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# **Expert Committee on Biological Standardization Blood Products & IVD Track**

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# WHO Biological Reference Preparations

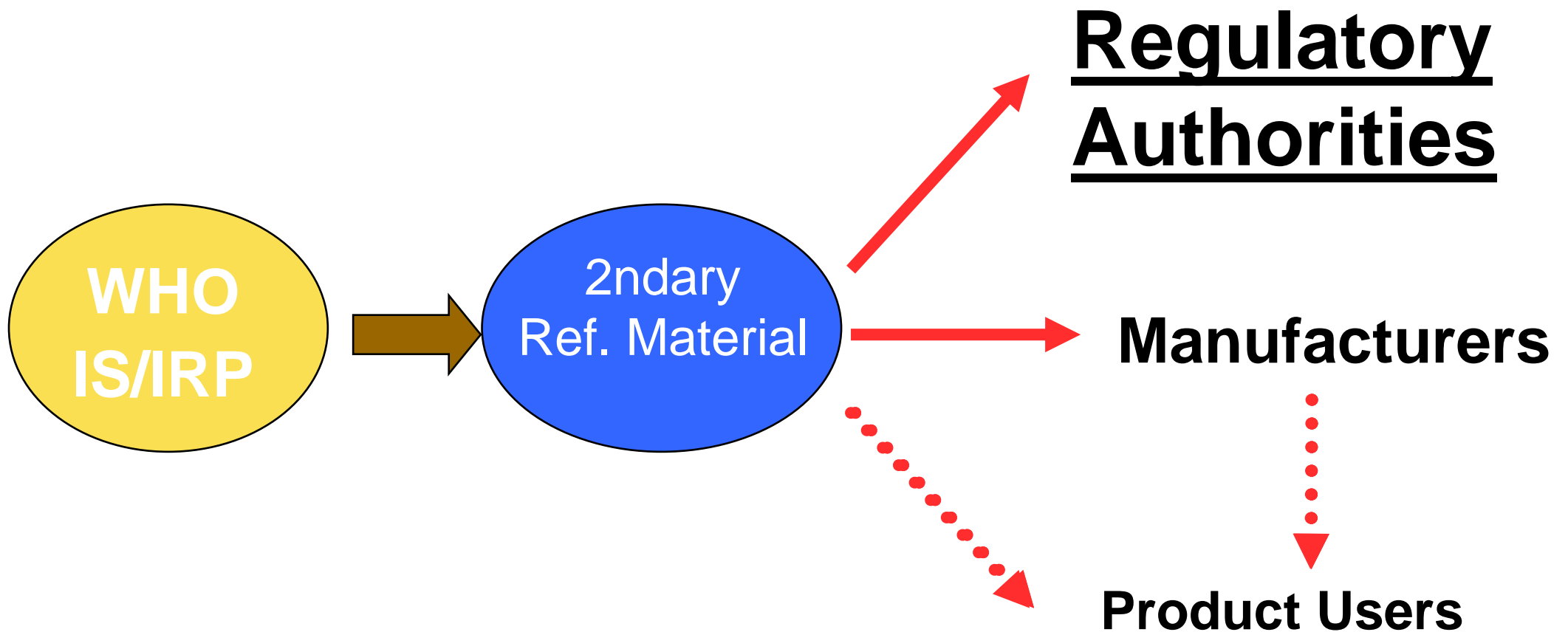
## Global measurement standards

- ❑ Tool for comparison of biological measurement results worldwide
- ❑ Facilitate transfer of laboratory science into worldwide clinical practice
- ❑ Underpin appropriate 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



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

# WHO Biological Reference Preparations ([www.who.int/bloodproducts](http://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

| HSS/EMP/QSM: WHOCC11



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, 1 <sup>st</sup> IS (IU)	Test developers, manufacturers, regulators, blood establishments, fractionators, reference laboratories, diagnostic laboratories
	Anti-HIV, 1 <sup>st</sup> Ref Panel (no unitage) (HIV-1 subtypes: A, B, C, CRF_01, O; HIV-2)	
NAT	HIV-1 RNA 2 <sup>nd</sup> IS (IU)	
	HIV-1 RNA Genotype 1 <sup>st</sup> Ref Panel (no unitage) (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, 2 <sup>nd</sup> 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 1 <sup>st</sup> IS (IU)	
	Hepatitis B virus DNA 2 <sup>nd</sup> IS (IU) – genotype A2	
	Hepatitis B virus DNA Genotype 1 <sup>st</sup> Reference Panel Genotypes A, B, C, D, E, F, G (no unitage) -	
	Hepatitis C virus RNA 2 <sup>nd</sup> 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 1<sup>st</sup> International Standard
- HBV-DNA
  - Replacement of the 2<sup>nd</sup> International Standard
- HCV-RNA
  - Replacement of the 3<sup>rd</sup> 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 1<sup>st</sup> IS (2010)**
  - strain B95-8 propagated in cell culture; collaborative study in parallel with two other EBV-positive cells;
- **CMV DNA 1<sup>st</sup> 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

