

Risk-Benefit Assessment of Snake Antivenom Immunoglobulins

Polyvalent antivenoms intended for use in the treatment of snakebite envenoming by *Bungarus caeruleus*, *Daboia russelii*, *Echis carinatus* and *Naja naja* in Pakistan, India, Nepal, Bangladesh, Bhutan, or Sri Lanka

The World Health Organization (WHO), acting through its Regulation and Prequalification Department, is now calling for applications from licensed manufacturers of snake antivenom immunoglobulin products who wish to have those products evaluated for potential listing by WHO as recommended for procurement.

The current call applies only to polyvalent snake antivenom immunoglobulin products that are manufactured for the treatment of envenoming by the following species of WHO category 1 medically important snake species:

Common krait (*Bungarus caeruleus*)
Russell's viper (*Daboia russelii*)
Saw-scaled viper (*Echis carinatus*)
Indian cobra (*Naja naja*)

Products for the treatment of envenoming by these species are typically marketed in Pakistan, India, Nepal, Bangladesh, Bhutan, and Sri Lanka. The call is open to licensed manufacturers and products that are registered and have marketing approval from a competent national regulatory authority. This call relates to products that are primarily intended for the treatment of snakebite envenoming by these species in these countries.

Eligibility

1. To be eligible for risk-benefit assessment by WHO, an antivenom product must consist of a polyspecific antivenom immunoglobulin preparation, with claimed efficacy in treating envenoming by *Bungarus caeruleus*, *Daboia russelii*, *Echis carinatus* and *Naja naja* (sometimes referred to as the “big four” species)¹.
2. The manufacturer of the product must submit the specified number of antivenom product samples from at least two (2) batch lots of the product to WHO, along with the specified quantities of each of the immunizing venoms used to manufacture the antivenom. These samples will be comprehensively evaluated in a laboratory by WHO as part of the risk-benefit assessment process.
3. If the product submitted is determined by WHO to demonstrate a risk-benefit ratio that justifies its use in treating snakebite envenoming, the manufacturer agrees, as a condition of listing, to submit an application for the product to be considered for subsequent WHO prequalification if and when an antivenoms prequalification procedure is established by WHO.
4. The manufacturer agrees that by submitting an application for risk-benefit assessment, the manufacturer/applicant will be deemed to have accepted and agreed to the eligibility criteria and all of the terms, conditions and other requirements set out in this document.
5. The manufacturer agrees to provide WHO with post-marketing information (current or future) relevant to the safety and efficacy of the product.

¹ WHO may consider assessing a candidate snake antivenom product that does not meet all the above criteria. In such instances, the application letter and documentation provided to WHO must substantiate the need for the product, and the specific benefit it provides.

The public health impact of snakebite envenoming

In the absence of treatment, snakebite envenoming results in high morbidity and mortality with grave socio-economic consequences for victims, families, and communities. Globally WHO estimates that there are between 81,000 and 138,000 snakebite-related deaths occur each year, and that long-term consequences for survivors (including amputation, other disabilities, and post-traumatic stress) affect at least 400,000 more².

The world's highest burden of snakebite envenoming morbidity and mortality occurs in the region bounded by Pakistan, India, Nepal, Bangladesh, Bhutan, and Sri Lanka. In India alone, recent estimates place the annual mortality at approximately 58,000 per year from as many as 1.8 million cases³. In Bangladesh, the results of a national survey estimated that there were 589,919 snakebites per year resulting in 6,041 deaths⁴. In Pakistan at least 8,200 people die each year, but the total number of cases is unclear⁵. Nepal and Sri Lanka experience 20,000 and 33,000 cases with 1,000 and 300 deaths respectively⁵.

Antivenoms: unavailable or poor quality

Despite this high burden, snake antivenoms are often unavailable to those in need, hampering effective treatment, and when they are, they may have been prepared from poor quality snake venoms that are not regionally representative, or have been poorly designed and manufactured and have limited efficacy. In some countries that use these products to address their significant snakebite problems there may be a lack regulatory capacity to assess the quality and specificity of the antivenom preparations manufactured in their country or coming into their countries. In such circumstances where the quality of products may not have been reliably or completely verified the confidence of health care providers and patients with respect to antivenom products has declined, leading to loss of demand despite abundant need, and an increase in morbidity and mortality.

