Quality Assurance for blood products and related biologicals

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Blood Products & related Biologicals
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Health Systems and Innovation Cluster
World Health Organization
OUTLINE

- Website addresses of interest
- Human Blood Derived Products
- WHO Biological Reference Preparations for blood products and blood safety IVDs
- Blood/Blood components as essential medicines
- Animal derived blood products
Web site addresses

http://www.who.int/bloodproducts

http://www.who.int/bloodproducts/snakeantivenoms

http://www.who.int/bloodproducts/catalogue
# Blood Products & related Biologicals

## Human blood derived products
- Blood components (red cells, platelets, plasma)
- Blood Coagulation Factors
- Polyvalent Immunoglobulins (IV, IM)
- Specific Immunoglobulins
  - Anti-hepatitis B
  - Anti-rabies
  - Anti-tetanus
  - Anti-rhesus (anti-D)
- Albumin

## Animal-derived immunoglobulins
- Anti-rabies
- Anti-venoms
- Anti-tetanus toxin
- Anti-diphtheria toxin
- Anti-botulism toxin

## Other biological products
Anticoagulant & fibrinolysis biological therapeutic products

## In vitro biological diagnostic devices (IVDs):
**Priority:** Support of international regulations

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*World Health Organization*
Blood Products & related Biologicals Mission (Strategic Plan)

A WHO normative programme:

WHO is mandated by its Member States to "...develop, establish and promote international standards for biological products." In practice, biological products cover: Vaccines, Blood and blood products; \textit{In vitro} biological diagnostic devices; other biological products.

An Essential Medicines Programme:

To support the achievement of the \textit{health related MDGs} by assisting governments and organizations to ensure equitable access to \textit{effective medicines of assured quality} and their rational use by prescribers and consumers.
Blood Products & related Biologicals

**WHO standard setting functions**: 

- Develop/establish/provide WHO Biological Reference Preparations
- Develop/adopt/provide evidence based WHO Guidelines on Quality Assurance and Control of specific products or procedures
- Support enforcement and implementation of WHO Norms and Standards: strengthen technical/regulatory capacity of NRAs & NCLs
- Support operational strategies to improve access to quality products

(*) Consistent with the WHO mandate through the Expert Committee on Biological Standardization
Blood Products and related Biologicals
Target Audiencies

- National/Regional Regulatory Authorities
- National/Regional Control and National/Regional Reference Laboratories
- Blood Establishments and Plasma Fractionators
- Manufacturers of animal derived blood products
- Manufacturers of in vitro diagnostic tests
- Public Health Departments/Public Healt Officers/Ministries of Health
- Medical Professionals, Health Workers
- Procurement agencies and NGO’s
How do we work?

- ECBS - Blood Products and related Biologicals Track
- WHO Blood Regulators Network: scientific/regulatory
- WHO Collaborating Centres: Priority setting in the development of IBRPs
- WHO disease control programmes (infectious diseases): Overview of global epidemiological data
- WHO Working groups for specific topics: research & public health institutions; manufacturers associations;
- Coordination with other standard setting organizations and professional organizations: ISBT, ISTH, IFCC, EDQM
Human Blood Derived Products
Blood products are defined as therapeutic substances derived from human blood, including whole blood, labile blood components and plasma-derived medicinal products (WHA 63.12)
Blood Products: Life-Saving Medicines

WHA Resolution 63.12

- Blood and blood components
  - Whole blood collected into containers, anticoagulant to prevent clotting, cold chain
  - Blood components, obtained from whole blood by separation (centrifuge or apheresis):
    - Red blood cells: Oxygen transport
    - Platelets: Hemostasis, preventing bleeding
    - Plasma: clotting factors, immunoglobulins etc.
    - Cryoprecipitate, FVIII source

- Plasma derivatives
  Plasma for "fractionation", further purification of plasma proteins, e.g.
  - Blood Coagulation Factors, e.g. Factor VIII for treatment of hemophilia A
  - Specific Immunoglobulins, e.g. anti-hepatitis B, anti-rabies, anti-tetanus, anti-D
  - IM and IV normal IgG
  - Albumin, involved in the regulation of body fluids, used for resuscitation
2. REQUESTS the Director-General:

- (1) to guide Member States in setting internationally recognized standards in updating their legislation, national standards and regulations for effective control of the quality and safety of blood products and associated medical devices, including in vitro diagnostic devices;

- (2) to advise and build capacity in Member States on leadership and management of blood supply systems in order to strengthen national coordinated and sustainable blood and plasma programmes by sharing best practices about the organizational structure of blood supply systems in order to increase efficiency and minimize errors;

