World Health Organization

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Launch of WHO Assessment and Listing of Snake Antivenoms

The public health impact of snake bites

In the absence of treatment, envenoming by snakes results in high morbidity and mortality with grave socio-economic consequences.

Annually, snake bites cause around 125,000 deaths and the permanent disabling or disfiguring of 400,000 people, mainly in developing countries. The individuals affected are mostly women, children and agricultural workers in poor rural communities. In sub-Saharan Africa — one of the regions most affected — about 30,000 people die from snake bite each year.[1]

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 equine hyperimmune plasma and enzymatically digested into antibody fragments.

Antivenoms: unavailable or poor quality

In sub-Saharan Africa snake antivenoms are often unavailable to those in need, or, if available, may have been prepared from venoms of snakes from other parts of the world, and have limited efficacy. Lack of proper regulatory oversight compounds the latter problem. In many countries where incidence of snake bite is high, the regulatory capacity needed to assess the quality and specificity of antivenom preparations (be these manufactured locally or imported) is lacking. In other words, the quality of products offered is unlikely to have been verified. Confidence among health care providers and patients with respect to antivenom products has therefore declined.

WHO response

In order to support decision-making by procurement agencies, public health officials and users of antivenoms, WHO is initiating independent assessment of antivenoms. This will consist of joint desk review assessment, conducted by an international group of regulatory, herpetological and medical experts. African regulators from the target African countries of antivenoms will be invited to join this group. Using information and data provided by the relevant manufacturers, the group will assign a risk–benefit ratio to each product assessed.

If considered necessary, the desk review assessment will be combined with WHO laboratory evaluation to confirm essential product features, such as proof of preclinical efficacy in an animal model, and/or supplemented by an on-site inspection. The review will determine whether the data submitted for an antivenom product demonstrates a reasonable likelihood that its quality, safety and efficacy 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 favourable 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.

A WHO prequalification process[2] for antivenoms may be developed if the experience gained in carrying out snake antivenom risk-benefit assessment confirms that this would generate significant

[1] See the WHO database and image library of snakes and antivenoms which categorize dangerous snake species according to the degree of public health risk that they present, available at: http://apps.who.int/bloodproducts/snakeantivenoms/database/.

[2] See for example, Annex 10: Procedure for prequalification of pharmaceutical products, in WHO Technical Report Series, No. 961, 2011. Geneva, World Health Organization.

public health benefit.

Call for manufacturers of antivenoms to submit an expression of interest in product assessment by WHO

This call for expressions of interest relates to antivenoms intended for use in sub-Saharan Africa.

Eligibility

- In order to be eligible for risk–benefit assessment by WHO, an antivenom product must consist of a polyspecific or monospecific antivenom immunoglobulin preparation, with claimed efficacy in treating envenoming by category 1 snake species[1] occurring in sub-Saharan Africa.
- The manufacturer of the product must agree to provide product samples upon request, for eventual targeted laboratory evaluation by WHO.
- In the event that the product submitted is determined to demonstrate a risk–benefit ratio that warrants its use in treating snake bite, the manufacturer must agree 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.
- The manufacturer must agree to provide WHO with post-marketing information (current or future) relevant to the safety and efficacy of the product.

WHO may consider assessing a candidate snake antivenom product that does not meet all of 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.

In submitting an application the applicant will be deemed to have accepted the above criteria.

Screening and assessment

Before initiating formal assessment, WHO will screen any application and its accompanying documentation. It will inform the applicant within five working days as to whether the application has been accepted for WHO assessment and indicate an approximate review time frame.

If a previous assessment and inspection(s) relating to the product was/were performed by a stringent national regulatory agency (NRA), WHO may take these into account when conducting its own assessment. This will contribute to optimizing the resources of the manufacturer and WHO, and serve to reduce the time required for assessment.

Submissions received before the end of February 2016 will be included in the first round of joint expert assessment planned for March 2016. Currently, in order to encourage applications from manufacturing companies of all sizes, no submission fees will be levied.

To facilitate assessment planning, manufacturers are asked to indicate their interest in submitting an application by email to: vaccprequalification@who.int

Application requirements: information to be submitted

The information to be submitted with an application is based on the *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins*, available at: http://www.who.int/bloodproducts/snake_antivenoms/snakeantivenomguideline.pdf?ua=1

These guidelines can be used as a resource when developing the content of the application. In the event that an applicant requires clarification regarding the information to be submitted, it is recommended that WHO be contacted at the above email address as early as possible.

Data requirements

A signed application letter must be submitted to WHO together with the information defined below.

Please follow the proposed order of information. Applications using ICH Common Technical Document (CTD) format for product dossiers may be used but this is not a requirement.

(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, production process, 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).
(e) Product label 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

Venoms

(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, 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. LD_{50} 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).

Antivenoms

(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).
(c) Selection of immunized animals with adequate immune response.
(d) Animal plasma for fractionation: please describe the following: collection as whole blood or plasma (e.g. plasmapheresis), separation of plasma from whole blood, storage of plasma, traceability of plasma units to individual animals, pooling of plasma.
(e) Purification of immunoglobulins, GMP conditions.
(f) Purification of the active substance (intact IgG, F(ab`)2 fragments, 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.

(4) Preclinical (non-clinical) data

(a) Provide details of all published and unpublished preclinical product evaluation data. Describe the preclinical evaluation process. How was acceptable safety and efficacy 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

Provide details of all published and unpublished human clinical data upon which the manufacturer relies to establish the appropriate dose, relative efficacy 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.

If human clinical efficacy 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 efficacy.

Submission

Applications for assessment should be mailed to:

WHO Prequalification Team
Regulation of Medicines and other Health Technologies
HIS/EMP/RHT/PQT
20 Avenue Appia
Geneva 27
CH-1211 Switzerland
or by email to: vaccprequalification@who.int

WHO assessment outcomes

WHO will post on its website a list of products that it considers to have a favourable risk–benefit ratio. However, confidential commercial information provided by applicants will not be published.

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.

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 it prior to disclosure by the applicant hereunder, 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 hereunder; 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; or
   (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 herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

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Suggestions relating to procurement

- 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 favourable 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.
- 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.