- **National regulatory bodies should expect producers either to provide trial data confirming the clinical efficacy and safety of their antivenoms or to support in country clinical testing of these products.**
- **Post-marketing surveillance studies should play a major role in the evaluation of efficacy and safety of antivenoms**
- **Observational studies are extremely important in ensuring the efficacy and safety of an antivenom when first used in a new geographical region**

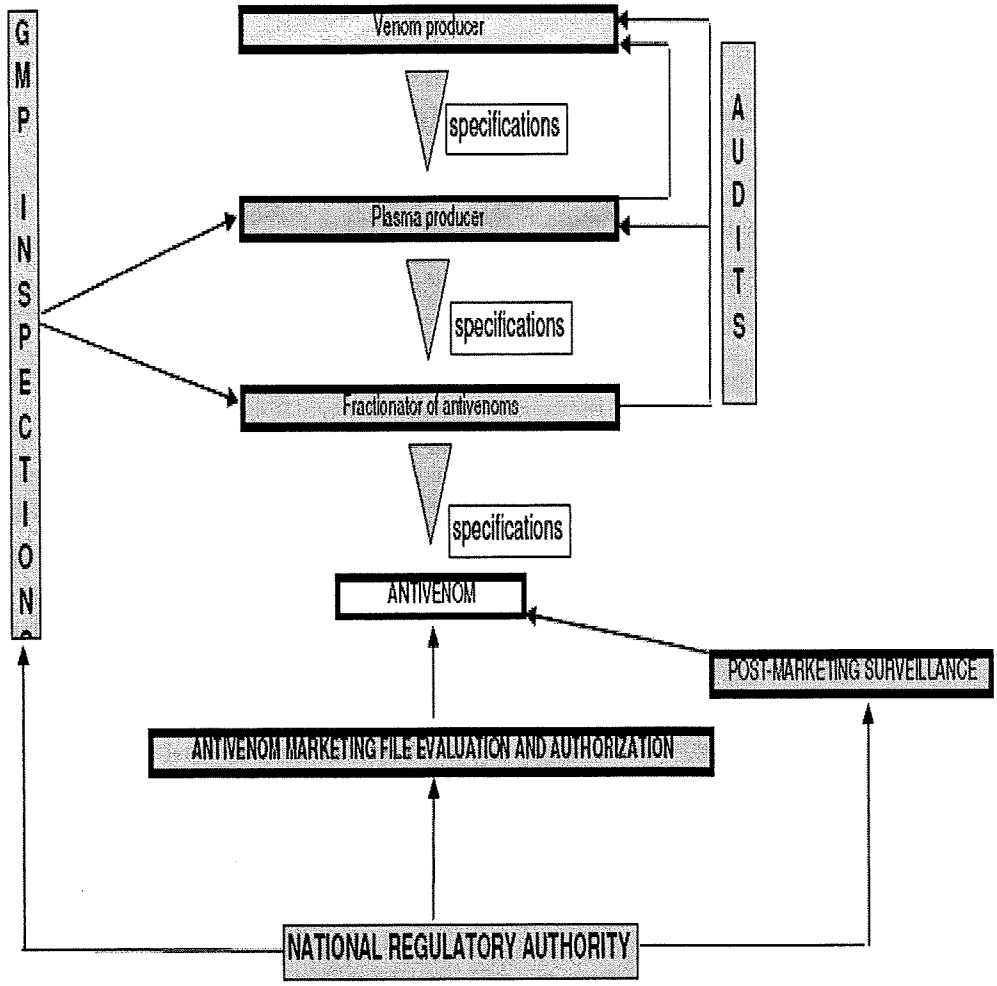
19 ROLE OF NATIONAL REGULATORY AUTHORITIES

National Regulatory Authorities should increasingly play a pivotal role in ensuring the quality, safety, and efficacy of antivenoms. WHO Guidelines for national regulatory authorities (NRA) on quality assurance of biological products (WHO g,h) state that NRAs should ensure that available biological products, whether imported or manufactured locally, are of good quality, safe and efficacious, and should thus ensure that manufacturers adhere to approved QA and GMP standards. The responsibilities should also include the enforcement and implementation of effective national regulations, and the setting of appropriate standards and control measures. The evaluation and control of the quality, safety and consistency of production of animal derived blood products involve the evaluation of the starting material, production processes and test methods to characterize batches of the product. This requires appropriate expertise by the NRA.

