DCVMN, 15-16 September 2010 Hyderabad, India

WHO Standardization of Vaccines and Biotherapeutics

- An update -

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Outline

- WHO standards for vaccines and other biologicals
- Evaluation of vaccines: stability, nonclinical and clinical
- Development of new and revision of existing standards
- Call for comments
- Implementation of WHO standards
- Strategic direction: networking
- DCVMN role in WHO biological standardization

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Biological Standardization as constitutional responsibility

- WHO is mandated by its Member States to "…develop, establish and promote international standards for biological products"
- Biological products for WHO cover vaccines, biological therapeutics, blood products and selected in vitro diagnostics
- Implemented by Expert Advisory Panel (EAP) and Expert Committee on Biological Standardisation (ECBS)
- Served by secretariat in the Quality Safety & Standards (QSS) Team

WHO Biological Standardization

Global written standards

Evolving concept

Global measurement standards

More than 250 WHO measurement Standards are available; define the IU

Global consensus

1) Standardization of assays
2) Development and refinement of QC tests
3) Scientific basis for setting specifications

http://www.who.int/biologicals/en/

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WHO Collaborating Centres for biological standardization

- NIBSC (all biologicals)
- CBER/FDA (all biologicals)
- PEI (blood products and related IVDs – expansion to vaccines under consideration)
- NIID, Japan (vaccines)
- TGA (vaccines)
- KFDA (Korea) – designation ongoing (vaccines and biotherapeutics)
- Under consideration: BTGD (Canada); NICPBP (China); Thai NCL
- Strategic direction: synchronized approach for the network of CCs for Biological Standardization

World Health Organization Goal

Ensure that "100%" of vaccines used in all national immunization programmes are of assured quality

Definition

- ✓ National Regulatory Authority (NRA) independently controls the quality of vaccines in accordance with the six specified functions defined by WHO
- ✓ No unresolved confirmed reports of quality related problems

Guided by WHO Expert Committee on Biological Standardization ECBS): Recommendations to assure quality, safety and efficacy of vaccines (WHO Technical Report Series (TRS)

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WHO Written Standards for Vaccines

- Technical specifications that help define safe and efficacious vaccines
- Intended to be scientific and advisory in nature
- Basis for vaccine prequalification
- Guidance for NRAs and manufacturers on international regulatory expectations for the production and quality control of vaccines, non-clinical and clinical evaluation of vaccines
- Facilitating international harmonization of vaccine licensure
- Living documents revised in response to scientific advances

Scope: Recommendations to assure quality, safety and efficacy of pneumococcal conjugate vaccine (an example)

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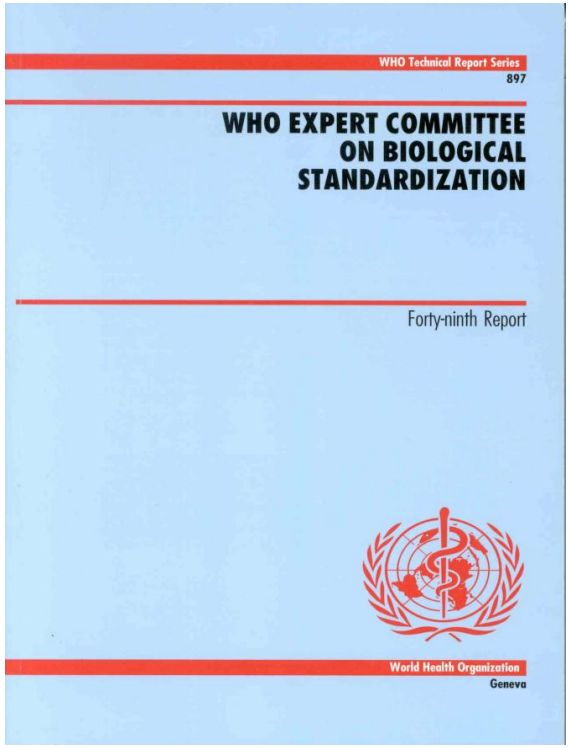
WHO Written Standards
A tool for harmonization of specifications worldwide



NRA/ NCL

National Pharmacopeias

Manufacturers

Product Users

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WHO Biological Reference Preparations
A tool for comparison of results worldwide

WHO
International Standards

Specifications to prepare and characterize WHO IS: WHO TRS 932 (2006)

- National Control Labs
- National Pharmacopeias
- Manufacturers
- Product Users

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Development and endorsement of WHO written standards

