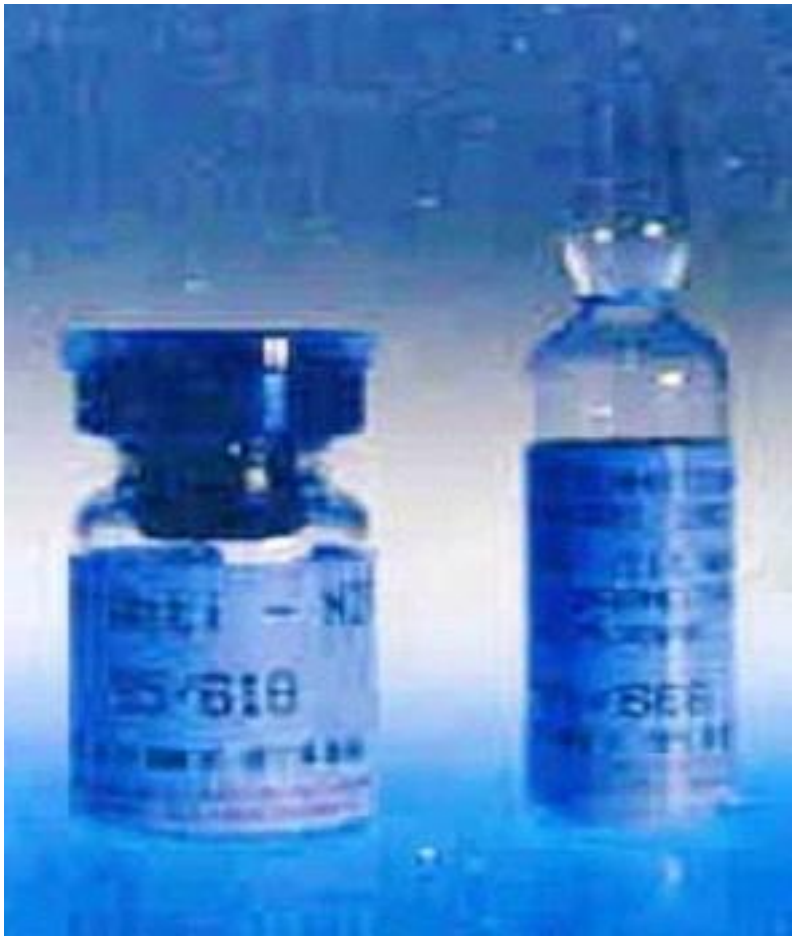
# Expert Committee on Biological Standardization

# Blood Products & IVD Track

Dr Ana Padilla
Blood Products & related Biologicals
Quality and Safety: Medicines
Essential Medicines and Pharmaceutical Policies Department
Health Services and Systems Cluster
World Health Organization