Yet if sufficient, quality-assured antivenoms were available, most of the deaths and the harm caused by snake bites could be prevented. Antivenoms are therefore included in the WHO Essential Medicines List. They are blood-derived, usually consist of immunoglobulin preparations, purified from animal-derived hyperimmune plasma, and enzymatically digested into antibody fragments.

WHO response

In 2018 the World Health Assembly adopted resolution 71.5 (2018: *Addressing the burden of snakebite envenoming*) which calls on WHO to ensure the quality and safety of snake antivenoms and this work directly addresses that request. WHO has developed a risk-benefit assessment procedure for snake antivenoms, to assist interested WHO Member States, United Nations' procurement agencies, international organizations and other stakeholders in determining the acceptability of using specific snake antivenom products, based on an evaluation of an essential set of available quality, safety, efficacy, and performance data. Furthermore, it provides manufacturers with independent product analysis, evaluation of Good Manufacturing Practices (GMP) and potential product recommendation. Overall, the risk-benefit assessment process is aimed at improving the availability of safe, effective antivenom immunoglobulin products to all who need them.

² World Health Organization. *Snakebite envenoming: A strategy for prevention and control*. 2019. <https://apps.who.int/iris/rest/bitstreams/1230920/retrieve>

³ Suraweera W, et. al. Trends in snakebite deaths in India from 2000 to 2019 in a nationally representative mortality study. *Elife*. 2020. 9: e54076.

⁴ Rahman R, et. al. Annual incidence of snake bite in rural Bangladesh. *PLoS Negl Trop Dis*. 2010. 4(10): e860.

⁵ Ralph R, et. al. The timing is right to end snakebite deaths in South Asia. *BMJ*. 2019. 364: k5317.

Risk-benefit assessment process

Manufacturers who wish to apply for risk-benefit assessment must submit to WHO a detailed product dossier addressing the specific terms of reference. The dossiers will be reviewed by a group of experts, and in parallel samples of the immunizing venoms, and the antivenoms themselves, will be subjected to robust laboratory analysis. WHO will also undertake inspections of manufacturing sites to verify adherence to Good Manufacturing Practices (GMP). Products which are found by WHO to be acceptable on the balance of the overall evaluation of risk-benefit may be recommended by WHO for procurement.

Dossier review

A joint desk review assessment will be conducted by a group of experts (which may include international regulatory, veterinary, biologicals manufacturing, quality control, herpetological and medical experts). Regulators from the countries where the antivenoms are manufactured and marketed are invited to join this group. Using information and data provided by the relevant manufacturers, the group of experts will assign a risk–benefit ratio to each product assessed.

Laboratory assessment

In parallel a comprehensive physicochemical, analytical, and biological laboratory assessment is undertaken for each product. The quality, potency and biological activities of the venoms used to raise the antivenom are examined along with venoms from other geographical regions throughout the range of each immunizing species. Venoms of other medically important snake species are also included in the assessment to determine the extent of any broader paraspecific coverage that products may provide. The antivenoms are evaluated against each of the venoms using a combination of *in vitro* and *in vivo* quality control and preclinical efficacy assays in accordance with recommendations in the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins⁶.

GMP inspections

WHO will conduct inspections of venom production facilities, small and large animal facilities, manufacturing and quality control facilities are part of a detailed evaluation of GMP compliance. Where deviations from GMP are identified manufacturers will be required to address these through a Corrective and Preventative Action (CAPA) process to the satisfaction of the WHO Prequalification Unit Inspection Service. Where GMP adherence is verified, manufacturers will receive a formal closure notice indicating that the relevant sites be considered compliant with GMP as published by WHO for the specific activities related to the manufacturing and quality control of the product.

