Target Product Profiles for small molecule or engineered antibody therapeutics for treatment of snakebite envenoming

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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
API	Active pharmaceutical ingredient. The specific drug substance defined by the manufacturer according to its physical and chemical composition.
Antivenom efficacy	The efficacy of an antivenom is a preclinical measure of the *in vivo* or *in vitro* 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.
BP	blood pressure
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.
CTC	controlled temperature chain
EATs	engineered antibody therapeutics, as defined in ref 1, includes: monoclonal antibodies of all isotypes, whether they are humanized, human, or chimeric, and regardless of the intended therapeutic mechanism of action; antibody fragments, such as single-chain variable fragments and antigen-binding fragments (Fab); single domain antibodies (nanobodies); bispecific or multi-specific antibodies; antibodies that have been chemically modified, such as through their conjugation to polyethylene glycol or an active drug substance; multiple MAb substances pooled within a final product (“antibody cocktail”).
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 5x LD_{50}) from death after an established period (usually 24-48 hours).
Envenoming	Pathological changes that follow the injection of venom by an organism (e.g., a venomous snake) into another organism (also called envenomation).
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCF	Health Care Facility
HCW	Health Care Worker
ICER	Incremental Cost Effectiveness Ratio
ICH	International Commission on Harmonization

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).
LMICs	Low- and middle-income countries
NTD	neglected tropical disease
POC	point of care
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 *in vivo* antivenom ED_{50} and corresponding venom LD_{50} data using the equation $P = n - 1\ LD_{50}/ED_{50}$ where n = number of LD_{50} in the challenge dose.
SBE	snakebite envenoming
SMI	small molecule inhibitor
SMTs	small molecule therapeutics
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

Introduction

Snakebites are responsible for considerable mortality and morbidity throughout much of the world[1,2]. The overall goal of this publication is to ensure safe, effective, affordable, and accessible treatments for all patients in need. For nearly 130 years the only specific treatments available for treatment of snakebites has been immunoglobulin preparations derived from the hyperimmune plasma of heterologous animals that have been immunised against the venoms of one or more species of snake. Some of these products have proven very effective but, for a variety of reasons, many other such antivenoms have been clinically inadequate. Moreover, these animal plasma-derived antivenoms are specific to particular groups of snake species and, for some species of snake, no effective products exist[1-3]. They all require a hospital setting for use which can be challenging to deliver promptly after a snakebite in many rural settings.

This document defines the first public-benefit Target Product Profiles (TPPs) for treatment of snakebite envenoming (SBE) using either small molecule therapeutics (SMTs) or engineered antibody therapeutics (EATs). There are two SMTs currently in early-stage clinical trials[4,5]. Considerable research effort is being focused on development of EATs though none have yet moved to commercial development and clinical evaluation[6]. Early data suggests that peptide therapeutics such as high affinity toxin-binding polypeptides pose a promising way forward in the neutralization of small protein toxins such as neurotoxic and cytotoxic 2-finger toxins[7]. The aim of these TPPs is to inform product developers, regulatory agencies, procurement agencies and funders about research and development considerations related to SMTs and EATs, and facilitate the most expeditious development of products that address an important public health need. It can also be used as general (if not complete) guidance for the development of peptide therapeutics such as toxin-binding polypeptides. This will help stakeholders bridge the gaps between early-stage development, commercialisation and market introduction. The document defines TPPs for SMTs and EATs deployed in (a) health care facility (HCF) settings or (b) in pre-hospital environments by first responders. Once products become available, have been clinically evaluated and experience obtained regarding use, safety and effectiveness it is likely that additional TPPs may be required for products with broader use cases.