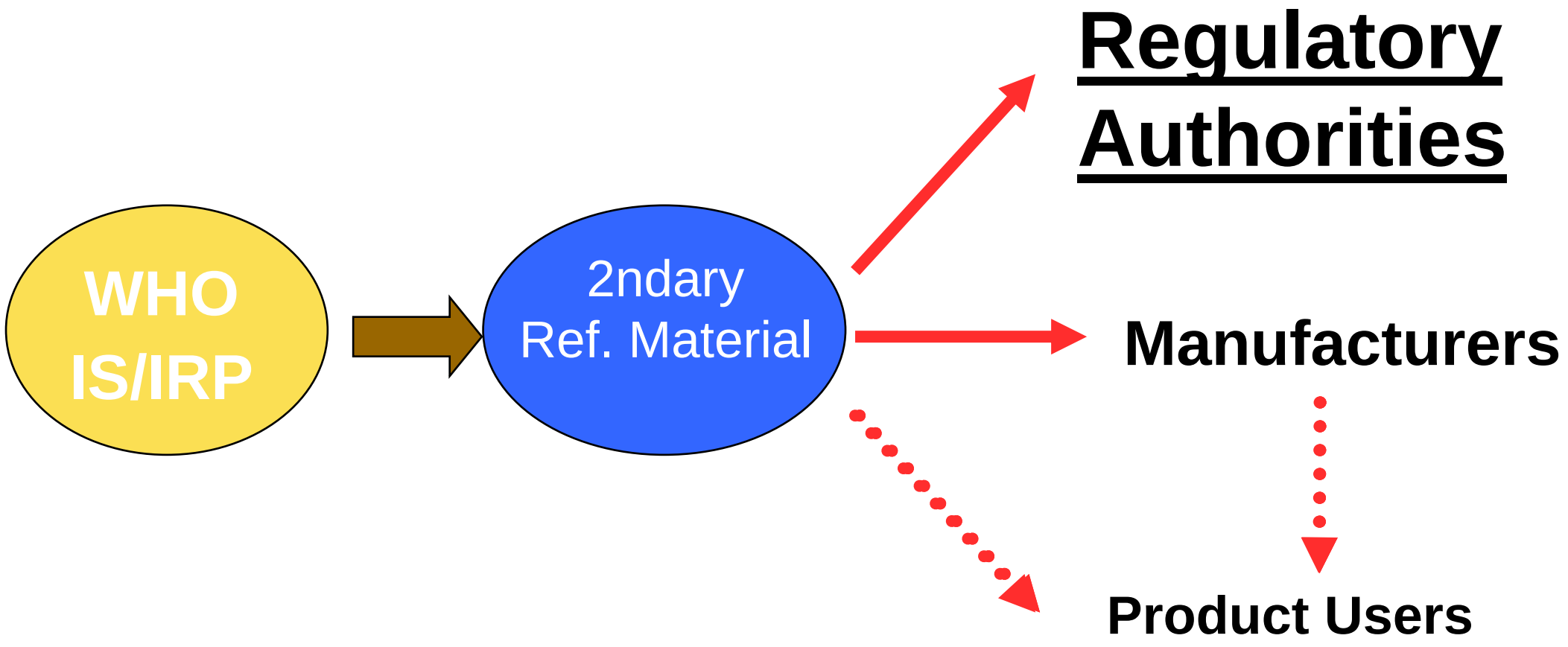
# WHO Biological Reference Preparations
# Global measurement standards

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



# WHO Biological Reference Preparations

## A tool for comparison of results worldwide






World Health Organization

| Analytical Sensitivity | Standards required by CTS EU IVD Directive | WHO standards available |
|---|---|---|
| **Screening and rapid assays** | | |
| anti-HIV-1/2 | none | none |
| anti-HTLV-I/II | none | none |
| anti-HCV | none | Planned |
| **HBsAg** | 0.5 ng/ml (French or UK-standard)<br>**2.6 IU (WHO HBsAg 2nd IS)** | **2nd WHO International Standard for HBsAg: 33 IU/ampoule**<br>**WHO dilutional reference panel** |
| anti-HBc | none | Planned |
| **NAT assays (qualitative and quantitative)** | | |
| HIV | Analytical sensitivity (IU/ml) defined on WHO standards | HIV-1 RNA 1st IS (1999) $10^5$IU/ml |
| HCV | | HCV RNA 2st IS (2003) $10^5$IU/ml |
| HBV | | HBV DNA 1st IS (1999) $10^6$IU/ml |
| HTLV I/II | | none |
| **Confirmatory assays** | | |
| anti-HIV-1/2 | none | none |

# WHO Biological Reference Preparations (www.who.int/bloodproducts*)

- **Nucleic Acid Technology:**
  - HBV/HCV/HIV/Parvovirus/HAV (IS)
  - HIV genotype reference panel
- **Immunoassays:**
  - HBsAg; Anti-HBs; Anti-HBc
  - HIV p24 antigen
  - Anti-HIV subtype reference panel
- **vCJD reference materials**
- **Blood grouping reagents**
- **Platelets immunology**
- **Blood Coagulation disorders**

(*) WHO Catalogue of Biological Reference Preparations



World Health Organization

# 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 | |
|---|---|---|
| **Test** | **Current** | **Users** |
| Serology | HIV-1 p24 antigen, 1st IS (IU) | Test developers, manufacturers, regulators, blood establishments, fractionators, reference laboratories, diagnostic laboratories |
| | Anti-HIV, 1st Ref Panel (no unitage)<br>(HIV-1 subtypes: A, B, C, CRF_01, O; HIV-2) | |
| NAT | HIV-1 RNA 2nd IS (IU) | |
| | HIV-1 RNA Genotype 1st Ref Panel (no unitage)<br>(A,B,C,D, AE, F, G, AG-GH, groups N & O) | |
| | HIV-2 RNA 1st IS (IU) | |