- (3) to augment the support offered to Member States for developing and strengthening their national regulatory authorities and control laboratories so as to increase their competence in the control of blood products and associated medical devices, including in vitro diagnostic devices, and to foster the creation of regional collaborative and regulatory networks where necessary and appropriate;

- (4) to ensure sustainable development and provision of WHO International Biological Reference Preparations (International Standards) for use in the quality control and regulation of blood products and related in vitro diagnostic devices;

- (5) to improve access by developing countries to WHO International Biological Reference Preparations and to the scientific information obtained in their validation in order to ensure the appropriate use of these preparations;

- (6) to develop, provide and disseminate guidance and technical support to strengthen national coordinated blood and plasma programmes and introduction of blood component separation and plasma fractionation technology, to meet local needs, and promote effective regulatory oversight of blood services and implementation of good manufacturing practices in plasma-fractionation programmes, under the responsibility of regulatory authorities;

- (7) to provide guidance, training and support to Member States on safe and rational use of blood products and to support the introduction of transfusion alternatives including, where appropriate, autologous transfusion, safe transfusion practices and patient blood management;

- (8) to encourage research into new technologies for producing safe and effective blood substitutes;

- (9) to inform regularly, at least every four years, the Health Assembly, through the Executive Board, on actions taken by Member States and other partners to implement this resolution.

(English plenary meeting, 21 May 2010 – Committee B. second report)
WHA Resolution 63.12
Overall Goals

- To raise quality standards in blood establishments (BE)
- To reduce risk of transmission of infectious diseases
- Effective regulatory systems for blood products worldwide
- To make safe blood products available to patients
The Need for Blood Regulation: WHAR63.12, May 2010

- WHA resolution 63.12 recognized that:
  - “stringent regulatory control is vital in assuring the quality and safety of blood products…” and
  - urged Member States to “update their national regulations … in order to ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards.”

- Strengthening regulatory systems for blood products and building technical capacity of national and regional blood regulatory authorities is recognized as a fundamental need to assure global availability of safe blood products.
TRACEABILITY FROM DONOR TO PATIENT

Blood donation → Blood Components ——> Plasma for Fractionation ——> Plasma-Derived Medicinal Product ——> Patients

DONATION INFORMATION ——> COMPONENTS PREPARATION ——> FRACTIONATION VIRAL INACTIVATION ——> TREATMENT

Good Manufacturing Practices
Good Manufacturing Practices (GMP)*: an essential tool for improvement of safety

GMP implementation in Blood/Plasma Establishments: a key element to

Quality and safety of blood components in blood establishments and plasma contract fractionation programs

Supporting access to blood plasma products

*WHO Guidelines on Good Manufacturing Practices for Blood Establishments
Plasma Contract Fractionation Programs (Need for GMP implementation)

GMP - common principles

Nat. Reg. Authority

Quality Assurance Program

PLASMA SUPPLIER

across countries

FRACTIONATOR

GMP Licensing

Licensing

GMP

Nat. Reg. Authority

World Health Organization
TRACEABILITY
FROM DONOR TO PATIENT

Blood donation → Blood Components → Plasma for Fractionation → Plasma-Derived Medicinal Product → Patients

DONATION ISSUES, e.g.
- donor population
- donor selection
- donor protection
- collection process

COMPONENTS PREPARATION, e.g.
- production process
- testing
- process control
- release
- storage & transport

World Health Organization
2. REQUESTS the Director-General:

2. (4) to ensure sustainable development and provision of WHO International Biological Reference Preparations for use in the quality control and regulation of blood products and related in vitro diagnostic devices;

(5) to improve access by developing countries to WHO International Biological Reference Preparations and to the scientific information obtained in their validation in order to assure appropriate use of these preparations.
WHO Biological Reference Standards*
Global measurement standards

- Tool for comparison of biological measurement results worldwide
- Facilitate transfer of laboratory science into worldwide clinical practice
- Underpin appropriate clinical dosage
- Facilitate convergence of international regulations (e.g. blood products; blood safety related IVDs)

*Established by the WHO Expert Committee on Biological Standardization
WHO Biological Reference Preparations
Blood Products and related Biologicals

60% of total IS or Ref Panels established between 1999-2009

<table>
<thead>
<tr>
<th>Category</th>
<th>In vitro Diagnostic Tests</th>
<th>Coagul.Factors/Thrombolytic Agents</th>
<th>Immunological Reagents</th>
<th>Total</th>
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<tr>
<td>Blood Safety and General Hematology</td>
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<td>Immunological Reagents</td>
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<tr>
<td>Total</td>
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</table>

