An Overview of WHO & IABs

- WHO
  - History
  - Responsibilities
  - Biologicals Unit
- IABs
  - Description
  - Relationship to WHO
  - Examples of collaboration
  - Opportunities for the future

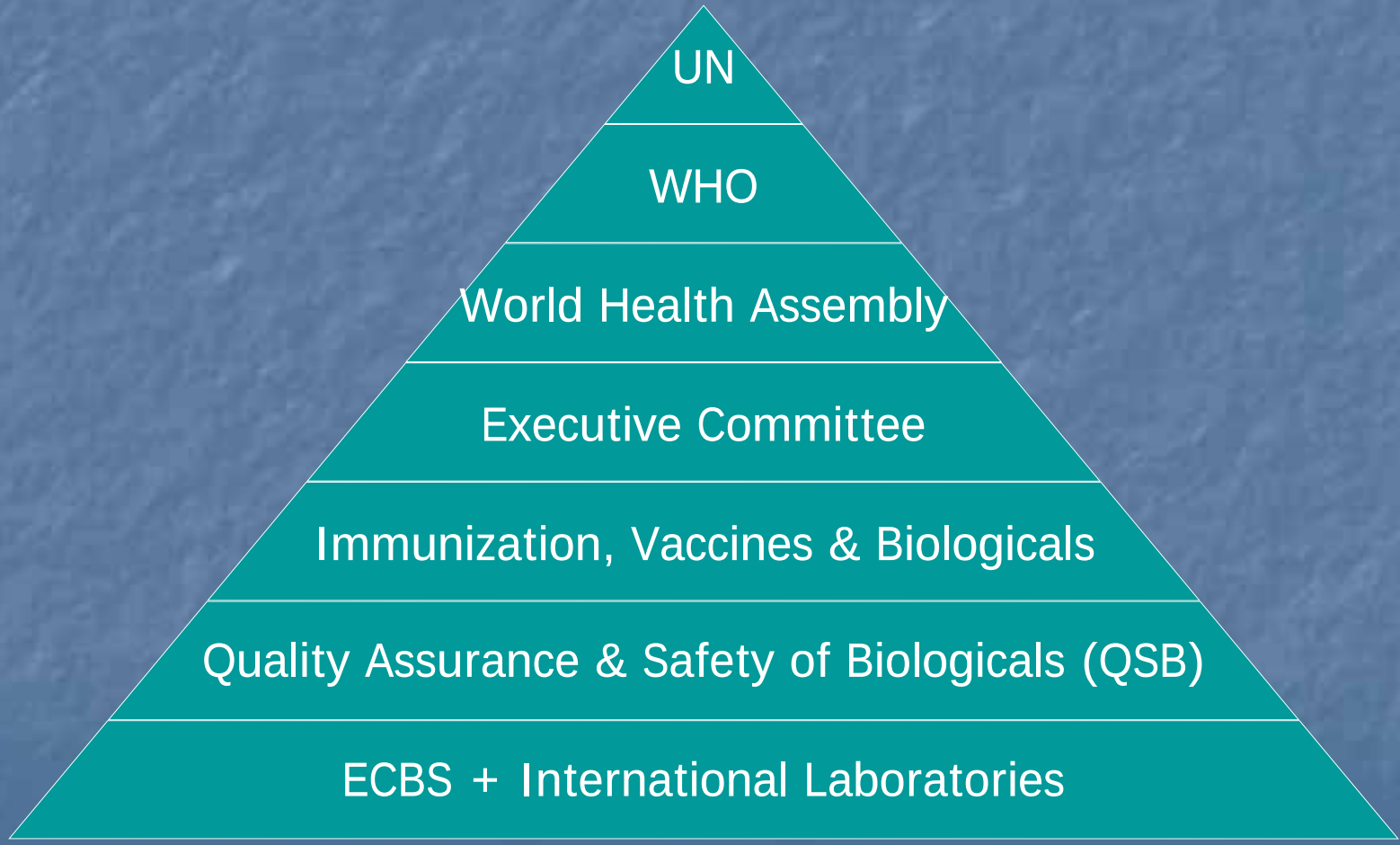
WHO

- Established in 1948
- United Nations Agency for health
- 192 Member States
- Annual World Health Assembly
- Executive Committee