During most of the 20th Century the production of antivenoms was largely a function of public health agencies in countries where SBE was endemic. Few commercial manufacturers invested in the field, and of those that did, unreliable market demand sometimes led to sporadic production or product abandonment altogether. Only in the mid-1980s and 1990s did new commercial producers emerge and begin developing and marketing products. Many of these did so by copying the design of existing products, and where their templates were products that already had poor effectiveness, rather than improving the situation, some of these new antivenoms only made the problems worse[8]. A key factor contributing to weak investment in product research and development has always been the lack of political priority and resources for SBE. Indeed, snakebite has been referred to by some as "the world's most neglected tropical disease", based largely on the lack of prioritization by public health organizations and ministries of health alike[9]. A major consequence of poor prioritization has been a lack of investment in research, particularly in relation to improving treatment and broadening the range of therapeutic options available[10]. As with many other diseases affecting poor communities in LMICs there is often a perception that a commercial market for these products simply does not exist[10].

Strong advocacy from a range of stakeholders through the first decades of the 21st Century have succeeded in changing some of these perceptions[11]. In 2017, these efforts resulted in the addition of SBE to the WHO list of priority neglected tropical diseases (NTDs), and as momentum has grown, so too has funding investment in snakebite research[11]. Already there has been a marked uptick in publications in the field, and with new funding initiatives there have been opportunities to explore some of the dramatic changes in the technologies available to develop new therapies. The overall position is certainly more positive now than it has been for many years. Two areas that have attracted much attention have been (a) the exploration of libraries of small molecules and drug candidates developed by the pharmaceutical industry for other applications, which could be mined to identify promising candidates to act against some of the specific toxins found in snake venoms as SMTs, and

(b) the use of new technologies for producing different types of antibodies and their components in bioreactors to create a new arsenal of EATs to neutralize venoms and their components[12].

While there are currently no commercially marketed SMTs or EATs for SBE, there is clearly a need to provide guidance to ensure that products meet the needs of end users and are designed with relevant use cases in mind. While no EATs are near-to-market, two SMTs are in early human clinical trials for the treatment of snakebite envenoming[4,5].

Approach to developing the TPP

These TPPs were developed in line with the procedure defined in the WHO Target Product Profiles: Generic Methodology (Harmonized guidance document dated 25 January 2019). To do this, World Health Organization (WHO) convened a globally representative Technical and Scientific Advisory Group (TSAG) to generate public-sector TPPs for treatment of snakebite envenoming. TPP development followed an iterative process, where all decisions were arrived at by consensus, followed by a period of public consultation before the final version was generated.

Unmet need

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[1]. An additional 400,000 people per year suffer from disabilities such as amputations, scarring leading to impaired limb function and post-traumatic stress disorder. 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 treatments as a key priority for addressing snakebite morbidity and mortality[1]. Defining TPPs for SMTs and EATs is an essential early step towards ensuring that as these types of products emerge, they are appropriately designed to meet relevant needs. This will provide researchers, regulators, manufacturers, procurement agencies and medical professionals with essential information about the characteristics that define well-designed, quality-assured products. Thus, it represents an opportunity to define the product landscape for both SMTs and EATs, drive innovation and development of improved treatments for snakebite envenoming, and lead to better outcomes for the victims of this neglected tropical disease.

Rationale

Venoms are complex biochemical mixtures that are made up of a variable assortment of proteins and peptides with a multitude of physical targets and pharmacological activities. Venom variation occurs both between and within species and it is perhaps because of this remarkable complexity and diversity that there have been so few explorations of possible use of small molecule inhibitors or engineered antibodies as potential treatment options; the effects of an inhibitor or antibody will only involve a single toxin or toxin class within a venom and there are practical limits as to how many different inhibitors or antibodies can be combined in a cocktail. The underlying scientific reasoning that has driven recent interest in these products assumes that by negating the effects of one, or a few, key toxins within the venom, SMTs or EATs can be effective in abrogating the overall clinical outcome. Venom complexity provides evolutionary redundancy for a snake to kill its prey or ward off a perceived predator[13]. In this view, venom complexity requires that many, or preferably all, toxin components are abrogated, and this is what a high quality conventional antivenom achieves. Nevertheless, this does not mean that the simplicity of the assertion that inhibition of a single toxin can modulate the effects of a complex venom and potentially save lives and reduce morbidity should not be investigated. Repurposed SMTs as well as EATs have been previously identified for example, for the treatment of Zika virus[14], an antiprotozoal SMI was evaluated for treatment of influenza[15], and several antiviral SMTs and EATs have been repurposed for clinical assessment in the treatment of SARS-CoV-2[16].