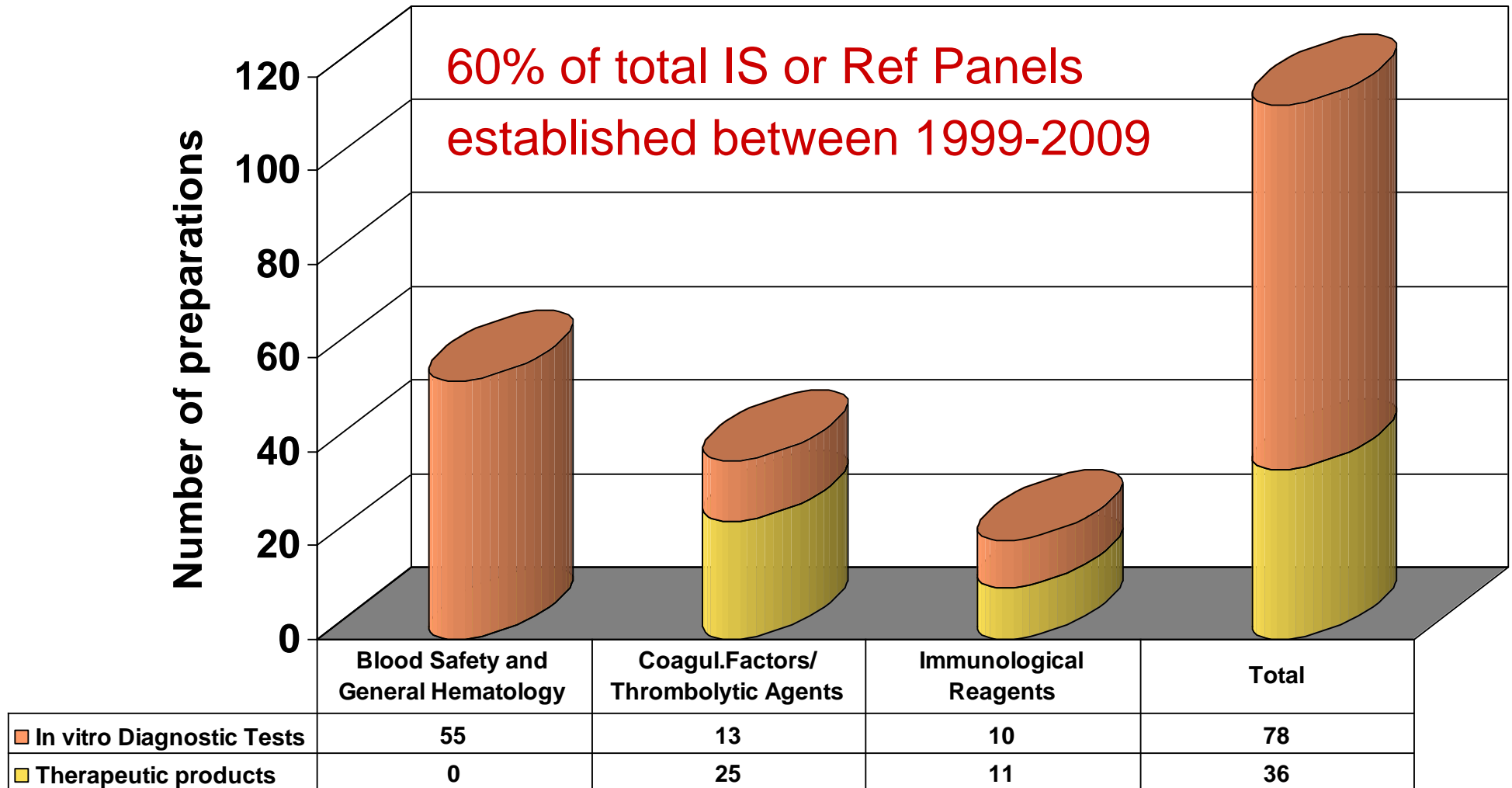
# Parasites (2): ECBS endorsed/new projects

- 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













WHO Catalogue of Biological Reference Preparations: [www.who.int/bloodproducts](http://www.who.int/bloodproducts)



# 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 log <sub>10</sub> IU / vial; 5.19 log <sub>10</sub> 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 log <sub>10</sub> .	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 

#Name?

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/)

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# 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,.....)