WHO Biologicals

- Guidance for the safety, quality and consistency of biologicals
  - Vaccines, blood & blood products, biotechnology products
- Global standardisation activities
  - “develop, establish and promote international standards with respect to Biological products”
- WHO Biologicals unit
- Expert Committee on Biological Standardization (ECBS)
- International Laboratories for Biological Standards

WHO Structure



Work of the WHO Biologicals Unit

- League of Nations
  - IS for diphtheria antitoxin
  - Insulin
- United Nations
  - 1948 - WHO
  - 1950s – polio vaccines
  - 1960s – Factor VIII
  - 1970s – Hepatitis B vaccines
  - 1980s – rDNA products
  - 1990s – HIV (blood and blood products, and vaccine development)

How the WHO Biologicals Unit Functions

- Authoritative collaborative studies to develop data for the establishment of International Standards (ISs) and Reference Reagents (RRs)
- Consensus-building on the selection of ISs and Guidance documents
- Support to Member States, especially developing countries, but not exclusively (ex. Influenza vaccine composition)

WHO Standards

- International collaborative studies
- Data review by experts
- Establishment of ISs and RRs by ECBS
- ISs and RRs become official when the report of the ECBS is accepted by the WHO Executive Committee and World Health Assembly

WHO Guidance Documents

- International Requirements
- 1998 Independent Review of the Biologicals Unit
  - Requirements → Guidelines
    - Comments and recommendations for manufacturers and NRAs
  - Coordination activities
    - Collaborative studies
    - Consensus on international regulatory issues

WHO Summary

- Managing the IS and RR programmes
- Developing guidance documents
- Support for Member States

IABs

- Founded in 1955
- Branch of IUMS
- ~450 members in 50 countries
- Original focus was on improving quality and comparability of data related to human and veterinary biological products
- Provides an international forum for scientific discussions and the development of a consensus in order to resolve issues
- In official relations with WHO and works closely with the Biologicals Unit

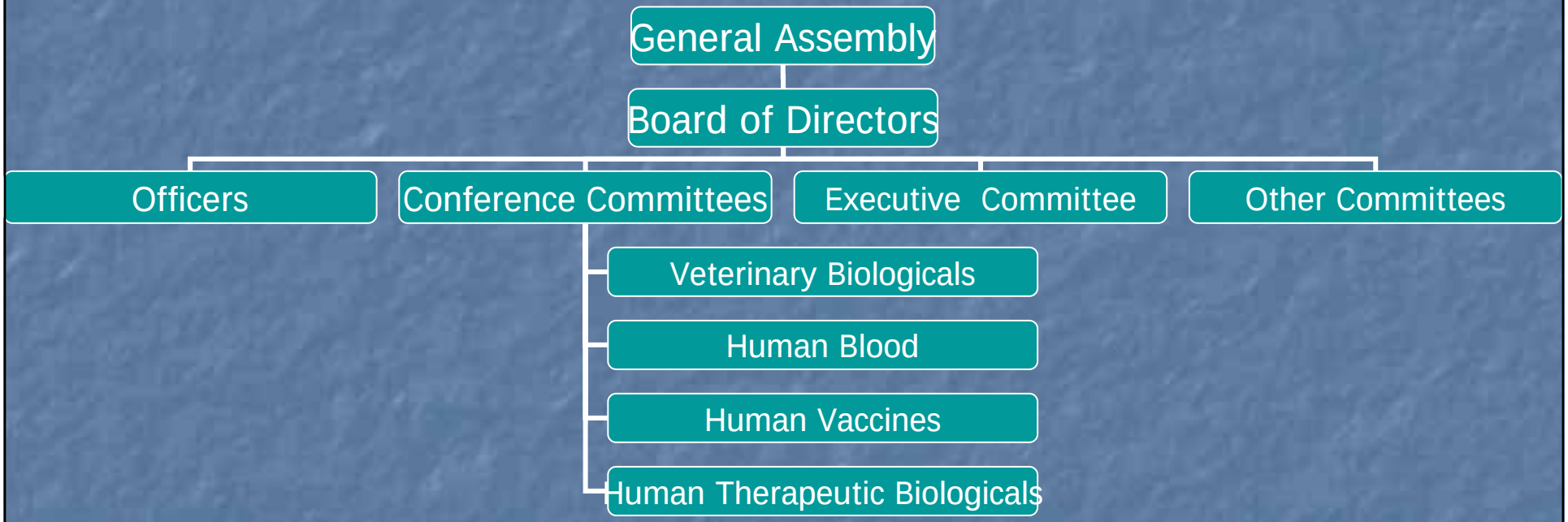
IABs Board of Directors (selected)