Several pieces of evidence collectively suggest that inhibition of a small number of toxin components, or even just one, within a venom may be worthy of exploration. Although there are many venomous

snake species, some common classes of toxins are widespread[17,18], and broadly targeting these may expand the potential therapeutic benefits of SMTs and EATs. At the same time, while venoms can contain a large number of different toxins, and proteomic analyses in particular have helped to build a substantial body of data, our understanding of the relative complexity of the physical and pharmacological actions of these proteins can still be improved. As this knowledge improves, we may find that the mapping of toxin interactions reveals common targets that render specific SMTs and EATs capable of broad cross-species activity, as well as opening doors to exploring a wider range of candidate treatments[12]. Finally, there is already evidence that conventional antivenoms can be very effective despite only poorly recognizing some venom components, supporting the view that the pathophysiological consequences of envenoming are not entirely dependent on all of the toxins present[5,17].

Use-case scenarios

There are two potential use-case scenarios in which therapeutics based on SMTs, or EATs would be potentially beneficial:

1. For treatment of SBE in patients admitted to an appropriate HCF setting. This would possibly be as an adjunct to other conventional treatment, such as administration of animal plasma-derived antivenoms and support of effective respiration.
2. For post-snakebite pre-hospital treatment by a trained first responder or health care worker (HCW) following suspected bites by venomous snakes as an interim measure to help delay progression to serious illness during the time that it takes to transport the patient to an appropriate HCF for more comprehensive management.

Clearly the formulation and presentation of SMTs and EATs for these uses will vary, and there will need to be consideration given to specific indications and limitations of use, yet it seems feasible that products can be developed for each of these use-cases, with appropriate safeguards, characteristics, and usage criteria.

Although not all snakebites result in envenoming, when this does occur it is a time-critical, acute medical emergency, and for this reason anyone with a suspected snakebite should be transported to a HCF as soon as possible[19,20]. The default approach in these TPPs is that guidance and products defined by these TPPs should have safety profiles consistent with the environment and resource settings in which they will be used including, but not limited to, appropriate consideration of the qualifications or experience of HCWs and first responders who may be authorised to use them. As new classes of products for the treatment of SBE there will need to be steps taken to ensure that HCWs are educated about the products and trained in their use. At the same time, any HCW authorized to use these and other treatments, such as conventional animal plasma-derived antivenoms should be trained in the diagnosis and emergency treatment of SBE.

While recognizing that safe use of SMTs and EATs is of paramount concern, and that different countries will impose a range of restrictions on their use based on policy, practice guidelines and resource settings, there is nevertheless a strong case for pre-hospital use by trained first responders. Many of the potentially severe effects of SBE can develop rapidly after a snakebite and administration of safe, effective treatment prior to arrival at a HCF can save many lives and reduce the impact of local tissue injury that leads to long-term disability. Deploying SMTs and EATs as post-bite emergency treatments to potentially abrogate the early development of severe envenoming would meet an important unmet need that conventional animal-plasma-derived antivenoms are not suitable to address.

Scope of TPPs

There are 168 countries in the world with endemic populations of medically important venomous snakes and we envisage that products based on these TPPs should be available and accessible to anyone at risk of envenoming: including pregnant people and children, and particularly economically disadvantaged people living in rural communities in low resource settings.

These TPPs aim to provide essential guidance for SMTs and EATs amenable to the use-cases defined above. For each characteristic of these TPPs, we defined both optimal and minimal criteria; the former as targets to which all should aspire and the latter as acceptable intermediary goals.