The evaluation and control of the quality, safety and consistency of production of antivenoms is summarized in Figure 7 and involve the evaluation of:

- The preparation of the starting plasma material from immunized animals, including the preparation of snake venom batches representative of the poisonous animals of the geographic region to which the antivenom is made for, and the control and traceability of the immunized animals and of the immunization process;
- The fractionation process used to produce the antivenoms;
- The test methods used to control batches of the product;
- The preclinical data supporting the expected efficacy of the products for treatment of local envenomings;
- The clinical efficacy of locally manufactured or imported antivenoms against the species of snakes found in the country, through active marketing surveillance.

Figure: Inspections and Audits system in the production of antivenoms



19.1 Control of the neutralizing efficacy of venoms by antivenoms preparations

One aspect of critical importance is to ensure that each batch of antivenoms used to treat envenomings has the capacity to neutralize the medically relevant venoms prevalent in the country or the region within the country where the antivenom is intended to be used. This can be achieved by testing the antivenoms against the local venoms using the lethality test and the determination of the Medium Effective Dose (ED_{50}), described in Section 15. Depending upon the situation, the neutralization of lethality test is to be performed by the manufacturer within the scope of the marketing authorization of the antivenom preparation or the batch approval process.

An antivenom preparation that fails to neutralize the local snake venoms should not be marketed.

19.2 Establishment license and inspections

In many countries NRAs have implemented a control system based on licensing the establishments, inspecting them regularly, and enforcing the implementation of the legal requirements and applicable standards. This should apply to the production of animal hyperimmune plasma for fractionation, and the manufacturing process of the antivenoms.

A QA system for manufacture of animal derived plasma products should cover all stages leading to the finished product, from production of plasma (including information on venom preparation, animal immunization, and animal health control) to the fractionation of plasma into the finished products and their control. Manufacturers of antivenoms should therefore be subject to inspection and approved by a national regulatory authority.

Establishments involved in all or some stages of the manufacture of antivenoms need to have an establishment licence and need to be inspected by the competent national regulatory authority. To obtain the license the establishments have to fulfil a defined set of requirements to guarantee that their operation ensures the safety, quality and efficacy of the antivenoms.

A system control for the venoms and for the animals should be in place, as part of the procedures used for the production of animal plasma for fractionation

19.3 Impact of Good Manufacturing Practices

Implementing the principles of GMP in the production of therapeutic products is acknowledged as essential at assuring the quality and safety of biological medicinal products. For antivenoms, GMP becomes even more important and more complex due to the biological nature of the production process and the complexity and local specificities of snake envenomings.

Therefore, taking into account the principles of GMP and the existence of an appropriate QA system to address and implement these requirements at all manufacture stages should be a pivotal element of antivenoms quality and safety. The following benefits are expected:

- Ensures the application of QA principles in all steps involved into the production of animal plasma and the fractionation process of antivenoms
- reduces errórs and technical problems at all stages of manufacture of plasma for fractionation and antivenoms
- contributes to the release of products which comply with quality and safety requirements
- ensures adequate documentation and full traceability of plasma for fractionation and antivenoms production stages
- enables continuous improvement in production of plasma for fractionation and antivenoms
- provides suitable tools for the NRA to assess the compliance status of a manufacturer of antivenoms, either local or abroad.
- supports regional co-operation networks that may result in the formation of competence centres by centralising activities in order to reach compliance at the required level.

An establishment licensing system for antivenom manufacturers by the competent national regulatory authorities should therefore exist. The main requirements to obtain an establishment license may include especially:

- Quality Assurance System and GMP applied to all steps of production
- Personnel directly involved in collection, testing, processing, storage and distribution of antivenoms appropriately qualified and provided with timely and relevant training,
- Adequate premises and equipment available,
- An adequate control system to ensure traceability of antivenoms manufacture to be enforced through accurate identification procedures, through record maintenance, and through an appropriate labeling system,
- Post-marketing information system

19.4 Inspections

Enforcement of the implementation of GMP is performed aiming to ensure the compliance of the manufacturer with the existing provisions. It is the responsibility of the inspector of the NRA for ensuring that manufacturers adhere to the approved standards of GMP and QA.