- Drafting group meeting to initiate drafting (scope, structure, approach, and major scientific/technical issues)
- Informal consultation (regulators, academicians, industry experts)
- **Web publication of a draft: call for comments (*new procedure since 2009)**
- Distribution to EAP and Member States as "BS document" to obtain comments
- ECBS review - discussion, revision, and decision (-> report to SAGE & Exec Board)
- Internal clearance (DGO approval)
- **Web publication of electronic document (final document available)**
- Editing & proofreading
- Printing as Annex to WHO TRS

Stability, Nonclinical and Clinical Evaluation of Vaccines

Principles for different aspects of vaccine evaluation available in the following guidelines:

1) Stability evaluation of vaccines – adopted in 2006

http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/index.html

2) Nonclinical evaluation of vaccines – TRS 927 (2005)

http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/index.html

3) Clinical evaluation of vaccines – TRS 924 (2004)
http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/en/index.html

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Expert Committee on Biological Standardization, Oct 2009: key outcomes

New/ revised

Guidelines/ Recommendations

- live attenuated influenza vaccines **Adopted**

- pneumococcal conjugate vaccines **Adopted**

- lot release of vaccines by National Control Laboratories; *needs further work*

- similar biotherapeutic products **Adopted**

New reference materials for vaccines

- Diphtheria vaccine (adsorbed), 4th IS **Adopted**

- BCG vaccine, 3 reference strains **Adopted**

- Bordetella pertussis serotype 2 and serotype 3, two IS's for serotyping **Adopted**

- Human papillomavirus type 16 antibodies, 1st IS **Adopted**

Revision of written standards
- status and plan for submission to the ECBS -

Recommendations/ Guidelines	ECBS
1. Cell substrates (TRS 878) 2. Yellow Fever Vaccine (TRS 872) 3. Hepatitis B recombinant (TRS 786, 889) 4. Independent vaccine lot release (new)	2010
5. Dengue (TRS 932) 6. BCG (TRS 745 and 771) 7. DTP vaccines (TRS 800) 8. Acellular pertussis vaccine (TRS 878) 9. Combined vaccines based on DTP – new 10. OPV (TRS 904 and 910) 11. IPV 12. Malaria vaccine – new	2011 2012/ 2013

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Call for comments – until 8 Oct 2010

- Documents that support establishment of new/ revised standards (both written and measurement) are posted on the WHO biologicals web site for public consultation until 8 October 2010
- ECBS: 18 – 22 October 2010
- You can find the document at the following link: http://www.who.int/biologicals/expert_committee/en/index.html
- Please provide comments through DCVMN or directly

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Guidelines for vaccine lot release: key issues

- Approaches that NCLs can follow: criteria for choosing appropriate approach
- Roles and responsibilities of regulators and manufacturers
- Conduct of lot release
- Protocol Review
- Independent testing
- Data monitoring
- Evaluation of the lot and decision making process
- Lot Release certificate

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Cell substrates: revision of WHO TRS 878, annex 1

I Good cell culture practice

II Microbial agents

III Tumorigenicity

Details available in the meeting reports:
Biologicals 36 (2008) 203-211
Biologicals 38 (2010) 162-9