Manufacturing Considerations

Active Pharmaceutical Ingredient (API)

APIs are the components in a product that have the intended therapeutic effect for which the SMT or EAT is designed. In SMTs this will be the specific form of the SMI that exerts a pharmacological effect which protects the victim from the toxic effects of one or more venom components. In the case of EATs, like conventional antivenoms, the API is the specific immunoglobulin molecule that has the ability to recognise and bind to one or more venom components and facilitate neutralization of the activity of those toxins. Manufacturers must carefully define APIs and their specifications. Relevant guidance governing the manufacture, quality control and regulation of APIs contained in SMTs, and EATs should be considered by both manufacturers and regulatory agencies (see for examples refs 21-24). All excipients should be in the category of 'Generally Regarded as Safe' as defined by the USA Federal Drugs Administration and will be defined according to the route of administration.

Finished product form

A particular consideration for treatment of snakebites is that most occur in rural, often remote regions of Low- and Middle-Income Countries (LMICs) where presence of a reliable cold-chain may be problematic and so products that do not rely on a cold-chain for distribution and storage are often preferred. Furthermore, many snakebites occur in ICH climatic zones III (>22°C and >15 hPa) to IVb (>22°C and >27 hPa) where ambient temperature frequently exceed 25°C. Products that will be deployed in these settings should meet the ICH climatic zone IVb thermal tolerance range and manufacturers should demonstrate that their products comply with this specification.

A more sophisticated approach to distribution of temperature-sensitive vaccines in settings where a cold chain may be problematic is the use of a 'controlled temperature chain' (CTC)[25-27]. Such considerations for antivenom products deserve serious consideration[28]. Allied to this, there may be a helpful role for use of Vaccine Vial Monitors, especially for 'last mile' delivery, to ensure any products have been stored and transported in compliance with climatic requirements. We have phrased our optimal and minimal requirements in conventional terms below though recognise that a CTC approach should also be considered, in which eventuality the relevant WHO guidelines should be followed[29].

Performance

Pre-clinical efficacy

The functional preclinical efficacy of SMTs and EATs should be established by the manufacturer during the development process in accordance with product specifications and any minimum requirements imposed by relevant regulatory authorities or pharmacopeia. Preclinical efficacy assays should demonstrate that the product functionally neutralizes or abrogates the activity of the toxins against which it is targeted, and that the effect of this is to prevent death or severe disease for hospital patients and to delay disease progression for post snakebite prophylaxis. In other words, there is little benefit in blocking the effect of a specific toxin, if this alone does not prevent the worst outcomes of clinical envenoming. Manufacturers should demonstrate that SMTs and EATs meet equivalent preclinical efficacy requirements as those mandated for conventional animal plasma-derived antivenoms to ensure that parity across very different classes of products.

It is also important that preclinical efficacy data should demonstrate that the product as formulated has the potential to neutralize *in vivo* a biologically relevant amount of venom. In the absence of empirical data on the mass of venom injected by different snake species in a bite, TSAG recommends using neutralization of the average adult venom yield for each of the commonest species of snake in an intended geographical market as an acceptable proxy. This is because the amount of venom produced by different species varies considerably, just as venom composition varies. For example, while the average adult venom yield of carpet vipers (*Echis* spp.) ranges from 10-30 mg, larger species such as

Asian or African cobras (*Naja* spp.) have been recorded as having yields ranging from 200 mg to more than 2,000 mg, and large vipers such as Russell's viper (*Daboia russelii*) or puff adders (*Bitis arietans*) can produce 150 mg to more than 500 mg, depending on the species. It is therefore essential that the recommended dose of any treatment contains sufficient capacity to counteract the effects of biologically relevant volumes of specific venoms or the toxins they contain.

Products should not be marketed based on preclinical efficacy studies alone and should be subject to clinical evaluation to validate the proposed dosage and its safety profile before the product is marketed.

Clinical effectiveness

The dose of injected venom from a snake does not vary according to the size or weight of bitten persons, and therefore all patients, irrespective of body size, need to receive the same, standardized drug dose.