The inspections and control measures should be carried out by officials, representing the competent national regulatory authority, and should involve persons which are specialised inspectors, trained in GMP inspections, and familiar with antivenoms or biological products technologies.

Inspections may follow common inspection procedures, including an opening meeting, a tour of the facility, inspection of main areas and activities (such as snake farms; animal husbandry practices; animal identification and suitability for blood/plasma collection; serum/blood/plasma collection process and storage; plasma fractionation process; testing and availability of test results for venoms, antivenoms, and raw materials; storage, transportation and shipment; quality assurance [incl. self inspection, change control, etc.], documentation [SOP, records, donor record files, log books, etc.], personnel and organisation, qualification and process validations, error and corrective action system, recalls and complaints, product quality controls), and a final meeting summarizing the inspection outcome. A thorough inspection includes the observation of staff during performance of operations and comparison with established standard operating procedures. The inspection cannot only be considered as compliance of good manufacturing procedures but also as an indirect product quality assessment by checking product-specific validation and quality control data.

A written report should summarise the main aspects of the inspection including its scope, a description of the company, the deficiencies listed, specified and classified (e.g. critical – major – minor), and a conclusion. The written report will be sent to the manufacturer. The manufacturers are requested to notify the national regulatory authority about the specific steps which are taken or planned to correct the failures and to prevent their recurrence. If necessary follow-up inspections should be performed e.g. to check the successful implementation of specific corrective actions.

The national regulatory authority should have the authority to withdraw an establishment licence in case where inspection results showed critical non-compliance with the requirements or product specifications. In the marketing authorization procedure of an antivenom, information on the collection and control of the venoms and of the starting animal blood or plasma needs to be documented as part of the dossier.

In summary, the enforcement and implementation of licensing and inspection regulatory systems for antivenoms constitute fundamental tools to ensure the quality of antivenoms produced or distributed to treat envenomings in a country.

AUTHORS AND ACKNOWLEDGEMENTS

These Guidelines were developed under the coordination of Dr A. Padilla, Scientist, Quality Assurance and Safety: Blood Products and related Biologicals in WHO. They cover comprehensively existing experience in the manufacture, control, preclinical and clinical assessment of antivenoms to serve as a guide to national regulatory authorities, manufacturers, clinicians and public health officers.

The development of this evidence-based document has been achieved thanks to the collaboration of a large number of experts supporting different specific areas in the Guideline. The process and experts contributing to the drafting of the document are listed below:

The first Draft was prepared by late Dr. Cassian Bon, Museum National d'Histoire Naturelle, France; Dr. Thierry Burnouf, Consultant, WHO; Dr. Jose-Maria Gutierrez, Instituto Clodomiro Picado, Costa Rica; Dr A. Padilla, Quality Assurance and Safety of Blood Products and related Biologicals, WHO; Professor Kavi Ratanabanangkoon, Chulabhorn Research Institute, Thailand; and Professor DA Warrell, University of Oxford, UK.

The Draft was submitted for preliminary discussion to the Expert Committee on Biological Standardization (58th Meeting) followed by a detailed discussion within the WHO Blood Regulators Nerwork (BRN), members of which are: Dr J. Epstein, Food and Drug Administration (FDA), USA; Dr A. Farrugia, Therapeutic Goods Administration (TGA), Australia; Dr P. Ganz, Health Canada, Canada; Dr E. Griffiths, Health Canada, Canada; Dr M. Heiden, Paul-Ehrlich Institute (PEI), Germany; Dr I. Sainte Marie, Agence française de Sécurité sanitaire des Produits de Santé (Afssaps), France; Dr C. Schärer, Swissmedic, Switzerland; Dr R. Seitz, Paul-Ehrlich Institute (PEI), Germany (Chairman); Dr P. Zorzi, Agence française de Sécurité sanitaire des Produits de Santé (Afssaps), France.

