest possible geographic range of each species, to ensure that all medically important toxin groups are represented in the immunizing venom pool for the product. Pooled venoms should be designed to have minimal compositional overlap and broad geographic representation of venom variants.
6. Active Pharmaceutical Ingredient (API)	Intact (whole) IgG immunoglobulin molecules obtained through appropriate technology	Either intact (whole) IgG immunoglobulin molecules or F(ab') ₂ immunoglobulin molecule fragments obtained through appropriate technology.
7. Finished Product Form	Lyophilized final product forms are optimally acceptable.	Either liquid or lyophilized final product forms are minimally acceptable.
8. Specific Immunoglobulin Content (Active Pharmaceutical Ingredient [API] content)	Not less than 90% of the total protein content must consist of intact active pharmaceutical ingredient [e.g.: intact (whole) IgG or F(ab') ₂ fragments of IgG that have been defined by the manufacturer as the Drug Substance in the Product Dossier/Master File]. Total API content to be included in vial labelling.	Not less than 85% of the total protein content must consist of intact active pharmaceutical ingredient [e.g.: whole IgG or F(ab') ₂ fragments of IgG that have been defined by the manufacturer as the Drug Substance in the Product Dossier/Master File]. Total API content to be included in vial labelling.

^b WHO has proposed the initial development of venom reference standards for *Bungarus caeruleus*, *Daboia russelii*, *Echis carinatus* and *Naja naja*. A process for developing these materials will be established in 2024.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
9. Preclinical efficacy (including potency of the antivenom)	Preclinical determination of median effective dose (ED ₅₀), potency (P) and toxin-specific activity bioassays ^(c) demonstrates the potential of the antivenom to neutralize <i>in vivo</i> at least the average adult venom yield of each species by the proposed initial dose of the product.	Preclinical determination of median effective dose (ED ₅₀) and potency (P) demonstrates the potential of the antivenom to neutralize <i>in vivo</i> at least the average adult venom yield of each species by the proposed initial dose of the product.
10. Safety and tolerability ^(d)	Incidence of anaphylaxis ^(e) <2.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <10%.	Incidence of anaphylaxis <5.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <20%.
11. Interactions with other medicinal products	There are no interactions with other medicinal products.	There are no serious interactions with other medicinal products, and minimal minor interactions.
12. Dose regimen	All patients, regardless of age, sex or body weight should receive the same dose. An initial dose should optimally be sufficient to neutralize 100% of the average adult venom yield of each of the species for which it is intended regardless of the specific activity of the venom. The specific volume of the initial dose, and its clinical effectiveness and safety will have been established through well-designed and administered randomized controlled trials (RCTs) that have been published and peer-reviewed. Additional doses may be administered based on the observed clinical picture and considering the natural time course for reversal of functional and physiological disturbances.	All patients, regardless of age, sex or body weight should receive the same dose. An initial dose should optimally be sufficient to neutralize 100% of the average adult venom yield of each of the species for which it is intended regardless of the specific activity of the venom. The specific volume of the initial dose, and its clinical effectiveness and safety will have been established through well-designed and administered clinical dose-finding and safety studies that have been published and peer-reviewed. Additional doses may be administered based on the observed clinical picture and considering the natural time course for reversal of functional and physiological disturbances.
13. Frequency of administration	Administration of a single dose of antivenom. This dose should be sufficiently potent to neutralize 100% of the average adult venom yields of each of the snake species for which the product is intended. Additional doses may be given based on the observed clinical picture over time, but ideally the initial dose should be adequate to neutralize all the injected venom, without the need for re-dosing.	
14. Route of Administration	Administered by controlled intravenous infusion (regulated iv drip or mechanical infusion pump). Antivenom may be diluted further with an appropriate volume of isotonic fluid to a total volume of not more than 200 millilitres, infused over a period of up to 60 minutes.	Administered undiluted by slow-push intravenous injection at a maximum rate of no more than 5.0 mL/minute, and with a total volume of not more than 200 millilitres given over a period of up to 60 minutes.

c See: Chapter 19.3 World Health Organization. *Guidelines for the production, control, and regulation of snake antivenom immunoglobulins*. Expert Committee on Biological Standardization. Technical Report Series no. 1004. Appendix 5. 2018. Geneva Switzerland.

d Expected characteristics in naïve populations. There is heightened risk in specific groups of people (e.g., snake handlers) who may be hypersensitized through previous exposure to equine or ovine (exogenous) immunoglobulin products.

e Here, anaphylaxis is minimally defined as the occurrence of one or more of the following clinical events: shock and other cardiovascular effects, bronchospasm, upper airway obstruction and/or angioedema.