Any new product should be evaluated in clinical trials before marketing authorization or licensing, except in cases where alternative pathways based on robust clinical surveillance and ethical oversight have been approved by national authorities. Studies of clinical effectiveness using appropriate initial doses, optimally based on results of independent preclinical efficacy testing by a competent laboratory and preliminary dose-finding clinical investigations should be robustly designed, ethically supervised, and comprehensively documented. Broad claims of multi-species or multi-genus effectiveness should be based on empirical clinical evidence, rather than pre-clinical studies, supposition or extrapolation. All clinical studies need, of course, 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. The International Council for Harmonization (ICH) GCP Guideline[30] 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 optimal and minimal parameters for clinical effectiveness the TSAG took the view that any new product should match or exceed current best available data for conventional antivenoms[31,32]. It was assumed that for products used in pre-hospital management of patients the interval between the snakebite itself and application of the treatment should ideally be less than 4 hours, and that for treatments administered in a HCF, the timing might range between 4-6 hours optimally (and within 6-8 hours minimally). Pre-hospital treatments will be particularly useful in situations where the likelihood of admission to a HCF within 4-6 hours is reduced due to local conditions and distances.

Bioavailability and route of administration

SMTs and EATs for SBE should be rapidly bioavailable with a large volume of distribution after administration, consistent with nature of snakebites as medical emergencies. The route of administration will considerably influence this bioavailability and there will be 'trade-off' considerations regarding ease of use of a product and bioavailability. In the case of oral administration, it is important to understand that patients with delayed presentation may not be able to receive these drugs by that route safely, especially if the airway is compromised or there is established cranial and bulbar nerve palsy. Intramuscular injection routes should be avoided in the design of products to treat SBE by species that cause coagulopathy and other haemostatic pathologies, except perhaps in the case of pre-hospital auto-injection products that are intended for use very soon post-bite, and prior to development of any bleeding abnormality, as prophylaxis against such effects.

Operational Characteristics

Combinations of therapies and adjunctive therapies

Most SMIs are active against specific target receptors and hence may only inhibit the activity of particular classes of toxins that also interact with the same molecular targets, the same applies for

individual antibodies or fragments raised against a single toxin antigen (unless they have been multimerised with different binding sites to varying toxins). Snake venoms on the other hand are mixtures of multiple toxin classes that can each be made of multiple toxin variants. In some cases, the dominant clinical effects of a snake venom are due to the activity of just one toxin class and a single SMI or antibody will form the basis for a corresponding SMT or EAT. In many instances however, multiple toxins contribute to pathogenesis with functional redundancy and so any SMT or EAT will either need to be administered in combination with other products that have additional targets, or be composed of mixtures of drugs or antibodies, that target different toxins. For avoidance of doubt, if the mixture has been approved through a regulatory pathway as a mixture with robust preclinical and clinical data, this would be considered as a single 'product' in the context of these TPPs. Any new product may also be employed in combination with another new product or as adjunctive therapy with a conventional antivenom. This case would apply to a SMT or EAT used as pre-hospital treatment. It is essential that any new product can be used adjunctively with conventional antivenoms.

Costs, affordability and access

We take the view that cost-effectiveness is more important than cost *per se* and that 'fair pricing' is equally important. We would emphasise that our concept of 'fair pricing' is from the perspective of those who represent the patients receiving a product and also from those who will fund the treatment. In many settings, the two will be the same (i.e., 'patient pays') though in other jurisdictions treatment may be paid by, for example, a government, hospital and/or via insurance. All assessments of cost effectiveness and fair pricing must pertain to the total treatment costs, not just the 'cost per dose' which is the prevalent measure used currently for conventional antivenoms. We strongly recommend the transparent use of Incremental Cost Effectiveness Ratio (ICER) calculations to demonstrate value. We have not prescribed what an appropriate ICER threshold should be because this will vary widely between countries.