Because of the importance of these Guidelines to improve production and control of antivenoms worldwide, two WHO Bi-Regional Workshops were organized in Asia and Africa, these being the Regions where snakebite envenomings constitute a major public health problem. The Workshops aimed to discuss the Draft Guidelines with clinical toxinologists, manufacturers, national poison centers and regulators directly invoved in manufacture and regulation of antivenoms and, in the treatment of snakebite envenomings in those Regions. The Workshops were conducted by the World Health Organization with the collaboration of the following Facilitators:

Dr T. Burnouf, Human Protein Process Sciences, Lille, France; Dr J. P. Chippaux, Institut de Recherche pour le Développement (IRD), La Paz, Bolivie; Dr J. M. Gutierrez, Instituto Clodomiro Picado, University of Costa Rica, San José, Costa Rica; Dr G. Müller, University of Stellenbosch, Cape Town, South Africa (retired); Dr A. Padilla, World Health Organization, Geneva Switzerland; Professor H. J. de Silva, Faculty of Medicine, University of Kelaniya, Sri Lanka; Professor P. Gopalakrishnakone, Yong Loo Lin School of Medicine, National University of Singapore; Dr R. Harrison, Liverpool School of Tropical Medicine, United Kingdom; Dr D. Lalloo, Liverpool School of Tropical Medicine, United Kingdom; Prof. K. Ratanabanangkoon, Chulabhorn Research Institute, Bangkok, Thailand; Professor D. Theakston, Liverpool School of

Tropical Medicine, United Kingdom (retired); Mr D. Williams, Australian Venom Research Unit/Nossal Institute for Global Health, School of Medicine, University of Melbourne.

Acknowledgements are due to the following participants to the WHO Bi-Regional South-East Asian and West Pacific Workshop on Production, Control and Regulation of Antivenoms in Jakarta, Indonesia, for their professional contributions and interactive discussions:

Mrs A. Abas, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health Malaysia; Mrs S. S. Akter, Institute of Public Health, Dhaka, Bangladesh; Professor R. Alam, Dhaka Medical College, Bangladesh; Dr S. Amudhavalli, King Institute of Preventive Medicine, Chennai, India; Mr A. Azhari, Bio Farma, Bandung, Indonesia; Mr I. Baru, Drug Registration, Department of Health, Papua New Guinea; Dr B. Bissumbhar, World Health Organization, Geneva, Switzerland; Dr Chhuo Meng, Poisons Centre, Calmette Hospital, Phnom Penh, Cambodia Mr M. C. Dancel, Research Institute for Tropical Medicine, Muntinlupa, Philippines; Mr A. Fernandes, Bharat Serum and Vaccines Ltd, Mumbai, India; Dr S. Gnanaiah, King Institute of Preventive Medicine, Chennai, India; Dr A. Gnanathasan, Department of Clinical Medicine Faculty of Medicine, Colombo, Sri Lanka; Ms L. St. Halimah, Bio Farma, Bandung, Indonesia; Dr Heng Bun Kiet, Department of Drugs and Food, Ministry of Health, Cambodia; Dr T. N. Huu, Pasteur Institute, Ho Chi Minh City, Vietnam; Mrs W. Jariyapan, Department of Medical Sciences, Ministry of Public Health, Thailand; Dr Jing Zhang, Lanzhou Institute of Biological Products, People's Republic of China; Dr M. V. Khadilkar, Haffkine Biopharmaceutical Corporation Ltd, Mumbai, India; Professor S. Khomvilai, Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand; Dr M. Kuppusamy, VINS Bioproducts LTD, Hyderabad, India; Mrs D. Kusmiaty, National Agency of Drug and Food Control, Indonesia; Dr Li Jingyu, Shanghai Serum Biological Technology Co LTD, People's Republic of China; Dr F. Malbas, Research Institute of Tropical Medicine, Muntinlupa, Philippines; Brig. Gen. S. M.A. Matin, Directorate of Drug Administration, Bangladesh; Ms M. T. S. Modina, Bureau of Food and Drugs, Philippines; Ms A. Mohamed Ariff, National Poison Center, Penang, Malaysia; Mr A. Nair, VINS Bioproducts LTD, Hyderabad, India; Mr N. T. Nguyen, Poison Control Centre, Hanoi, Vietnam; Ms L. Nitisaporn, The Government Pharmaceutical Organization, Thailand; Dr L. R. Panganiban, National Poison Management and Control Center, University of the Philippines, Manila, Philippines; Dr V.V. Pillay, Amrita Institute of Medical Sciences & Research, Cochin, Kerala, India; Mr K. Ragas, CSL Biotherapies, Parkville Victoria, Australia; Dr Y. Sano, World Health Organization, Regional Office for the Western Pacific; Dr B. Santoso, World Health Organization, Regional Office for the Western Pacific; Dr M. Shahjahan, World Health Organization, Country Office of Indonesia; Dr Shumin Zhang, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China; Dr L. S. Slamet, National Agency of Drug and Food Control, Indonesia; Mr J. Smith, CSL Biotherapies, Parkville Victoria Australia; Dr D. Sundari, Poison Information Center, Jakarta, Indonesia; Dr M. Takahashi, National Institute of Infectious Diseases, Tokyo, Japan; Mr B. Thapa, Ministry of Health and Population, Nepal; Dr C. L. Thapa, Ministry of Health And Population, Dumkauli Primary Health Care Center, Nepal; Dr M. Toriba, Japan Snake Institute, Japan; Mrs D. Vu Bach, Drug Registration Department, Ministry of Health, Vietnam; Professor J. White, Women's and Children's Hospital, North Adelaide, Australia; Dr Zhou Jing, Center for Acute Poisoning Control, Beijing, China