15. Product Stability	For lyophilized products: At least 5 years in conditions up to and including ICH climatic zone IVb (temperature of $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and relative humidity of up to $75\% \pm 5\%$).	For lyophilized products: At least 3 years in conditions up to and including ICH climatic zone IVb (temperature of $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and relative humidity of up to $75\% \pm 5\%$). For liquid products: At least 3 years in conditions up to and including ICH refrigerated zone (temperature of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$).
16. Storage	For lyophilized products: Room temperatures up to ICH climatic zone IVb ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and relative humidity of up to $75\% \pm 5\%$).	For lyophilized products: Room temperatures up to ICH climatic zone IVb ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and relative humidity of up to $75\% \pm 5\%$). For liquid products: ICH refrigerated zone (temperature of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$).
17. Presentation	A single container (e.g.: vial, ampoule, or intravenous infusion bag) that holds sufficient active pharmaceutical ingredient to neutralize 100% of the average adult venom yields of each of the snake species for which it is intended.	A single container (e.g.: vial, ampoule, or intravenous infusion bag) or a carton/box that is clearly labelled as containing vials that must be given together in order to constitute a clinically effective initial dose comprising sufficient active pharmaceutical ingredient to neutralize 100% of the average adult venom yields of each of the snake species for which it is intended.
18. Packaging	Each outer package (e.g.: box or carton) should contain one complete initial dose, presented in a single container (e.g.: vial, ampoule, or intravenous infusion bag). Lyophilized presentations should be accompanied by an adequate volume of isotonic fluid or sterile water for injection (WFI) to ensure complete reconstitution of the product. Package inserts should be provided in the language of the country where the product is being marketed. Inserts should meet the requirements of internationally accepted guidelines (e.g., ICH, WHO) and national regulations in the country of manufacture and the country where the product will be marketed. Information on the total protein content and the total active pharmaceutical ingredient (API) content should be included on vial labels and package inserts.	

OPERATIONAL CHARACTERISTICS

CHARACTERISTIC	OPTIMAL	MINIMAL
19. Costs	A cost effectiveness study is conducted and demonstrates that antivenom is highly cost-effective.	If cost effectiveness studies can't be performed, evidence to support fair pricing of antivenom is requested. Once the cost effectiveness study is performed, antivenom is found cost effective.
20. Supportive and adjunctive therapy	Information is available in the WHO Guidelines on the Management of Snakes in South-East Asia	
21. Training & education needs	Knowledge of common local snake species including non-venomous ones, history and clinical examination, criteria for antivenom treatment, monitoring vital signs (including orthostatic blood pressure), POC tests (20WBCT, urine reagent sticks), resuscitation of shocked patients, nursing sick patients (positioning), iv access, iv cannula placement, management of iv infusion, criteria for use of/administration of adrenaline/epinephrine and other ancillary drugs.	



A



B



C



D



E



F







G

- A. *Bungarus caeruleus* (West Bengal, India)
- B. *Bungarus bungaroides* (Sikkim, India)
- C. *Bungarus niger* (Mizoram, India)
- D. *Daboia russelii* (West Bengal, India)
- E. *Hypnale hypnale* (Kandy, Sri Lanka)
- F. *Naja naja* (West Bengal, India)
- G. *Protobothrops himalayanus* (Sikkim, India)

Credit: Vishal Santra



Specific characteristics of TPPs

	Broad-spectrum South Asian polyvalent antivenoms	10
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	South Asian polyvalent antivenoms for neurotoxic envenoming	14
	South Asian polyvalent antivenoms for non-neurotoxic envenoming	16



Broad-spectrum South Asian polyvalent antivenoms

Products that are intended for all the major genera of WHO Category 1 medically important venomous snakes throughout South Asia.

Venoms should be representative of each of the WHO Category 1 genera. Minimally this would involve the use of venoms from *Bungarus caeruleus*, *Daboia russelii*, *Echis carinatus* and *Naja naja* (e.g.: proposed WHO reference standard venoms), but optimally it should include additional species of Category 1 medical importance for which current polyvalent antivenoms do not provide effective neutralization.