While the 'cost-of goods' for EATs for other conditions has been reported to be in the same range as for conventional antivenoms[34,35], pricing of antivenom treatment costs based on manufacturers dosing recommendations in the absence of clinical trial data, often under-estimate the true current cost of effective treatment[36]. We know of no equivalent analyses for snakebite SMTs, but by analogy with Covid-19 drugs, these may be dramatically lower[37]. Whilst cost-of-goods is not the sole determinant of the price for a product, where the costs for SMTs or EATs are lower, we would expect that this advantage will be reflected in the price, particularly in markets where it is the patient who has to pay out of pocket. This in turn is expected to improve affordability and make snakebite treatments more accessible to those who need them. A result of such a development would be to potentially increase the size of the market for treatments because one of the important drivers of the currently widespread under-reporting of snakebite incidence is the lack of availability of affordable and effective products.

Any SMT or EAT for use as post-bite pre-hospital treatment would be potentially transformational for the treatment of snakebite. Because SBE is a time-critical, acute medical emergency, early intervention will always be helpful. If a product is sufficiently safe and easy to use by people with minimal or no clinical qualification then it may be possible to expand distribution more widely, well beyond the conventional hospital settings required for treatment with conventional antivenoms.

Small-molecule and engineered antibody therapeutic TPP list

We set out here two TPPs for potential small-molecule and engineered antibody therapeutics:

TPP TITLE	USE CASE
SMT or EAT for treatment in a hospital setting.	For treatment of in-patients in a hospital setting, possibly adjunctive to treatment with conventional antivenoms. Snakebite envenoming by a WHO category 1 or 2 snake species.
SMT or EAT for post-snakebite prophylaxis.	For post-snakebite prophylactic use of a SMT before a victim reaches a hospital, for any species of snake.

Following the convention in our previous guidelines on conventional antivenoms for use in sub-Saharan Africa and south Asia, we describe first the characteristics that are common to both TPPs. We then describe the specific product characteristics for each in a second section and the two sections should be read in conjunction.

Common Characteristics of Target Product Profiles for Small Molecule and Engineered Antibody Therapeutics

The following characteristics are common to both TPPs and should be read in conjunction with the specific TPP characteristics of each in the next sections of this document.

SMTs that may have applications in the two relevant Use Cases below potentially include, but are not restricted to, inhibitors of Phospholipase A_2, metalloproteinases and serine proteases. Metal ion chelators for metalloproteinases have also been explored as having potential. EATs include monoclonal antibodies and fragments thereof (e.g., IgG, IgY, F(ab')2, single domain antibodies) and peptide aptamers. We do not specify what the biochemical targets should be as this is as yet unclear.

Scope

CHARACTERISTIC	OPTIMAL	MINIMAL
1. Special populations	None.	
2. Geographic working range	Worldwide.	
3. Contraindication	None.	Pregnant women and children under 2 years old.
4. Intended end-users	End users include procurement agencies and health care professionals.	
5. Cost	Cost of total course of treatment should be markedly lower than for equivalent conventional antivenom.	Cost of total course of treatment should be lower than for equivalent conventional antivenom.

Manufacturing considerations

CHARACTERISTIC	OPTIMAL	MINIMAL
6. Finished Product Form	Injectables (including auto-injectables), sublingual, intranasal, tablets and suspensions, patch technologies, suppositories. For EATs delivered iv, lyophilized	Injectables, tablets and suspensions. For EATs delivered iv, either liquid or lyophilized final product forms are minimally acceptable.

	final product forms are optimally acceptable.	
7. Intended use profile	A treatment for snakebite envenoming more effective than a WHO-assessed conventional antivenom.	A treatment for snakebite envenoming used as an adjunctive treatment in advance of or alongside a WHO-assessed conventional antivenom.
8. Active Pharmaceutical Ingredient (API)	Small molecule inhibitors, immunoglobulins or aptamers that bind to specific, identified biochemical components of snake venoms. For EATs, the specific Ig or fragment to be not less than 90 % of total protein content. For SMTs the API should be not less than 99 %.	
9. Packaging	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 active pharmaceutical ingredient (API) content should be included on vial labels and package inserts. For EATs, Vial labelling to specify immunoglobulin/single domain antibody/nanobody/aptamer and total protein content. Each 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.	