# Retroviruses- ECBS endorsed/new projects

- HIV-1 RNA
  - Replacement of the 2nd International Standard
  - HIV-1 RNA genotypes reference panel (extension)
- Human T-Lymphotropic virus type I and type II
  - An anti-HTLV I/II antibody reference panel

# ECBS: Hepatitis Viruses (IVD Technologies)

| | WHO International Standard or Reference Panel | |
|---|---|---|
| **Test** | **Current** | **Users** |
| Serology | Hepatitis B surface antigen, 2nd IS (IU) - adw2 | Test developers, manufacturers, regulators, blood establishments, fractionators, reference laboratories, diagnostic laboratories |
| | Anti-Hepatitis B virus core antibodies (IU) | |
| | HBsAg genotype reference panel (ECBS 2011) | |
| NAT | Hepatitis A virus RNA 1st IS (IU) | |
| | Hepatitis B virus DNA 2nd IS (IU) – genotype A2 | |
| | Hepatitis B virus DNA Genotype 1st Reference Panel Genotypes A, B, C, D, E, F, G (no unitage) - | |
| | Hepatitis C virus RNA 2nd IS (IU) | |

Current IS both for HBsAg and HBV DNA are genotype A2: 1% of HBV infections worldwide

# Hepatitis Viruses – ECBS endorsed/new projects

- HAV RNA
  - Replacement of the 1st International Standard
- HBV-DNA
  - Replacement of the 2nd International Standard
- HCV-RNA
  - Replacement of the 3rd International Standard

# Hepatitis Viruses – ECBS endorsed/new projects

- HCV core antigen
  - HCV combo / HCV core assays
  - Increasing importance for blood screening/therapy monitoring
- HDV-RNA
  - HDV coinfection with HBV infection
  - Therapy monitoring dependant on HDV viremia
- HEV-RNA (proposal for establishment 2011)
  - Zoonotic (swine) virus with increasing importance
  - Major cause of acute hepatitis worldwide

# Flaviviruses: ECBS endorsed/new projects

- WNV-RNA
  - NAT blood screening in the US
  - Still low WNV prevalence in Central Europe
- Dengue Viruses (DENV 1-4 RNA)
  - DENV epidemiology and diagnostics;
  - Access to viral isolates acquired from infected humans;
  - Standardization of diagnostic assays needed

# Herpes Viruses – New WHO reference preparations

- EBV DNA 1st IS (2010)
  - strain B95-8 propagated in cell culture; collaborative study in parallel with two other EBV-positive cells;
- CMV DNA 1st IS (2011)
  - CMV strain Merlin propagated in cell culture; collaborative study evaluated the material in parallel with strain AD169 and purified Merlin DNA;