Final review

All the findings will be subject to final review by the dossier review panel to determine if on balance they demonstrate a reasonable likelihood that the quality, safety, and efficacy of the product are acceptable, and that, when used to treat snake bite in the countries in which it is marketed, its benefits will outweigh any foreseeable risks and uncertainties associated with its use.

Antivenoms with a positive risk-benefit ratio will be entered into a list on the WHO website, where it can be accessed readily by procurement agencies and other relevant parties. Where a product is excluded from the risk-benefit assessment due to any unsatisfactory finding, failure, or other deficiency, WHO will also publish the finding on the WHO website. Public

⁶ 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.
https://www.who.int/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf

Risk-Benefit Assessment Reports and Public GMP Inspection Reports for all the products assessed with also be published by WHO on the WHO website.

Application process

1. Manufacturers must first confirm that the product for which they wish to submit an application meets the eligibility criteria listed earlier in this document and read the background information on the preceding pages.
2. To facilitate assessment planning and logistics to coordinate the shipping of the required venom and antivenom samples so that they arrive in Geneva, manufacturers are asked to indicate their interest in submitting an application by email to: antivenoms@who.int
3. All applications must be writing in the format specified further below. The application dossier and other written materials can be submitted in digital format (e.g., Adobe Acrobat *.PDF).
4. A covering letter must be included with the application. This letter should clearly identify the product, the name and contact details of the manufacturers nominated company representative and indicate acceptance of the terms and conditions of the call for applications, which includes the contents of this document in their entirety.

Application dossier preparation and specific data requirements

All application dossiers must be prepared in the ICH Common Technical Document (CTD) format. For specific information refer to the [International Council for Harmonization \(ICH\) CTD format guidance](#). Please follow the proposed order of information set out below:

1. Basic product information
 - (a). Name of the product
 - (b). Indication
 - (c). Instructions for use
 - (d). Information about the manufacturer, manufacturing sites, distributors
 - (e). National regulatory agency approvals that have already been granted.
2. Overview of design, production, and quality control
 - (a). Design of the antivenom, e.g., monospecific antivenoms; polyspecific antivenom obtained by mixing of multiple monospecific antivenoms or obtained by polyspecific immunization; whole IgG, F(ab')₂ or Fab; host organism (e.g., equine, ovine).
 - (b). Chosen definition for an antivenom “batch”; quality control procedure for individual batches.
 - (c). Detailed information about product starting materials (including venoms and hyperimmune plasma), production processes, quality control of intermediate and finished products, testing methods, including quality control, product validation, physical and biochemical specifications.
 - (d). Evidence of the operation of a quality management system established for the manufacturing site(s) at which the antivenom is being produced; evidence of adequate compliance with good manufacturing practice (GMP). Evidence of best practice animal health and welfare throughout the whole-of-life of animals used in the production of antivenom (equids, snakes, laboratory animals).
 - (e). Product label content and package insert (e.g., instructions for use) content.
 - (f). Details of how the applicant monitors the safety, quality, and efficacy of the product in the markets in which it is sold and used.