Performance

CHARACTERISTIC	OPTIMAL	MINIMAL
10. Preclinical efficacy	Preclinical determination of median effective dose (ED_{50}), potency (P) and functional toxin-specific activity bioassays demonstrates the potential of the proposed initial dose of the product to completely neutralize *in vivo* the lethal and specific activities of the average adult venom yield of each of the species for which the product is intended as a sole treatment.	Preclinical determination of median effective dose (ED_{50}), potency (P) and functional toxin-specific activity bioassays demonstrates the potential of the proposed initial dose of the product to significantly delay the lethal and specific activities of the average venom yield of each of the species for which the product is intended to be used as an adjunct treatment.
11. Bioavailability	Fast acting with high volume of distribution.	
12. 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.
13. Product Stability and Storage	For non-liquid products: At least 5 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%).	For non-liquid products: At least 2 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%).

		For liquid products: At least 2 years in conditions up to and including ICH refrigerated zone (temperature of 5°C ± 3°C).

Operational Characteristics

CHARACTERISTIC	OPTIMAL	MINIMAL
14. Costs	Where the novel treatment replaces use of a conventional antivenom, a cost effectiveness study is conducted and demonstrates that it is more cost-effective than the existing antivenom. Where the novel treatment is adjunctive, then the combination should be more cost-effective than antivenom alone.	If cost effectiveness studies can't be performed, evidence to support fair pricing of drug is requested. Once the cost effectiveness study is performed, drug is found cost effective.
15. Registration, prequalification, and programmatic suitability	Must be licensed and approved by national regulatory authorities in countries of use.	

Specific Characteristics of Target Product Profiles for treatment in a hospital setting.

Scope

CHARACTERISTIC	OPTIMAL	MINIMAL
16. Target population	All individuals and age groups presenting to a health facility with signs and symptoms of snakebite envenoming.	
17. Indication	For the treatment of snakebite envenoming by an unidentified WHO Category 1 or Category 2 snake.	
18. 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 personnel and infrastructure and can be administered by trained health workers in accordance with recognized standards and existing national regulatory requirements.	The product is deployed to specific levels of the health system that meet optimum criteria for personnel and infrastructure and can be administered by trained health workers in accordance with recognized standards and existing national regulatory requirements.

Manufacturing Considerations

CHARACTERISTIC	OPTIMAL	MINIMAL
19. Product Stability and storage	At least 2 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%).	At least 2 years in conditions up to and including ICH refrigerated zone (temperature of 5°C ± 3°C).
20. Presentation	A single container (e.g.: vial, ampoule) that is clearly labelled as constituting a clinically effective initial dose comprising sufficient API to ablate development of clinical symptoms of envenoming for each of the snake species for which it is intended.	

Performance

CHARACTERISTIC	OPTIMAL	MINIMAL
21. Therapeutic objective	SMTs or EATs deliver effective treatment alone or in combination with other SMTs/EATs respectively.	To improve clinical outcomes of envenomation as adjunct to conventional antivenom.
22. Clinical effectiveness	When administered within 6-8 hours of a bite by a species that has toxins against which the product is preclinically effective, randomised controlled trials demonstrate that sole treatment with the product results in: • case fatality rate (CFR) reduced to <2%, • amputations reduced to <2%, • persistence of coagulopathy at 24 hours post-treatment reduced to <6%,	When administered within 4-6 hours of a bite by a species that has toxins against which the product is preclinically effective, randomised controlled trials demonstrate that in combination with conventional antivenom treatment, adjunct use results in a substantially better overall clinical outcome, and an improved outcome relative to the specific clinical effects of those