Acknowledgements are also due to the participants to the WHO Bi-Regional African and Eastern Mediterranean Workshop on Production, Control and Regulation of Antivenoms in Addis Ababa, Ethiopia for their contributions and willingness to share expertise and information:

Dr F. Aljenoobi, Food and Drug Authority, Saudi Arabia; Dr B. Allali Kouadio, Pasteur Institute, Côte d'Ivoire; Dr S. Ansar Ahmad, Ministry of Health, Pakistan; Dr M. Atef Abu Zeid, National Antivenom & Vaccine Production Center, Riyadh, Saudi Arabia; Dr S. Bah, Institut National de Recherche en Santé publique, Bamako, Mali; Dr S. Bokata Masika, University of Kinshasa, Democratic Republic of Congo; Dr C. M. Baldé, Ministry of Health, Pasteur Institute, Guinea; Dr B. Bissumbhar, World Health Organization, Geneva, Switzerland; Dr M. Chisale, World Health Organization, Regional Office for Africa; Professor A. Diouf, Poison Centre, Health Ministry and Prevention, Senegal; Dr N. Durfa, Federal Ministry of Health, Nigeria; Dr B. Ed Nignpense, Poisons Information & Control Centre, Ridge Hospital, Accra, Ghana; Dr M. El-Sayed Aly Ibrahim, National Regulatory Authority, Egypt; Dr A. G. Etoundi Mballa, Hôpital Central de Yaoundé, Cameroon; Dr N. D. Fall Diop, Ministry of Health and Prevention, Senegal; Dr V. Gomwe, Medicines Control Authority, Zimbabwe; Mr M. Haladou, Ministry of Health, Niger; Dr G. Habib, Organization for Biological Products and Vaccines, Giza, Egypt; Dr C. Ilonze, National Agency for Food and Drug Administration and Control, Nigeria; Mrs N. Khalid Nomani, National Institute of Health, Pakistan; Dr F. Kolon Diallo, Direction Nationale de la Pharmacie et du Laboratoire, Ministry of Health, Conakry, Guinea; Dr H. Langar, World Health Organization, Regional Office for the Eastern Mediterranean; Mr T. Makoe, South African Vaccine Producers Ltd, Johannesburg, South Africa; Ms M. Masanja, Food and Drugs Authority, Tanzania; Professor A. Massougbodji, Unity of Parasitology, Cotonou, Benin; Dr A. Mhenni, Pasteur Institute, Tunisia; Dr A. Mohanna Mohamed, Egyptian Organization for Biological Products and Vaccines, Giza, Egypt; Dr F. Moin Siyoi, Pharmacy and Poisons Board, Ministry of Health, Kenya; Professor C. Nhachi, University of Zimbabwe Medical School, Harare, Zimbabwe; Dr G. Noreddine, Pasteur Institute, Morocco; Mr A. Okello Okonye, National Drug Authority, Uganda; Mr K. C. Yemoa, Direction des Pharmacies et du Médicament, Ministère de la Santé, Cotonou, Benin.