# Parasites (1): ECBS endorsed/new projects

- Toxoplasma gondii: serology

  Proposed IgM reference preparation

- Toxoplasma gondii DNA: NAT assays

  Proposed International Standard

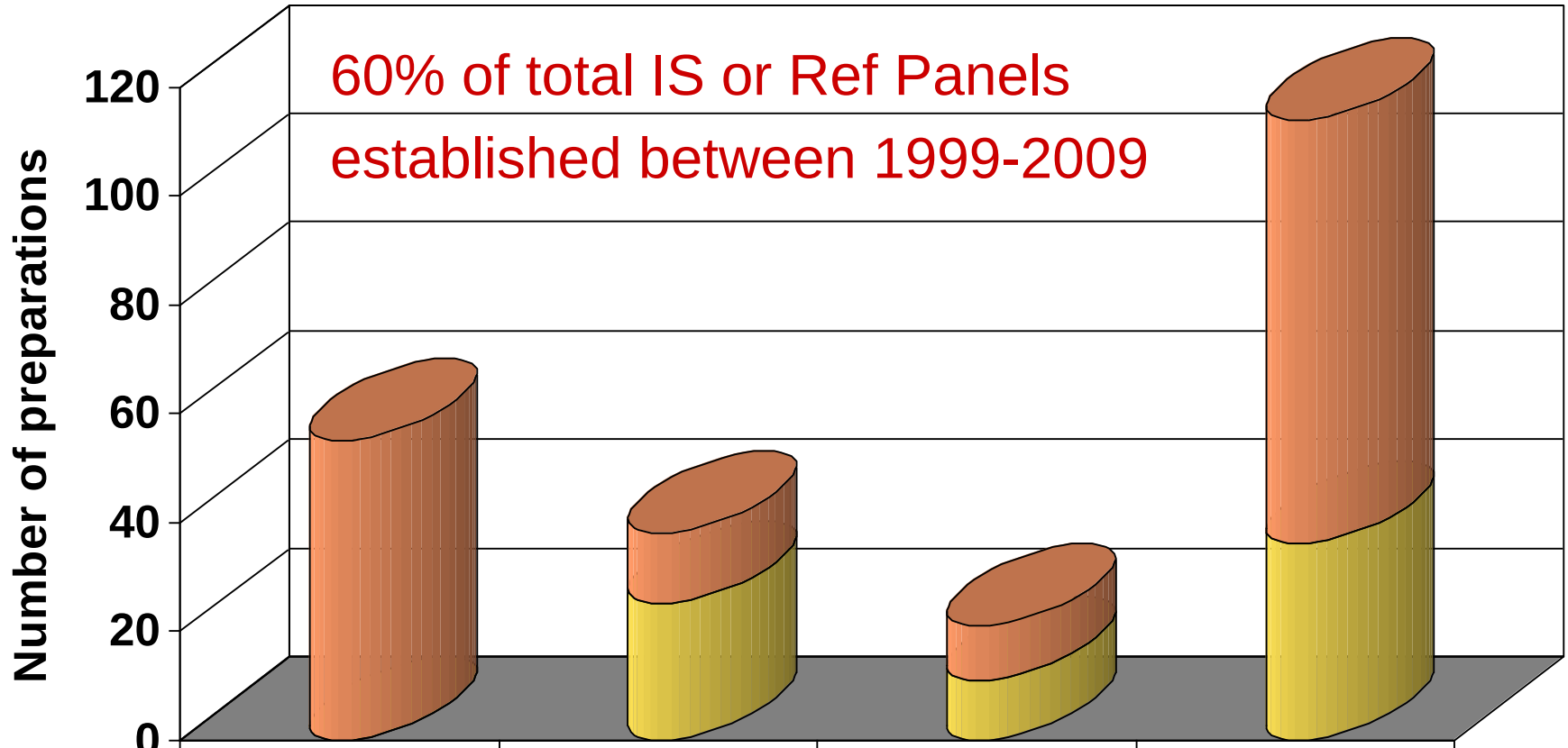
# Parasites (2): ECBS endorsed/new projects

- Trypanosoma cruzi antibody panel (Chagas disease)
  - WHO consultations (2007 and 2009)
  - WHO Reference Panel representing group I and group II
    Selection of antibody low-positive plasma for small pools
    WHO Collaborative Study in 2010

***Proposal for establishment to ECBS 2011***

# WHO Biological Reference Preparations

## Blood Products and related Biologicals




| | Blood Safety and General Hematology | Coagul.Factors/ Thrombolytic Agents | Immunological Reagents | Total |
|---|---|---|---|---|
| In vitro Diagnostic Tests | 55 | 13 | 10 | 78 |
| Therapeutic products | 0 | 25 | 11 | 36 |

