Vaccine standardization in the context of PQ

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Outline

- WHO standards for vaccines
- Vaccines of assured quality
- Written and measurement standards - 40 years analysis
- Basis for vaccine PQ
- Development of new and revision of existing standards - plan for 2011/2013
- Summary
- Way forward
Global written standards

Global measurement standards

Global consensus

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

WHO Biological Standardization

370 WHO measurement Standards are available; define the IU

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

67 WHO Written Standards

Evolving concept
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 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) - designated in 2011 (vaccines and biotherapeutics)
- Under consideration: BTGD (Canada); NICPBP (China); Thai NCL
- Strategic direction: synchronized approach for the network of CCs for Biological Standardization
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)
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
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))
Written Standards
Established/Revised for Vaccines & Biologicals
No. of Written Standards for Vaccines & Biologicals for 4 Decades (N=174)

- 1971-1980: 35
- 1981-1990: 56
- 1991-2000: 38
- 2001-2010: 40
No. of Written Standards for Vaccines & Biologicals for 4 Decades (N=174):
Analysis by Area

V, Vaccine; Bi, Biologicals; BL, Blood; Ph, Pharmaceuticals
Living Written Standards for Vaccines & Biologicals (1948 – present, N=67): Basis for Vaccine PQ

<table>
<thead>
<tr>
<th>Category</th>
<th>Count of PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi, Biotherapeutics other than blood</td>
<td>5</td>
</tr>
<tr>
<td>BL, Blood Products</td>
<td>5</td>
</tr>
<tr>
<td>V, Vaccine</td>
<td>45</td>
</tr>
<tr>
<td>VB, Vaccine+Biologicals</td>
<td>15</td>
</tr>
<tr>
<td>VBPh, Vaccine+Biologicals+Pharmaceuticals</td>
<td>10</td>
</tr>
</tbody>
</table>

Bi, Biotherapeutics other than blood; BL, Blood Products; V, Vaccine; VB, Vaccine+Biologicals; VBPh, Vaccine+Biologicals+Pharmaceuticals
WHO International Biological Reference Preparations (IBRPs):
An analysis of 10-year data
Living Measurement Standards for Vaccines & Biologicals
(1948 – present, N=370)

- Vaccines / Toxoids / Toxins: 16%
- Blood Products: 28%
- Cytokines, Growth Factors, Endocrine: 24%
- Others: 32%

Sum of Numbers
WHO International Biological Reference Preparations (IBRPs) Established in 2001-2010: Analysis for Proportion by Area

- **Blood**: 33%
- **CyGFEndo**: 20%
- **All biologicals**: 3%
- **Antibiotics**: 1%
- **Vaccine-related antigens**: 22%
- **Vaccine - serology (Antibodies)**: 6%
- **Stability in-use**: 1%
- **IVD**: 14%

Sum of Number

Established in 2001 - 2010: Analysis for Proportion by Area
<table>
<thead>
<tr>
<th>Recommendations/ Guidelines</th>
<th>ECBS</th>
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</thead>
<tbody>
<tr>
<td>1. Cell substrates (TRS 878)</td>
<td>2010</td>
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<tr>
<td>2. Yellow Fever Vaccine (TRS 872)</td>
<td>2011</td>
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<tr>
<td>3. Hepatitis B recombinant (TRS 786, 889)</td>
<td>2012/2013</td>
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<tr>
<td>4. Independent vaccine lot release (new)</td>
<td>Adopted</td>
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<tr>
<td>5. Dengue (TRS 932)</td>
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<td>6. BCG (TRS 745 and 771)</td>
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<tr>
<td>7. Acellular pertussis vaccine (TRS 878)</td>
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<td>8. DTP vaccines (TRS 800)</td>
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<td>9. Combined vaccines based on DTP - new</td>
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<td>10. OPV (TRS 904 and 910)</td>
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<td>11. IPV (TRS 926)</td>
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<tr>
<td>12. Malaria vaccine - new</td>
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<tr>
<td>13. Risk assessment - new</td>
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Summary

- Total no of living WHO Written Standards for vaccines and other biologicals is 67 as of 2010.
- Development of Written Standards for vaccines has been a major part of work, comprising 72% of total written standards in the previous 4 decades.
- 85% of them (57/67) have served as the basis for WHO prequalification of vaccines.
- Total no of living WHO Measurement Standards for vaccines and biologicals is 370 as of 2010.
- An analysis of the latest 10-year data on the establishment of Vaccine-related antigen preparations comprise 22% (33 of N=152 2001-2010).
Way forward

- Issues of importance for defining strategic direction for coming 10 years and beyond:
  - Better way for measuring impact of WHO standards in the regulation of vaccines
  - More precise indicators
  - Link with NRA strengthening
  - Use of WHO standards for vaccine PQ
  - Scope of work
    - Vaccines, some biotherapeutics, biologicals in general
    - Pre-normative, normative and post-normative
  - Collaboration with other standard setting bodies
  - Funding of vaccine standardization
Many thanks

- To all collaborators who contributed to the development of standards
- To my colleagues Jinho Shin, Christoph Conrad and Sue Jenner for the analysis of 40 years data
- Colleagues from PQ team Nora Dellepiane and Sergio Nishioka