IV Oncogenicity and infectivity of cell DNA

V Determination of rcDNA

VI Evaluation of cell substrates in the context of new vaccines & biologicals

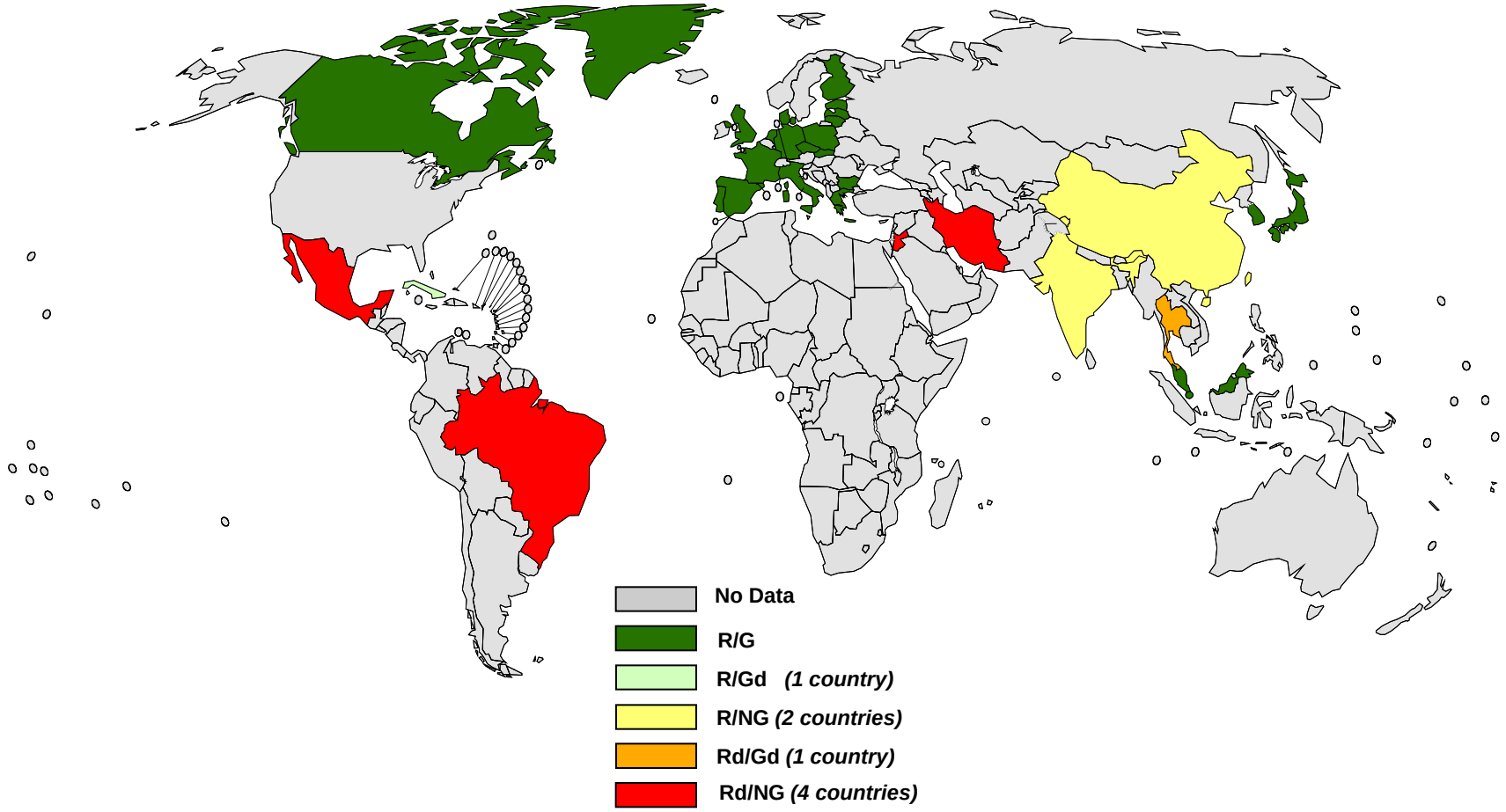
New appendix: Risk assessment in the case of adventitious agents findings (triggered by the recent example of PCV)

Next: IABS workshop: 19 – 20 May 2011, Baltimore, USA
- Focus on adventitious agents -

Implementation – an example

- WHO Guidelines on SBPs as a basis for setting national requirements
- The final version of the Guidelines on evaluation of similar biotherapeutic products (SBPs) is available on WHO Biologicals website (http://www.who.int/biologicals/en/) since April 2010
- The document was adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization, in October 2009
- You can download the draft by clicking on the link under the column "HIGHLIGHTS" on the above website or directly at: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
- First implementation workshop held in Seoul in August 2010; hosted by KFDA; forum of regulators, manufacturers of biotherapeutic products and other experts (eg, academia)

Regulations/ Guidelines for SBPs in selected countries (Aug 2010)