Examples of additional Category 1 species that could be used:

- *Bungarus*: *B. niger*, *B. sindanus*, *B. walli*
- *Echis*: *E. c. sochureki*
- *Hypnale*: *H. hypnale*
- *Macrovipera*: *M. lebetina*
- *Naja*: *Naja kaouthia*, *Naja oxiana*
- *Trimeresurus*: *T. erythurus*, *T. septentrionalis*

Other combinations, or additional venoms, including those from Category 2 (e.g., *B. ceylonicus*, *Ophiophagus hannah*, *T. malabaricus*, *T. septentrionalis*) could be used by a manufacturer at their discretion. The goal should be to select venoms from species that will induce the broadest possible immune response in plasma donor animals, resulting in polyvalent antivenom with the ability to neutralize as wide a range of venoms across as large a geographical area as possible. Venoms used should be a pool from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.

An ideal immunizing venom pool should exhibit minimal compositional redundancy. Also ideally, all the toxins present in the pool should have similar “opportunity” to elicit an immune response. The immunogenic surface area presented by a toxin depends on the molecular mass of the toxin. Thus, optimally pooled venoms should contain compositionally similar toxins, and when possible, those with similar LD₅₀. Manufacturers tend to immunize different horses with different venom pools (e.g., viperid venom pool, elapid venom pool) and then combine the different hyperimmune plasma into a single product. A more effective approach is to immunize groups of horses with different venom pools (1). The different hyperimmune plasma pools should be fractionated and purified separately, and the specific immunoglobulins combined proportionally to yield the final formulation.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.



Naja oxiana (Himachal Pradesh, India) © Vishal Santra

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
22. Indication	For the treatment of snakebite envenoming by an unidentified WHO Category 1 or Category 2 South Asian snake; to be used in conjunction with other treatment support interventions to address disease manifestations.	For the treatment of snakebite envenoming by an unidentified WHO Category 1 South Asian snake; to be used in conjunction with other treatment support interventions to address disease manifestations.
23. Contraindication	None	None

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
24. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
25. Clinical effectiveness (including selected outcome measures)	<p>When administered within 6–8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <1%. • amputations to <1%. • persistence of coagulopathy at 24 hours post-antivenom to <3%. • Progress to acute kidney injury (AKI) post-antivenom is <5% • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <5%. 	<p>When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <2%. • amputations to <2%. • persistence of coagulopathy at 24 hours post-antivenom to <6%. • Progress to AKI post-antivenom is less <10% • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <10%.



South Asian monovalent antivenoms

Products that are intended for either a single widespread species, a single genus, or species that are important causes of snakebite envenoming in a defined area.

Examples of species for which new monovalent antivenoms might be raised:

- Species specific: *Ophiophagus hannah* – rare presentation
- Genus specific: “green” pit vipers from the genera *Trimeresurus*/*Craspedocephalus*, other genera of vipers such as *Hypnale* or *Protobothrops*
- Locally important species: *Gloydius himalayanus* in Nepal and north-west India, *Echis c. sochureki* in Rajasthan

Venoms should be representative of geographical range of the Category 1 or 2 species or genus against which the product is being raised.

The venoms used should be a pool from specimens from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.



Hypnale hypnale © Wolfgang Wuster

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
26. Indication	For the treatment of snakebite envenoming by a known species of WHO Category 1 or 2 South Asian snake; to be used in conjunction with other treatment support interventions to address disease manifestations.	
27. Contraindication	None	None

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
28. Total Protein content	Minimum depends on the species and the average adult venom yield but should not be more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
29. Clinical effectiveness (including selected outcome measures)	<p>When administered within 6–8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <1%. • amputations to <1%. • persistence of coagulopathy at 24 hours post-antivenom to <3%. • Progress to AKI post-antivenom is <5% • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) to <5%. 	<p>When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <2%. • amputations to <2%. • persistence of coagulopathy at 24 hours post-antivenom to <6%. • Progress to AKI post-antivenom is <10% • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) to <10%.



South Asian polyvalent antivenoms for neurotoxic envenoming

Products that are intended for use in treating snakebites that produce clinical syndromes defined by the presence of neurotoxic signs and symptoms.

Venoms should be representative of each of the WHO Category 1 or 2 genera that have neurotoxicity as the dominant action of the venom. Minimally this would involve the use of venoms from species in the genus *Bungarus* and *Naja* but might also include *Ophiophagus hannah*.