The 2nd Draft of this Guideline was prepared, taking into consideration the information and discussions held at the above Workshops. The following experts contributed to the preparation of this Draft: Dr T. Burnouf, Human Protein Process Sciences, Lille, France; Dr J. M. Gutiérrez, Instituto Clodomiro Picado, University of Costa Rica, San José, Costa Rica; Dr A. Padilla, World Health Organization, Geneva Switzerland; Professor H. J. de Silva, Faculty of Medicine, University of Kelaniya, Sri Lanka; Professor P. Gopalakrishnakone, Yong Loo Lin School of Medicine, National University of Singapore; Dr K. Regas, CSL Biotherapeutics, Victoria, Australia; Dr R. Harrison, Liverpool School of Tropical Medicine, United Kingdom; Dr D. Lalloo, Liverpool School of Tropical Medicine, United Kingdom; Prof. K. Ratanabanangkoon, Chulabhorn Research Institute, Bangkok, Thailand; Professor D. Theakston, Liverpool School of Tropical Medicine, United Kingdom (retired); Professor Julian White, Women's and Children Hospital, Adelaide, Australia.

The information in the Appendix of these Guidelines on distribution of venomous snakes of highest medical importance worldwide, provides extremely valuable and detailed information

that will assist manufacturers, regulators, public health officers, governements and non governmental organizations as well as procurement international agencies to make informed decisions with regard to the antivenoms to be considered within a particular region, country or territory. This Appendix was prepared by Mr D.Williams, Australian Venom Research Unit/Nossal Institute for Global Health, School of Medicine, University of Melbourne; Dr Mark O'Shea, Australian Venom Research Unit, School of Medicine, University of Melbourne and Dr Wolfgang Wüster, School of Biological Sciences, University of Wales; Australian Venom Research Unit, School of Medicine, University of Melbourne. The final Draft of the Appendix was reviewed by Dr D. Broadley, The National Museum of Zimbabwe, Zimbabwe; Dr J. P. Chippaux, Institut de Recherche pour le Développement (IRD), La Paz, Bolivia; Dr B. Currie, Menzies School for Health Research, Darwin, Australia; Dr J. M. Gutiérrez, Instituto Clodomiro Picado, University of Costa Rica, San José, Costa Rica; Dr S. Seifert, USA; Professor D.A. Warrell, University of Oxford, UK; Professor J. White, Women's and Children Hospital, Adelaide, Australia.

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APPENDIX: WORLWIDE DISTRIBUTION OF MEDICALLY IMPORTANT VENOMOUS SNAKES

This schedule lists venomous snake species considered to represent the greatest threat to public health in various countries or regions around the world. Only species which fall into one of the two categories listed below are shown, and category listings are in alphabetical order according to genus and species. Definitions of the categories used in this listing are:

CATEGORY 1: Highest Medical Importance

Definition: Highly venomous snakes which are common or widespread and cause numerous snakebites, resulting in high levels of morbidity, disability or mortality.

CATEGORY 2: Secondary Medical Importance

Definition: Highly venomous snakes capable of causing morbidity, disability or death, but for which (a) exact epidemiological or clinical data may be lacking, and/or (b) are less frequently implicated (due to their activity cycles, behaviour, habitat preferences or occurrence in areas remote to large human populations).

There are numerous other venomous species that rank as lesser threats in countries listed here, and interested readers should refer to one of the major references in the bibliography for further information if desired.

It should also be noted that the organisation of countries, territories and other areas into regions in this Appendix does not follow the WHO Regional Organisation, but is instead arranged bio-geographically in alphabetical region/country order. This was necessary in order to reflect the bio-geographical distribution of major groups of venomous snakes throughout the world. For example, the venomous snakes of the eastern Indonesian Province of Papua have bio-geographical origins in Australo-Papua, and are evolutionarily distinct from the venomous snakes of Asian origin which occur west of the Wallace Line. For this reason, we have listed the medically important snakes of Indonesian Papua in the Australo-Papuan region, rather than the South-East Asian region.

Users of this Appendix should also recognise that the relative risk of injury from a particular species may vary from one country to another, and in some cases, even within different areas inside the same country. For this reason, some species that have been listed under Category 1 in one country, may have been listed under Category 2 in another country as a reflection of the different risk posed by that species in different locations. Assignment to Category 1 or Category 2 was based in some cases on the importance of a species as a cause of snakebite. In Europe for example the overall incidence of snakebite is trivial compared to that in West Africa or India, but where a European species (such as *Vipera berus*) is a major cause (or sole) cause of envenoming where it occurs, this warrants ranking it as a medically important species in that setting.