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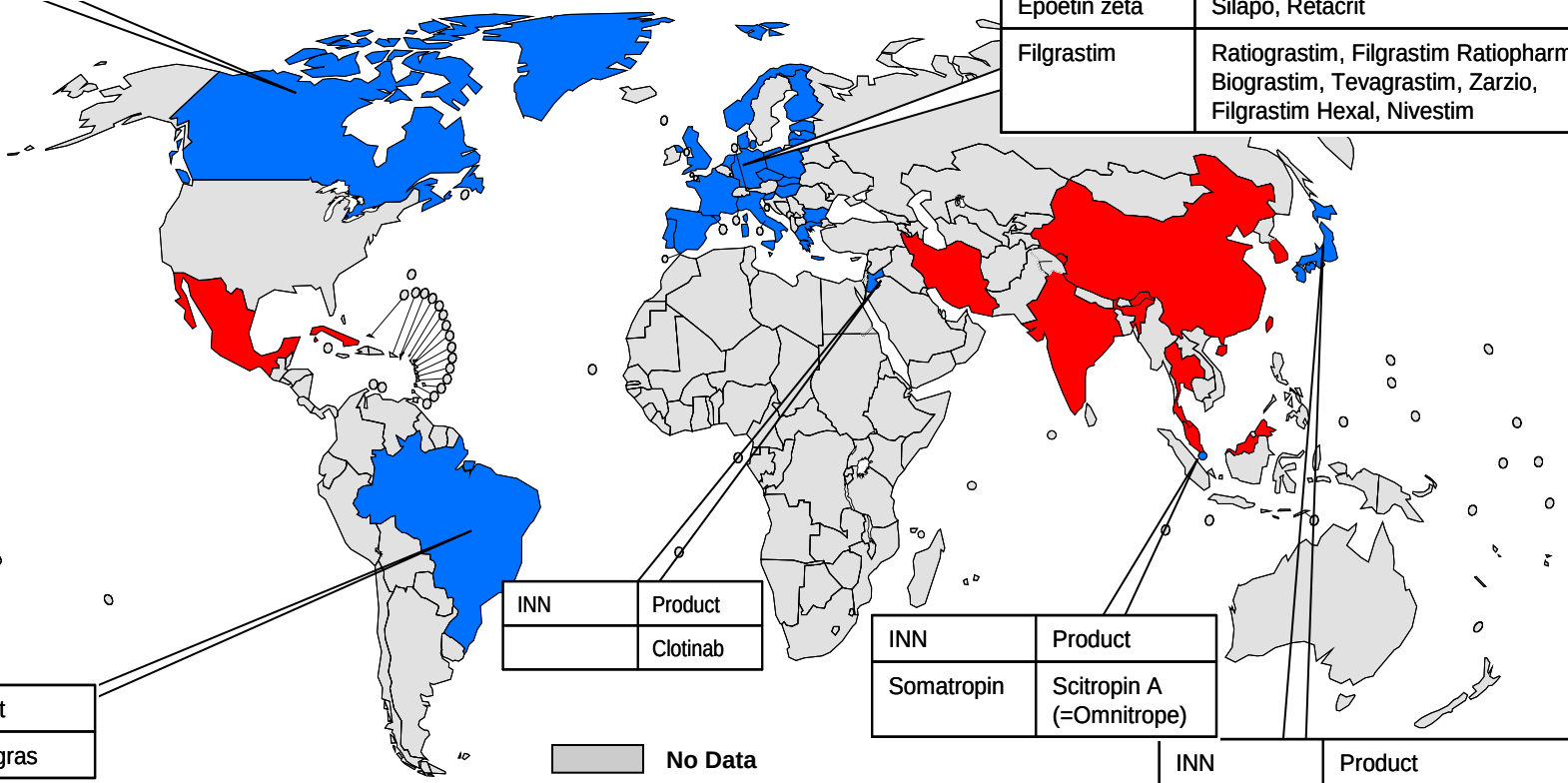
Approved SBPs – Global Picture (Aug 2010)

INN	Product
Somatropin	Omnitrope

INN	Product
Somatropin	Omnitrope, Valtropin
Epoetin alfa	Binocrit, Epoetin alfa Hexal, Abseamed
Epoetin zeta	Silapo, Retacrit
Filgrastim	Ratiograstim, Filgrastim Ratiopharm, Biograstim, Tevagrastim, Zarzio, Filgrastim Hexal, Nivestim



INN	Product
	Clotinab

INN	Product
Somatropin	Scitropin A (=Omnitrope)

INN	Product
Filgrastim	Tevafilgras

INN	Product
Somatropin	Somatropin BS "Sandoz" (=Omnitrope)
Epoetin alfa	Epoetin alfa BS "JCR"

No Data

Yes ***(26 countries)***

No ***(8 countries)***

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Strategic direction: networking