- (g). Details of how patients and healthcare providers are informed adequately about the potential product benefits, risks, and contraindications.
3. Data on manufacturing quality
- 3.1. Venoms⁷
- (a). Provide details of the snake species (geographic origin, taxonomic nomenclature, health status) whose venoms are used in the production of the antivenom; details of source of venoms (supplier) and supplier GMP compliance (animal origins, traceability, animal husbandry, veterinary oversight, venom production, processing, and storage methods).
 - (b). Describe the methods used to ensure venom quality during the manufacturing process (e.g., biochemical characterization [i.e., protein content, SDS-PAGE, chromatography analysis, stability assays], specific activity testing [i.e., LD₅₀ assays, coagulant, myotoxicity, haemorrhagic, haemotoxicity, necrotic assays], identification of venom batches used in production of antivenoms, venom storage [i.e., lyophilized, vacuum-dried or frozen liquid preparations]).
 - (c). Immunizing venom mixture preparation (e.g., single venom administered to individual host animals, or multiple venoms administered to individual host animals), dosing schedule and adjuvant selection.
- 3.2. Antivenoms⁷
- (a). Immunization host animals: selection of animal type (e.g., horses, sheep), selection of individual animals, quarantine, vaccination, and veterinary control procedures.
 - (b). Design and method of immunization (e.g., preparation of venom doses, type and use of adjuvants, immunization scheme (e.g., immunization sites, booster dosing), care of animal during immunization and injection site reaction management.
 - (c). Selection of immunized animals with adequate immune response.
 - (d). Animal plasma for fractionation: please describe the following: collection of whole blood or plasma (e.g., plasmapheresis), plasma separation from whole blood, plasma storage, traceability of plasma units to individual animals, plasma pooling.
 - (e). Purification of immunoglobulins, GMP conditions.
 - (f). Purification of the active pharmaceutical substance [intact IgG, F(ab')₂ fragments or Fab fragments].
 - (g). Optional additional steps in production processes, e.g., chromatography, filtration.
 - (h). Formulation, analysis of bulk.
 - (i). Dispensing and labelling.
 - (j). Stability: use of preservatives; freeze-drying; stability studies; storage conditions; stability data to demonstrate that the antivenom will maintain the minimum potency considered to be efficacious for the claimed shelf life under the conditions of use.
 - (k). Process steps contributing to virus safety; studies on virus safety; estimation of virus safety of the final product.
 - (l). Quality control (QC) tests, acceptance criteria for antivenom batch QC.

⁷ Refer also to Appendix 1

4. Preclinical (non-clinical) data

- (a). Provide details of all published and unpublished preclinical product evaluation data. This includes internal product quality control data, particularly pertaining to finished products, potency testing and other assays of activity. Describe the preclinical evaluation process. How was acceptable safety, efficacy and dosage established?
- (b). What criteria were used in the design of preclinical product assessment strategies? Was an appropriate animal model used (e.g., mouse protection tests using ED₅₀ assays)?
- (c). Give details of all *in vivo* and *in vitro* preclinical tests conducted during development of the product.

If the pre-clinical data are not complete at the time of submission, the applicant must submit a justification for the lack of complete data and propose a timeline for the submission of additional data or provide a justification as to why the product is assumed to be suitable for use in treating envenoming in humans by the relevant species, to the satisfaction of WHO.

5. Clinical data

- (a). Provide details of all published and unpublished human clinical data upon which the manufacturer relies to establish the appropriate dose, relative clinical effectiveness, and initial acceptable safety. Safety data from other antivenoms made by the manufacturer using the same product platform may be considered as supportive data for review. Manufacturers can also submit copies of third-party clinical studies that demonstrate acceptable safety and clinical effectiveness.
- (b). Provide details of any past, present, or future clinical trials of the antivenom, including trial registry identification numbers, clinical protocols, trial outcomes, publications, and reports. These should be provided regardless of whether the outcomes were positive or negative.

If human clinical effectiveness data are not available for the antivenom under consideration, WHO will consider whether the non-clinical data justifies its use as a potential surrogate that is thought to be reasonably predictive of clinical effectiveness.

Venom and antivenom samples for laboratory evaluation

1. WHO requires samples of each of the immunizing venoms that are used in the production of the antivenom so that the quality, potency, and specific activity of the immunizing venoms can be determined and compared with other samples of venom for each species from different geographical locations within the natural range of each snake. **A quantity of 500 milligrams of each immunizing venom is required.** This must be supplied in lyophilized form and packaged in accordance with International Air Transport Association (IATA) requirements for the shipping by air of [dangerous goods](#).
2. To conduct a range of *in vitro* and *in vivo* assessments of the antivenom against venoms of each immunizing species from multiple locations within their geographic range, and to evaluate paraspecific coverage of several other species, **WHO requires 50 vials each, from two different batch lots of antivenom** (e.g., batches produced at different times and with different batch numbers and expiry dates). These may be either liquid or lyophilized finished products. They should be packaged and shipped in accordance with the manufacturer's normal product export and shipping protocols considering all relevant international requirements set down by IATA.
3. Where manufacturers require approvals from local authorities or customs services in order to export any materials to WHO, early contact with WHO is imperative to ensure that necessary documentation is provided to facilitate these administrative matters.