	• need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) reduced to <10%. When used as an adjunct treatment, it improves outcome relative to the specific clinical effects of those toxins for more than 50% of treated patients.	toxins for at least 50% of treated patients.
23. Dose regimen	Multiple doses over <3 days.	Multiple doses over 5 days or less.
24. Route of Administration	Range of routes including injected, oral, sublingual, intranasal, rectal or by dermal patch application.	Injected or oral.
25. Safety and tolerability	Product is shown to be safe in well-designed randomised clinical trials and is well tolerated with no need for laboratory monitoring. For EATs, the safety profile is superior to that of gold-standard conventional antivenoms used in the region. Humanised or human antibodies strongly preferred.	Product is shown to be safe in well-designed randomised clinical trials and is well tolerated with no need for laboratory monitoring. The safety profile is at least equal to that of gold-standard conventional antivenoms used in the region. Non-humanised antibodies may be acceptable if safety criteria are not compromised.

Operational Characteristics

CHARACTERISTIC	OPTIMAL	MINIMAL
26. Supportive and adjunctive therapy	Standard of care at all levels of the health system. Product is used in combination with supportive clinical interventions to address disease manifestations.	Standard of care in secondary or tertiary facilities under direct supervision of medical doctor. Product is used in combination with conventional antivenoms specifically and other supportive clinical interventions to address disease manifestations.
27. 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, BP), point - of-care (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.	

Specific Characteristics of Target Product Profiles for post-snakebite prophylaxis

Scope

CHARACTERISTIC	OPTIMAL	MINIMAL
28. Target population	All individuals and age groups who are suspected of having been bitten by a WHO Category 1 or 2 snake.	
29. Indication	A suspected snakebite is sufficient to trigger treatment, without waiting for signs and symptoms of envenoming.	
30. Level of implementation in the healthcare system	The product is capable of being deployed at point-of-care or in a clinic with no medical supervision.	The product is capable of being deployed to and administered by trained health workers in accordance with recognized standards and existing national regulatory requirements.

Manufacturing Considerations

CHARACTERISTIC	OPTIMAL	MINIMAL
31. Product Stability and storage	At least 2 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%).	
32. Presentation	A single container (e.g.: vial, ampoule) that is clearly labelled as constituting a clinically effective initial dose comprising sufficient API to slow development of clinical symptoms of envenoming until standard care can be implemented.	

Performance

CHARACTERISTIC	OPTIMAL	MINIMAL
33. Therapeutic objective	Completely prevents onset of signs and symptoms of envenoming so that other specific treatment (e.g., conventional antivenom) is not required.	Delays onset of signs and symptoms of envenomation by at least 4-6 hours providing time for patient to reach medical facilities where normal standard of care can be implemented.
34. Clinical effectiveness	Prompt treatment (2-4 hours) negates need for emergency travel to a hospital for at least 50% of treated patients.	Prompt treatment (2-4 hours) delays onset of signs and symptoms of envenoming such that subsequent antivenom treatment in hospital shows superior outcomes to treatment with antivenom alone for at least 50 % of treated patients.
35. Dose regimen	Single dose.	Multiple doses.
36. Route of Administration	Oral, sublingual, auto-injection, rectal or by dermal patch application by non-health workers.	Injected (intravenous or intramuscular), oral, sublingual, auto-injection, rectal or by dermal patch application according to available pre-hospital standard of care and whether administered by

		health workers or non-health workers.
37. Safety and tolerability	Product is shown to be safe for pre-hospital emergency use in well-designed randomised clinical trials and is well tolerated with no subsequent need for laboratory monitoring.	

Operational Characteristics

CHARACTERISTIC	OPTIMAL	MINIMAL
38. Supportive and adjunctive therapy	No additional supportive or adjunctive care is necessary as the product completely prevents development of clinical signs and symptoms of envenoming.	Applicable pre-hospital standard of care (e.g., ambulance service or community first responder).
39. Training & education needs	Knowledge of common local snake species including non-venomous species, understanding of relevant signs and symptoms of snakebite envenoming by local species, appropriate first aid management of a potential patient, ability to provide basic wound care.	

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