WHO Catalogue of Biological Reference Preparations: www.who.int/bloodproducts



World Health Organization

# WHO International Biological Reference Preparations

## Held and Distributed by the WHO International Laboratories for Biological Standards

### BLOOD PRODUCTS AND RELATED SUBSTANCES: Blood safety

| PREPARATION | STANDARD | WHO TRS ECBS REPORT | MATERIAL | HELD AT | CODE | WHO/BS DOCUMENT |
|---|---|---|---|---|---|---|
| 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. | 1st International Standard, 2005 | No. 941, 56th Report | Monoclonal IgM (murine) | NIBSC | 03/188 | 06.2053 |
| 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. | 1st International Standard, 2005 | No. 941, 56th Report | Monoclonal IgM (murine) | NIBSC | 03/164 | 05.2024 |
| Anti-C complete blood typing serum, Lyophilized, 100 IU / ampoule | 1st International Standard, 1984 | No. 725, 35th Report | Human serum | NIBSC | W1004 | 84.1424 |
| Anti-c incomplete blood typing serum, Lyophilized, 64 IU / ampoule | 1st International Standard, 1976 | No. 610, 28th Report | Human serum | NIBSC | W1007 | 71.1038 |
| 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. | 1st International Standard, 2004 | No. 932, 55th Report | Monoclonal IgM (human) | NIBSC | 99/836 | 04.2000 Rev. 1 |
| Anti-E complete blood-typing serum, human, Lyophilized, 100 IU / ampoule. | 1st International Standard, 1983 | No. 700, 34th Report | Human serum | NIBSC | W1005 | 83.1424 |
| Anti-hepatitis B virus core antibodies (anti-HBc), human, Lyophilized, 50 IU / vial. | 1st International Standard, 2008 | To be published | Human plasma | NIBSC | 95/522 | 08.2098 |
| Anti-HIV antibodies (HIV-1 subtypes A, B, C, CRF01_AE, group O and HIV-2), Lyophilized, No unitage assigned. | 1st International Reference Panel, 2006 | To be published | Human plasma | NIBSC | 02/210 | 06.2032 |
| Hepatitis A virus RNA, Lyophilized, 50,000 IU / vial. | 1st International Standard, 2003 | No. 926, 53rd Report | Human plasma | NIBSC | 00/560 | 03.1959 |
| Hepatitis B surface antigen, subtype adw2, genotype A, Lyophilized, Dilutional panel (IU/vial: 8.25; 2.06; 0.52; 0.13). | 1st International Reference Panel, 2003 | No. 927 54th Report | Human plasma | NIBSC | 03/262 | 03.1987 |
| Hepatitis B surface antigen, subtype adw2, genotype A, Lyophilized, 33 IU / vial. | 2nd International Standard, 2003 | No. 927 54th Report | Human plasma | NIBSC | 00/588 | 03.1987 |
| Hepatitis B virus DNA, Lyophilized, 500,000 IU / vial. | 2nd International Standard, 2006 | To be published | Human plasma | NIBSC | 97/750 | 06.2034 |
| Hepatitis C virus RNA, Lyophilized, 4.89 log10 IU / vial; 5.19 log10 IU / ml. | 3rd International Standard, 2007 | To be published | Human plasma | NIBSC | 06/100 | 07.2055 |
| HIV-1 p24 antigen, Lyophilized, 1,000 IU / ampoule. | 1st International Reference Reagent, 1992 | No. 840, 43rd Report | Peptide in human serum | NIBSC | 90/636 | 92.1699 |
| HIV-1 RNA, Lyophilized, 363,078 IU / vial; 5.56 log10. | 2nd International Standard, 2005 | No. 941 56th Report | HIV-1 genotype B isolate diluted in human plasma | NIBSC | 97/650 | 05.2021 |
| HIV-1 RNA genotypes (set of 10 genotypes), Liquid, No assigned value. | 1st International Reference Panel, 2003 | No. 926, 53rd Report | HIV-1 isolates diluted in human plasma | NIBSC | 01/466 | 03.1961 |
| Human syphilitic plasma IgG and IgM, Lyophilized, 3 IU per ampoule relative to HS, the 1st IS for human syphilitic antibodies. | 1st International Standard, 2007 | No. 941 56th Report | Human plasma | NIBSC | 05/132 | 07.2059 |

# WHO BIOLOGICAL REFERENCE PREPARATIONS
## How are they developed & established?

- Candidate materials donated (industry, PHL, academy)
- Freeze-dried materials (when possible)
- WHO Collaborative studies to assign values (not funded)
- Wide international collaboration (WHO Working Groups)
- Established by WHO Expert Committee on Biological Standardization (ECBS)
- Held and distributed, on behalf of WHO, by the WHO International Laboratories for Biological Standards

# Web site addresses

http://www.who.int/bloodproducts

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

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

# Coordination of standards setting activities

- WHO CC plans of work in the development of IVD IRPs
  - Updates on emerging/re-emerging pathogens
  - New test strategies & emerging technologies
  - WHO Collaborative studies
- WHO disease control programmes (infectious diseases): Overview of global epidemiological data
- Collaboration of Regional Offices: participating laboratories and identification of candidate materials
- Coordination with other standard setting organizations and international organizations (ISBT, ISTH, EDQM, EC,….)