WHO Catalogue of Biological Reference Preparations: www.who.int/bloodproducts
<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>STANDARD</th>
<th>WHO TRS ECBS REPORT</th>
<th>MATERIAL</th>
<th>HELD AT CODE</th>
<th>WHO/BS DOCUMENT</th>
</tr>
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<tbody>
<tr>
<td>Anti-A blood grouping minimum potency reagent, Lyophilized, A 1 in 8 dilution defines the recommended minimum potency specification for anti-A blood grouping reagents.</td>
<td>1st International Standard, 2005</td>
<td>No. 941, 56th Report</td>
<td>Monoclonal IgM (murine)</td>
<td>NIBSC 03/188</td>
<td>06.2053</td>
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<td>Anti-B blood grouping minimum potency reagent, Lyophilized, A 1 in 4 dilution defines the recommended minimum potency specification for anti-B blood grouping reagents.</td>
<td>1st International Standard, 2005</td>
<td>No. 941, 56th Report</td>
<td>Monoclonal IgM (murine)</td>
<td>NIBSC 03/164</td>
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<td>Anti-C complete blood typing serum, Lyophilized, 100 IU / ampoule</td>
<td>1st International Standard, 1984</td>
<td>No. 726, 35th Report</td>
<td>Human serum</td>
<td>NIBSC W1004</td>
<td>84.1424</td>
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<td>Anti-D (anti-Rho) minimum potency reagent, complete, Lyophilized, A 1 in 3 dilution defines the recommended minimum potency specification for low protein anti-D blood reagents; a 1 in 8 dilution defines the recommended minimum potency specification for high protein anti-D reagents.</td>
<td>1st International Standard, 2004</td>
<td>No. 932, 55th Report</td>
<td>Monoclonal IgM (human)</td>
<td>NIBSC 99/836</td>
<td>04.2000 Rev. 1</td>
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<td>Anti-hepatitis B virus core antibodies (anti-HBc), human, Lyophilized, 50 IU / vial.</td>
<td>1st International Standard, 2008</td>
<td>To be published</td>
<td>Human plasma</td>
<td>NIBSC 95/522</td>
<td>08.2008</td>
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<td>Anti-HIV antibodies (HIV-1 subtypes A, B, C, CRF01_AE, group O and HIV-2), Lyophilized, No unitage assigned.</td>
<td>1st International Reference Panel, 2006</td>
<td>To be published</td>
<td>Human plasma</td>
<td>NIBSC 02/210</td>
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<tr>
<td>Hepatitis A virus RNA, Lyophilized, 50,000 IU / vial.</td>
<td>1st International Standard, 2003</td>
<td>No. 928, 53rd Report</td>
<td>Human plasma</td>
<td>NIBSC 00/580</td>
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<td>Hepatitis B surface antigen, subtype adw2, genotype A, Lyophilized, Dilutional panel (IU/vial: 8.25; 2.05; 0.52; 0.13),</td>
<td>1st International Reference Panel, 2003</td>
<td>No. 927 54th Report</td>
<td>Human plasma</td>
<td>NIBSC 03/282</td>
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<td>Hepatitis B surface antigen, subtype adw2, genotype A, Lyophilized, 33 IU / vial.</td>
<td>2nd International Standard, 2000</td>
<td>No. 927 54th Report</td>
<td>Human plasma</td>
<td>NIBSC 00/588</td>
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<td>Hepatitis B virus DNA, Lyophilized, 500,000 IU / vial.</td>
<td>2nd International Standard, 2000</td>
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<td>Human plasma</td>
<td>NIBSC 97/750</td>
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<tr>
<td>Hepatitis C virus RNA, Lyophilized, 4.80 log10 IU / vial; 5.19 log10 IU / ml.</td>
<td>3rd International Standard, 2007</td>
<td>To be published</td>
<td>Human plasma</td>
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<td>HIV-1 p24 antigen, Lyophilized, 1,000 IU / ampoule.</td>
<td>1st International Reference Reagent, 1982</td>
<td>No. 940, 43rd Report</td>
<td>Peptide in human serum</td>
<td>NIBSC 90/636</td>
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<td>HIV-1 RNA genotypes (set of 10 genotypes), Liquid, No assigned value.</td>
<td>1st International Reference Panel, 2003</td>
<td>No. 926, 53rd Report</td>
<td>HIV-1 isolates diluted in human plasma</td>
<td>NIBSC 01/466</td>
<td>03.1961</td>
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<td>Human syphilitic plasma IgG and IgM, Lyophilized, 3 IU per ampoule relative to HS, the 1st 15S for human syphilitic antibodies.</td>
<td>1st International Standard, 2007</td>
<td>No. 941 56th Report</td>
<td>Human plasma</td>
<td>NIBSC 05/132</td>
<td>07.2059</td>
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This Catalogue is available at the following WHO Web site address: [http://www.who.int/bloodproducts/ref_materials/](http://www.who.int/bloodproducts/ref_materials/)
### WHO Biological Reference Standards* Development & Establishment