Screening and assessment

Before initiating formal assessment, WHO will screen each application and its accompanying documentation. The applicant will be informed within five working days as to whether the application has been accepted for WHO assessment and an approximate time frame for the assessment will be indicated.

If a previous assessment and inspection(s) relating to the product was/were performed by a stringent national regulatory agency (NRA) or by WHO, these may be considered when conducting the risk-benefit assessment, depending on their relevance and recency. This will contribute to optimizing the resources of the manufacturer and WHO and serve to reduce the time required for assessment.

Costs

To encourage manufacturers of all sizes in this field to participate in the risk-benefit assessment process, WHO is not levying any costs or fees. Therefore applications accepted for evaluation will not be charged any fee.

Application preparation guidance

In preparing CTD product dossiers manufacturers are advised to consult the *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins* as a guide to the type of information that should be included in the dossier. This document is available at:

https://www.who.int/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf

Where additional information or clarification is required, intending applicants should contact WHO as early as possible for advice: antivenoms@who.int

Submission

Hard copies of the application letter, antivenom product dossiers and samples of venom and antivenom for laboratory assessment must be sent to:

Vaccines and Immunization Devices Assessment Team
Prequalification Unit, Regulation and Prequalification Department
World Health Organization
20 Avenue Appia
Geneva 27
CH-1211 Switzerland

Digital application documents must be sent by email to: antivenoms@who.int

The shipping of samples for laboratory testing must be coordinated with WHO. Please contact WHO (antivenoms@who.int) as soon as possible to begin the logistics process for sample submission.

Outcomes of the WHO risk-benefit assessment process

1. Subject to the protection of commercially sensitive confidential information, WHO will publish/post on its website and make publicly available the outcomes of all risk-benefit assessments that it carries out (including, but not limited to, any negative outcomes). This information will include a copy of the final decision notice, any recommendation notice issued, a GMP Public Inspection Report and a Public Risk-Benefit Assessment Report.
2. Recommendation notices will only be issued for products that WHO considers to have a favorable risk–benefit ratio. Products that do not receive a recommendation will be listed as “No recommendation made”.
3. Before including a product in the list, as part of its assessment process, WHO may consult

and/or coordinate with relevant NRA(s) and other parties, as appropriate. Listed antivenoms will be subject to review after two years.

4. As WHO is responsible for the risk-benefit assessment process, the ownership of all reports arising from or relating to the risk-benefit assessment process will be vested in WHO. Accordingly, the manufacturer/applicant understands and agrees that WHO shall have the right to use, publish, issue, distribute to and share with national regulatory authorities and other relevant authorities of WHO Member States, United Nations' agencies and other relevant international or intergovernmental organizations, and/or to make publicly available, any outcomes, findings, results, notices and/or reports—whether in draft or final form, and whether positive or negative—arising from or relating to the risk-benefit assessment process, any product submitted for assessment thereunder and/or any confidential information to which WHO may gain access during the course of the risk-benefit assessment process. However, WHO's aforementioned right shall be exercised subject to the protection of any commercially sensitive information of the manufacture.

Confidentiality

WHO will treat all information to which it gains access as part of the assessment process, and which has been marked by the applicant as confidential and proprietary, in accordance with the terms below.

1. WHO will take all reasonable measures to ensure that:
 - (a). confidential information is not used for any purpose other than as described in this document; and,
 - (b). is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.
2. WHO will not, however, be bound by any obligations of confidentiality and restrictions on use, to the extent it is clearly able to demonstrate that any part of the confidential information:
 - (a). was lawfully in its possession and known to WHO prior to disclosure by or on behalf of the manufacturer/applicant, as evidenced by documents predating the date of disclosure; or
 - (b). was in the public domain or the subject of public knowledge at the time of disclosure by or on behalf of the manufacturer/applicant; or
 - (c). becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
 - (d). becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to the applicant in respect thereof; or
 - (e). was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information;
 - (f). is required to be disclosed by law, provided that WHO shall in such case immediately notify the applicant in writing of such obligation and shall provide adequate opportunity to the applicant to object to such disclosure, or request confidential treatment thereof (provided always, however, that nothing contained in this call for applications shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or as submitting WHO to any national court jurisdiction).