Examples of species that could be used:

- *Bungarus*: *B. caeruleus*, *B. ceylonicus*, *B. fasciatus*, *B. niger*, *B. sindanus*, *B. walli*
- *Naja*: *N. kaouthia*, *N. naja*, *N. oxiana*, *N. sagittifera*
- *Ophiophagus*: *O. hannah*

Other combinations, or additional neurotoxic venoms could be used by a manufacturer at their discretion. The venoms used should be a pool from specimens from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.



Naja kaouthia (West Bengal, India) © Vishal Santra

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
30. Indication	For the treatment of snakebite envenoming by an unidentified species of WHO Category 1 or 2 South Asian snake that produces a clinical syndrome of envenoming dominated by neurotoxic effects (e.g., a neurotoxic species of cobra (<i>Naja</i> spp.) or krait (<i>Bungarus</i> spp.); to be used in conjunction with other treatment support interventions to address disease manifestations.	
31. Contraindication	Patients with snakebite envenoming who have evidence of coagulopathy, haemorrhagic effects, tissue necrosis and other cytotoxic venom effects without any clinical evidence of neurotoxic envenoming.	

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
32. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
33. Clinical effectiveness (including selected outcome measures)	<p>When administered within 6–8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <1%. • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <5%. 	<p>When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <2%. • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <10%.



South Asian polyvalent antivenoms for non-neurotoxic envenoming

Products that are intended for use in treating snakebites that produce clinical syndromes defined by the presence of haemorrhagic, cytotoxic or procoagulant signs and symptoms, and the absence of any signs or symptoms of neurotoxicity.

Venoms should be representative of each of the WHO Category 1 or 2 genera that lack neurotoxic activity and instead have haemotoxicity or cytotoxicity as the dominant actions of their venoms. Minimally this would involve the use of *Daboia russelii*, *Echis carinatus* and *Hypnale hypnale* venoms. Optimally it might also include *Macrovipera lebetina* and one or more *Trimeresurus/Craspedocephalus* or other viper venoms.

Examples of species that could be used (both regional and local species):

- *Daboia*: *D. russelii*
- *Echis*: *E. carinatus*
- *Eristicophis*: *E. macmahonii*
- *Gloydius*: *G. halys*, *G. himalayanuss*
- *Hypnale*: *H. hypnale*, *H. nepa*, *H. zara*
- *Macrovipera*: *M. lebetina*
- *Protobothrops*: *P. jerdonii*, *P. mucrosquamatus*
- *Trimeresurus/Craspedocephalus*: *C. gramineus*, *C. malabaricus*, *C. trigonocephalus*, *T. erythrurus*, *T. tibetanus*, *T. salazar*, *T. septentrionalis*

Other combinations, or additional venoms from other haemotoxic or cytotoxic species could be used by a manufacturer at their discretion. The venoms used should be a pool from specimens from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.



Trimeresurus malabaricus (Karnataka, India) © Mark O'Shea

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
34. Indication	For the treatment of snakebite envenoming by an unidentified species of WHO Category 1 or 2 South Asian snake that produces a clinical syndrome of envenoming dominated by haemorrhagic, cytotoxic or procoagulant effects (e.g., cytotoxic vipers species); to be used in conjunction with other treatment support interventions to address disease manifestations.	
35. Contraindication	Patients with snakebite envenoming who have evidence of neurotoxic envenoming (with or without tissue necrosis, and without coagulopathy or haemorrhagic effects).	

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
36. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
37. Clinical effectiveness (including selected outcome measures)	<p>When administered within 6–8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <1%. • amputations to <1%. • persistence of coagulopathy at 24 hours post-antivenom to <3%. • Progress to AKI post-antivenom is <5% • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <5%. 	<p>When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • CFR to <2%. • amputations to <2%. • persistence of coagulopathy at 24 hours post-antivenom to <6%. • Progress to AKI post-antivenom is <10% • need for debridement of dead tissue and/or skin grafting (excluding decompression or derroofing of blisters) to <10%.