<table>
<thead>
<tr>
<th>No.</th>
<th>Step Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Selection of candidate materials</td>
</tr>
<tr>
<td>2.</td>
<td>Characterization of candidate materials</td>
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<tr>
<td>3.</td>
<td>Dilution of materials (dilution matrix)</td>
</tr>
<tr>
<td>4.</td>
<td>Inactivation (if needed)</td>
</tr>
<tr>
<td>5.</td>
<td>Freeze-drying</td>
</tr>
<tr>
<td>6.</td>
<td>Feasibility studies</td>
</tr>
<tr>
<td>7.</td>
<td>Characterization of final product</td>
</tr>
<tr>
<td>8.</td>
<td>Stability studies (incl. statistical analysis)</td>
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<tr>
<td>9.</td>
<td>WHO international collaborative study (incl. statistical analyses)</td>
</tr>
<tr>
<td>10.</td>
<td>WHOCC &amp; Working Groups</td>
</tr>
<tr>
<td>11.</td>
<td>Report to ECBS and decision</td>
</tr>
<tr>
<td>12.</td>
<td>Storage and distribution</td>
</tr>
</tbody>
</table>

*Recommendations for the preparation, characterization and establishment of international and other biological reference standards (revised 2004); Annex 2, WHO TRS, No 932, 2005.*
In vitro diagnostic devices (IVDs)*
Medical devices used *in vitro* for the examination of human specimens

- **IVDs for infectious markers**
  - Viruses, bacteria, parasites, unconventional agents

- **IVDs for**
  - Blood/plasma screening (blood safety)
  - Confirmation of infection
  - Diagnosis and monitoring

- **Tests methods**
  - Serological assays (e.g. ELISA)
  - Nucleic acid amplification techniques (NAT)

*Priority: pathogens with impact on blood safety and international regulations*
### ECBS: HIV (IVD Technologies)


#### WHO International Standard or Reference Panel

<table>
<thead>
<tr>
<th>Test</th>
<th>Current</th>
<th>Users</th>
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<tbody>
<tr>
<td><strong>Serology</strong></td>
<td>HIV-1 p24 antigen, 1st IS (IU)</td>
<td>Test developers, manufacturers, regulators, blood establishments, fractionators, reference laboratories, diagnostic laboratories</td>
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<tr>
<td></td>
<td>Anti-HIV, 1st Ref Panel (no unitage) (HIV-1 subtypes: A, B, C, CRF_01, O; HIV-2)</td>
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<tr>
<td><strong>NAT</strong></td>
<td>HIV-1 RNA 2nd IS (IU)</td>
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<td>HIV-1 RNA Genotype 1st Ref Panel (no unitage) (A,B,C,D, AE, F, G, AG-GH, groups N &amp; O)</td>
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<td>HIV-2 RNA 1st IS (IU) -</td>
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<td>Test</td>
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<td>Users</td>
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<tr>
<td>Serology</td>
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<td><strong>Anti-Hepatitis B virus core antibodies</strong> (IU)</td>
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<td><strong>HBsAg genotype reference panel</strong></td>
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<td></td>
<td>A, B, C, D, E, F, G (no unitage) -</td>
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</tr>
<tr>
<td></td>
<td><strong>Hepatitis C virus RNA 2(^{nd}) IS (IU)</strong></td>
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</tbody>
</table>

Current IS both for HBsAg and HBV DNA are genotype A2: 1\% of HBV infections worldwide
Improving Access to Safe Blood Products
Whole Blood and Blood Red Cells as Essential Medicines
Improving Access to Safe Blood Products Through Local Production and Transfer of Technology in Blood Establishments

World Health Organization
Essential Medicines

**Principle:** A limited range of carefully selected essential medicines leads to better health care, better medicines management, and lower costs

**Definition:** Essential medicines are those that satisfy the priority health care needs of the population

**Selection:** Selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.
Whole Blood and RBC as Essential Medicines (I)

- Red cell replacement therapies (both Whole Blood and RBC) are essential in the treatment of hemorrhagic shock (e.g., bleeding at childbirth or from trauma) and for correction of anemia (e.g. due to malaria or sickle cell disease).