Suggestions relating to procurement

1. Any UN or other procurement agency, or Member State that intends to base a procurement decision on the WHO list of antivenom products that it considers to have a favorable risk-benefit ratio should ensure that only products from the manufacturing sites mentioned in this

list, and based on essentially the same data set and information that were submitted to WHO, are supplied to it.

2. Organizations using the list for procurement should perform other aspects of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities and other related aspects.

Appendix 1: Information to include in dossier preparation

Manufacturers must provide adequate information to enable a careful assessment of veterinary care and veterinary oversight practices throughout the whole of life production period for all animals. Evidence of compliance with national and international (e.g., OIE Welfare of Working Equids Standards, Chapter 7.12: <https://www.oie.int/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/>) regulatory standards, and requirements within countries (e.g., via animal welfare or ethics committees) should be included for each section. Copies of Standard Operating Procedures (SOP's) for all the activities related to animal use should be included. Information on record-keeping systems should also be provided, including examples.

Specific information required in relation to 3.1 (a):

- (a). Sourcing (e.g., purchase, collection from wild) and location acquired, selection of snake specimens, handling and transportation to facility.
- (b). Quarantine of new animals and health screening.
- (c). Prophylactic vaccinations and treatments (internal and external parasites) and biosecurity plan for the farm and any other premises used in the process.
- (d). Maintenance husbandry of snakes and monitoring of health – specimen identification with respect to traceability, specimen data. Emergency management of disease outbreak and lab diagnostics and veterinary services. Record keeping and SOP's.
- (e). Training of personnel involved in venomous snake handling, husbandry, and venom extraction processes including on SOP's
- (f). Venom extraction protocols, venom handling, sample identification and traceability, storage, drying (e.g., vacuum-drying, lyophilization, desiccation) - with particular attention to aseptic procedure requirements, removal of contaminants (e.g., blood, mucus, cells) and traceability of each batch of venom product to snake specimens (if applicable).

Specific information required in relation to 3.2 (a):

- (a). Selection of horses and transportation to facility
- (b). Quarantine of new animals and health screening. SOP development and updating
- (c). Prophylactic vaccinations and treatments (internal and external parasites) and biosecurity plan for the farm and any other premises used in the process.
- (d). Emergency care especially during the procedures e.g., hyperimmunization with venoms, injection site reactions, blood collection, post plasmapheresis, hyperimmunization associated amyloidosis
- (e). Maintenance husbandry of horses and monitoring of health (hoof care, teeth, body condition score). Emergency management including disease outbreaks. Veterinary services and oversight.
- (f). Prebleeding health check to ensure haemoglobin, total plasma protein and packed cell volume optimal

Specific information required in relation to 3.2 (b):

- (a). Preparation of the immunization dose, type of adjuvants used, aseptic procedure
- (b). Hyperimmunization procedure of horses ensuring aseptic procedure and number of injections and volume of blood removed and frequency of bleeding and resetting periods from the schedules.
- (c). Plasmapheresis in horses – ensuring aseptic procedure and care of horses until the cellular components of the blood is transfused back into the donor and monitoring and record keeping.
- (d). Blood collection procedure defining how much blood is removed, ensuring aseptic procedure and the interval of blood collection e.g., every 4 weeks and ensuring minimum antivenom titer before blood collection

- (e). Adverse event reporting
- (f). Training of personnel involved in hyperimmune plasma production process – with particular attention to aseptic procedure requirements and traceability of product.

Specific information required in relation to 3.2 (d):

- (a). Potency testing of the plasma for specific antivenoms
- (b). Plasma pooling for dispatch and how traceability is ensured.