Standardization of In vitro Biological Diagnostic Procedures

Existing, new and emerging technologies

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Outline of Presentation

• *In Vitro Biological Diagnostic Procedures*
  Biological Products
  Global measurement standards

• Existing, new and emerging technologies: approaches to development of standards

• Challenges/Limitations
Definition of Biologicals

Biological sources
Crude, semi purified extracts or purified fractions of microbial, animal or human tissues

Produced by biological processes
Traditional/ Recombinant DNA or High technology

Biological product
- Complex molecular structure
- Cannot be characterized by physicochemical criteria alone
- Used for diagnosis, treatment or prevention of diseases
Global measurement standards
WHO International Standards
WHO Biological Reference Preparations
WHO Biological Reference Preparations
Global measurement standards

PURPOSE/IMPACT

• Tool for comparison of biological measurement results worldwide (unit of measurement/biological system)

• To facilitate transfer of laboratory science into worldwide clinical practice

• To support harmonization of international regulations

• To accelerate transfer technology
WHO Biological Reference Preparations
Global measurement standards
A tool for comparison of results worldwide
WHO Biological Reference Preparations
In vitro Biological Diagnostic Procedures
Priority Drive: Safety

<table>
<thead>
<tr>
<th>Medical field application</th>
<th>number of preparations</th>
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<tr>
<td>Blood Safety and General Hematology</td>
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<td>Blood Coagulation and Thrombotic Disorders</td>
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<td>Immunological Disorders</td>
<td>7</td>
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<tr>
<td>Total</td>
<td>26</td>
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<tr>
<td>Therapeutic products</td>
<td>28</td>
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<tr>
<td>In vitro diagnostic tests</td>
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Therapeutic products
In vitro diagnostic tests
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

WHO Guidelines for the preparation, characterization and establishment of international and other standards and reference reagents for biological preparations (WHO TRS No. 800, 1990)
WHO Working Groups

- Scientific issues involved in the standardization of the new biological technology/type of product
- Selection & characterization of candidate materials
- Design protocols for WHO Collaborative studies
- Harmonization of procedures & reagents
- Issues concerning the appropriate use of materials
WHO Working Groups

- WHO Intnl. Labs. for Biol. Standards
- Research & Public Health Institutions
- Other Standard setting Organizations (e.g. BIPM; ISO)

WHO Consultations

- National/Regional Reg. Authorities
- Global representation
- Industry: Manufacturers Associations
- WHO Intnl. Scientific Societies (e.g. ISTH, IFCC)

WHO ECBS
Expert Advisory Panels

- WHO Working Groups
- WHO Consultations
Existing, New and Emerging Technologies

How do we approach standardization of:

- Existing technologies: Replacement of HBsAg IS
- New technologies: NAT IS
- Emerging technologies: Prion Diseases
“Existing” Technologies

Main Issues:

- Replacement of the subsequent batch in time: Subsequent batches calibrated versus (at least) the previous standard
- Continuity of Unit of biological activity defined by the 1st IS
- Changes in the methodology with time
Replacement of the 1st International Standard for HBsAg: WHO collaborative study

- No drift in the value of the HBsAg measurement standard (expressed in IU) since its establishment 20 years ago.

- Appropriate quantity to measure is biological activity (IU) and not protein concentration (ng/ml).

- Global regulatory recognition that all measurement for HBsAg diagnostic tests to be reported in IU and traceable to WHO IS.
“New” Technologies

Priority Drive

- Impact on Global Public Health
- Need for international harmonization of regulations
- Timely standardization of the technology
Nucleic Acid Based Technology (NAT)  
Blood safety & Clinical Diagnostic

NEED FOR INTERNATIONAL HARMONIZATION (1995)

- Powerful technology: detection of viral nucleic acid
- Reduction of viral load entering manufacturing processes
- Investigation of removal/partitioning of viral nucleic acid in manufacturing steps
- Clinical safety monitoring
- Tracing of viral transmission by a blood product
WHO Biological Reference Preparations

Standardization of Nucleic Acid based technology applied in the detection of blood-borne viruses

HCV RNA  
HBV DNA  
Parvovirus B19 DNA  
HAV RNA  
HIV-1 RNA  
HIV-1 RNA Ref. Panel

Aim
● to provide a tool for inter-laboratory data link (analytical sensitivity)

Impact
● Support blood products safety regulations worldwide  
● Measurement of viral load: monitoring the disease
“Emerging” Technologies
Study of Prion Diseases

Priority Drive

- Impact on Global Public Health
- Facilitate the exchange of information and knowledge
- Facilitate development and comparison of diagnostic approaches and assay systems for study of new diseases
Human Prion Diseases (vCJD/CJD)

In progress.....

Development of Reference Panels:
Brain, tissue and blood human derived materials from sporadic CJD & vCJD cases

- to facilitate CJD and vCJD diagnostic procedures aimed to identify infected individuals, organs and tissues

- to facilitate risk assessment of pharmaceutical manufacturing processes to remove infective agents
Challenges/ Limitations
Challenges (I)

- Biological standardization is a specialized scientific exercise with rapid development.
- Need to address existing, new and emerging technologies with impact in public health.
- Need to keep pace with new approaches in standardization.
- Coordination with other standard setting organizations (e.g. ISO).
The Reference system (ISO/DIS 17511)
(International Conventional Reference Materials)

Reference material
Reference method
Reference laboratory

The application of the reference system is intended to provide: traceability & quantification of uncertainty
Difficulties, based on scientific issues, have been identified in implementing the ISO 17511 for the development of biological reference materials as defined by WHO and in the biologicals field. This needs to be resolved.

More collaboration and communication needed
New Initiative

Use of the global measurement standards in the regulation and quality control of in vitro biological diagnostic procedures (high risk IVDs):

- WHO Consultation of regulatory authorities, manufacturers & standard developers (May 2004)
Challenges/Limitations (II)

• Proliferation of tests in the biological field: international-global issue

• Need for standardization essential to the regulation and quality control of those tests

• Need to assure access to appropriate reference materials by developing countries

• Need to promote appropriate use of biological reference materials
WHO Biological Reference Preparations
WHO Catalogue

• Web site address:
http://www.who.int/biologicals

Essential Health Technologies
Health Technology and Pharmaceuticals Cluster
World Health Organization