- However, the blood supply in most developing countries is not adequate to provide for these needs:
  - It has been estimated that 15 units of whole blood must be collected per 1,000 population to meet basic needs. But, on average, only 2.8 units per 1,000 population are collected in low income countries.
Whole Blood and RBC as Essential Medicines (II)

- Transfusion with Whole Blood is no less an essential therapy than RBCs
  - Whole blood is more available than RBC in many developing countries
  - Urgently collected Whole Blood has been lifesaving in front-line battlefield settings
  - Fresh Whole Blood may be a preferred resuscitation fluid in hemorrhagic shock

- Availability of safe blood transfusion is also an essential prerequisite for more advanced medical therapies (e.g. chemotherapy, surgeries and organ transplantation)
Whole Blood and RBC as Essential Medicines

Summary(I)

- The availability of safe blood and components for transfusion is essential to public health in all countries
  - Serious unmet needs for whole blood and RBC exist in many developing world countries
  - Adequate blood supplies are a necessary underpinning of more advanced medical therapies

- The characteristics of Whole Blood and RBC (and other blood components) support the view that they are biological medicines
  - The quality and safety of blood components depends on meeting recognized standards in manufacturing;
  - Consequently, blood components are regulated as biological medicines in many jurisdictions
Whole Blood and RBC as Essential Medicines
Summary (II)

- Having Whole Blood and RBC on WHO’s List of Essential Medicines, would help governments to justify increased efforts in blood donor recruitment and blood collection, which would improve medical care in the population.
  - If the medicine is deemed “essential,” steps will be taken to increase awareness, assure availability, and thereby prevent deaths and disabilities from blood shortages
- By having more blood collected under quality medical product standards, including regulatory oversight, transfusions will be safer and more effective.
The concept of Whole Blood and Blood Components as Essential Medicines has been unanimously endorsed by the WHO ECBS, the WHO Blood Regulators Network and the International Conference of Drug Regulatory Authorities

October 2012
In considering listing of Whole Blood and RBC as Essential Medicines, WHO should take notice of the needs:

– To establish and strengthen National Blood Regulatory Systems through education and technical support to regulators of medicines
– To promote establishment of adequate blood system infrastructures
– To assist Member States to avoid potential unintended consequences to existing blood systems
WHO Essential Medicines List

- Animal derived blood products
  - Snake anti-venom immunoglobulins
SNAKE ANTIVENOM IMMUNOGLOBULINS

VERY POOR REGULATORY CONTROL: Technology in the public domain

A - Collection of venoms

B – Horse Immunization Protocols

C – Starting material of animal derived sera

D – Fractionation & Purification process
WHO Guidelines and Recommendations

ANIMAL DERIVED BLOOD PRODUCTS

- WHO Guidelines on production, control and regulation of snake antivenom immunoglobulins

- WHO Database: clinically important venomous snakes species and its worldwide geographical distribution together with antivenoms for treatment of snakebite envenomings

- WHO website hosting both the Guidelines and database (maps, pictures, products, manufacturers)
WHO Database: Medically Important Snakes
Distribution maps, pictures & antivenoms

Red or orange question marks (⊕)
(Indicates expected presence not yet confirmed due to lack of exploration)

Allocation to CATEGORY 1 shown in red
(Indicates common, widespread species that causes numerous snake bites with high morbidity, disability or mortality)

Allocation to CATEGORY 2 shown in orange
(Indicates highly venomous and capable of causing morbidity, disability or mortality, but exact country data lacking, or less frequently implicated in these countries)

www.who.int/bloodproducts/snakeantivenoms
WHO web site: Target Audiences

- Central information source for data on the current availability of antivenoms for specific species.
- Aimed at a wide audience, that includes:
  - National Regulatory Agencies
  - Ministries of Health
  - Antivenom Manufacturers
  - Medical Professionals, Health Workers
  - Procurement Personnel in Industry and NGO’s
- Objective is to use the web site to distribute accurate data that can be used to plan improvements to existing supply and distribution.
Web site addresses

http://www.who.int/bloodproducts

http://www.who.int/bloodproducts/snakeantivenoms

http://www.who.int/bloodproducts/catalogue

E-mail addresses: padillaa@who.int; greenoughl@who.int