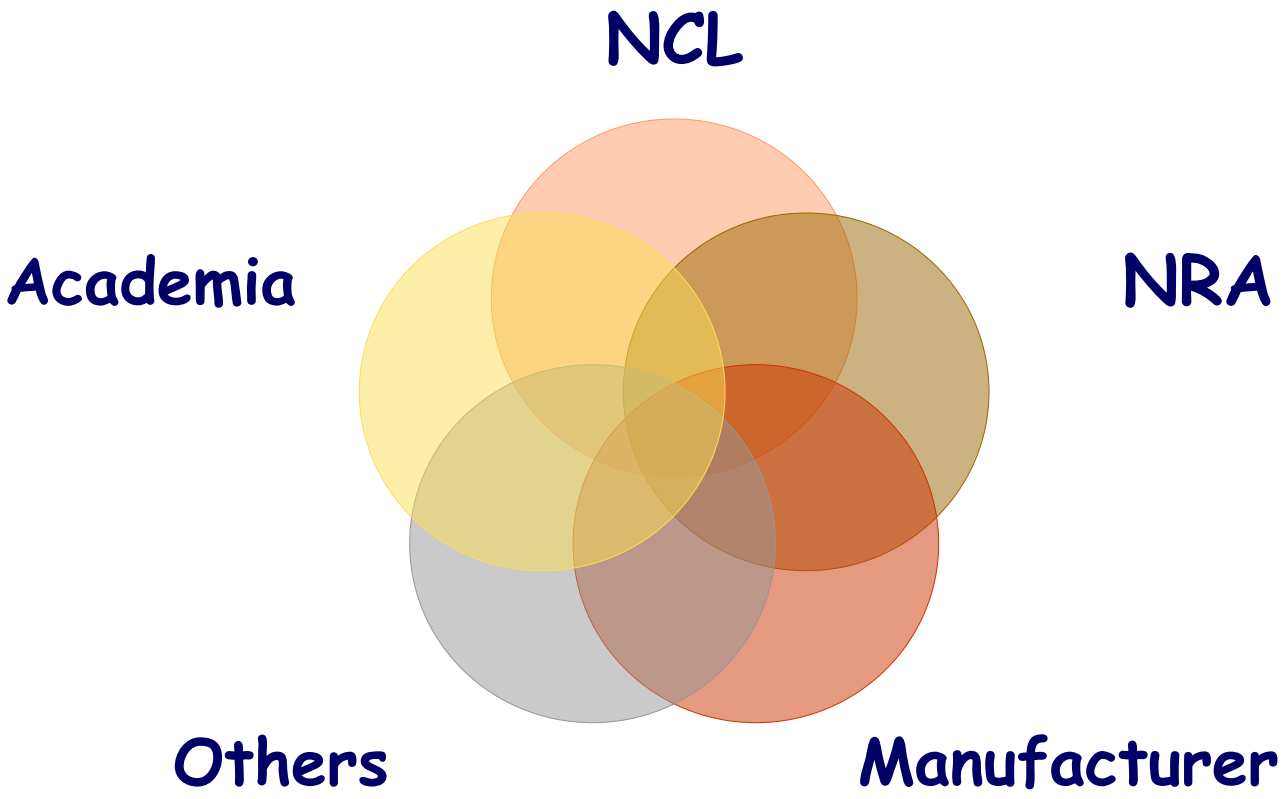
1. Continue working with existing networks of regulators and manufacturers:
   VWP of EMEA, DCVRN, AVAREF, EMR network of NCLs, ICDRA, IFPMA, **DCVMN**, EGA, IGPA, DIA, national networks and others

2. Reach more:
   1. Developers of vaccines and biotherapeutics- new users of standards
   2. New generation of biologicals regulators

3. Exchange better:
   1. With other standard setting bodies:
      1. Pharmacopoeias
      2. EDQM: Group 15
      3. Others?

4. Promote use of scientific evidence as a basis of regulation: collect, analyze, make information available (publish, present)

Concept of national workshops



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DCVMN role in developing and implementing WHO standards

- Input into development of new and revision of existing standards
  - Vaccine development – driving force for new standards
  - Experience with existing standards – critical for meeting the need of the users (eg, methodological advances in developing potency assays)
- Implementation of WHO standards into regulatory and ***manufacturers'*** practice
  - Vaccines – eg, Guidelines on Stability Evaluation of Vaccines; series of recommendations for specific vaccines
  - Biotherapeutics – eg, recently adopted Guidelines for Evaluation of Similar Biotherapeutic Products
- Information and knowledge sharing at:
  - regional level – SEARO; WPRO; PAHO/ AMRO; EMRO
  - national level – India, China, Iran

Could exchange of information be better?

Further information and contact

Biological standardisation website:

www.who.int/biologicals

Immunization website: www.who.int/immunization

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