References

1. Guidelines for the production, control and regulation of snake antivenom immunoglobulins. In: WHO Expert Committee on Biological Standardization: sixty-seventh report. Geneva: World Health Organization; 2017: Annex 5 (WHO Technical Report Series, No. 1004; <https://apps.who.int/iris/handle/10665/255657>, accessed 28 April 2023).
2. Snakebite envenoming: a strategy for prevention and control. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/324838>, accessed 28 April 2023).
3. Ralph R, Sharma SK, Faiz MA, Ribeiro I, Rijal S, et al. (2019). The timing is right to end snakebite deaths in South Asia. *Bmj*, 364, k5317.
4. Suraweera W, Warrell D, Whitaker R, Menon G, Rodrigues R, et al. (2020). Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. *Elife*, 9.
5. Warrell DA, Williams DJ. Clinical aspects of snakebite envenoming and its treatment in low-resource settings. *The Lancet* 401(10385): 1382-1398.
6. Ediriweera DS, Kasturiratne A, Pathmeswaran A, Gunawardene NK, Jayamanne SF, et al. Evaluating spatiotemporal dynamics of snakebite in Sri Lanka: Monthly incidence mapping from a national representative survey sample. *PLoS Negl Trop Dis*, 15(6), e0009447.
7. Rahman R, Faiz MA, Selim S, Rahman B, Basher A, et al. (2010). Annual incidence of snake bite in rural Bangladesh. *PLoS Negl Trop Dis*, 4(10), e860.
8. Snakebite information and data platform. Geneva: WHO Department of Control of Neglected Tropical Diseases; 2022 (<https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/snakebite-information-and-data-platform/>, accessed 28 April 2023).
9. World Health Organization Regional Office for South-East Asia. (2016). Guidelines for the management of snakebites. <https://apps.who.int/iris/handle/10665/249547> Accessed 28 April 2023.
10. Target product profiles for animal plasma-derived antivenoms: antivenoms for treatment of snakebite envenoming in sub-Saharan Africa. Geneva: World Health Organization 2023 (in press).
11. Senji Laxme RR, Khochare S, de Souza HF, Ahuja B, Suranse V, et al. (2019). Beyond the 'big four': Venom profiling of the medically important yet neglected Indian snakes reveals disturbing antivenom deficiencies. *PLoS Negl Trop Dis*, 13(12), e0007899.
12. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, et al. (2011). Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med*, 8(5), e1000435.
13. Abubakar IS, Abubakar SB, Habib AG, Nasidi A, Durfa N, Yusuf PO, et al. (2010). Randomised controlled double-blind non-inferiority trial of two antivenoms for saw-scaled or carpet viper (*Echis ocellatus*) envenoming in Nigeria. *PLoS Negl Trop Dis*. 4(7): e767.
14. Ademola-Majekodunmi FO, Oyediran FO, Abubakar SB. (2012). Incidence of snakebites in Kaltungo, Gombe State and the efficacy of a new highly purified monovalent antivenom in treating snakebite patients from January 2009 to December 2010. *Bull. Soc. Pathol. Exot.* 105: 175-178.
15. Korneyeva M, Hotta J, Lebing W, Rosenthal RS, Franks L, Petteway SR Jr. Enveloped virus inactivation by caprylate: a robust alternative to solvent-detergent treatment in plasma derived intermediates. *Biologicals*. 2002;30(2): 153–62.
16. Parkkinen J, Rahola A, Bonsdorff L, Tolo H, Torma E. A modified caprylic acid method for manufacturing immunoglobulin G from human plasma with high yield and efficient virus clearance. *Vox Sang*. 2006;90(2): 97–104.
17. Gutierrez JM, Leon G, Lomonte B. Pharmacokinetic-pharmacodynamic relationships of immunoglobulin therapy for envenomation. *Clin Pharmacokinet*. 2003;42(8): 721–41.
18. Otero-Patiño R, Segura A, Herrera M, Angulo Y, León G, Gutiérrez JM, et al. Comparative study of the efficacy and safety of two polyvalent, caprylic acid fractionated [IgG and F(ab')₂] antivenoms, in *Bothrops asper* bites in Colombia. *Toxicon*. 2012. 59(2): 344-55.
19. Calvete JJ, Lomonte B, Saviola AJ, Bonilla F, Sasa M, Williams DJ, et al. Mutual enlightenment: A toolbox of concepts and methods for integrating evolutionary and clinical toxinology via snake venomomics and the contextual stance. *Toxicon X*. 2021. 9-10:100070.
20. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [Current Step 4]; 9 November 2016 (https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf, accessed 13 June 2022).

DRAFT for public consultation



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