- Regulatory agencies for human Biologicals
  - BGTD (Canada)
  - PEI (Germany)
  - NIHS (Japan)
  - NIBSC (UK)
- Industry leaders
  - Serono (Switzerland)
  - Centocor (USA)
- Senior academicians
  - NIAID/NIH (USA)
  - University of California
- Permanent Advisors
  - WHO – Head of the Biologicals Unit
- Consultants to the Board
  - CBER – Director
  - NIBSC - Director

IABs Work

- Scientific conferences
- Publications
  - *Developments in Biologicals* (Series of conference proceedings)
  - *Biologicals* (Journal)
  - Newsletter
  - Website (www.iabs.org)

IBAs Organization



IABs Conferences

- Complimentary to WHO and NRAs
- Collaboration with WHO, NRAs, and other government agencies
  - Cell substrates as an example

Cell Substrates for Manufacture of Biological Products

- 1954
  - HeLa for live adenovirus vaccine
- 1960s
  - Human diploid cells for viral vaccines
- 1980s
  - Tumorigenic animal (CHO) and human (Namalwa) cells for rDNA therapeutics
  - Continuous cell lines (Vero) for vaccines
- 1990s & 2000s
  - Human and animal tumor cell lines (HeLa, BHK-21, C1271) for vaccines

Cell Substrates for Manufacture of Biological Products

Human Diploid Cells (HDCs) for Viral Vaccines

- Major issues
  - Human oncogenic agent might be present that is undetectable by available tests
  - Potential for transmitting the theoretical agent to recipients of vaccines produced in HDCs
- Response
  - Numerous IABs Cell Culture Committee meetings and generation of data (~10 years)
  - Clinical studies to evaluate safety
  - Approval of viral vaccines such as polio in Europe
  - Development of additional HDCs and one RhDC
  - Eventual approval of HDC vaccines in USA

Cell Substrates for Manufacture of Biological Products

Continuous Cell Lines (CCLs)

- Major issues
  - Oncogenic agent might be present that is undetectable by available tests
  - Cellular DNA might have an oncogenic potential
  - Possibility of transmitting a theoretical oncogenic agent or oncogenic DNA to recipients of products made in CCLs
- Response
  - Numerous IABs cosponsored conferences
  - Data developed to support safety
    - Viral clearance
    - Limit on cell DNA
  - Approval of products manufactured in some CCLs throught the world

Vaccine Cell Substrates - 2004

- Limitations on cell substrate choice continued to be an impediment to vaccine development – especially HIV
- Some scientific issues were unresolved
- Development of a consensus and recommendations were needed in order to move forward

Vaccine Cell Substrates - 2004

CONFERENCE TOPICS

- Oncogenicity of DNA and latent viruses
- Viral agent test methods
- Level of assurance provided by current tests
- Bovine and porcine viruses
- Novel vaccine cell substrates

Historical Highlites

1984	NIH/FDA	DNA, viruses, and transforming proteins 10pg DNA/dose
1986	WHO Study Group	DNA, viruses, and transforming proteins 100pg DNA/dose
1996	WHO ECBS	10ng DNA/dose
1999	FDA, NIH, WHO, IABs	DNA risk issues unresolved

Vaccine Cell Substrates - 2004

DNA Risk Assessment

- Animal studies, including 8-year nonhuman primate study with T-24 DNA (ras oncogene)
- Estimates of an oncogenic event calculated by 5 groups between 1986 and 1999, based on theoretical assumptions: 1 in 10^8 to 10^{12}
- Human experience
  - Adenovirus vaccine produced in HeLa cells
  - Human tumor cell inoculations
  - Blood: Transfusion / Leukemia

Vaccine Cell Substrates - 2004

DNA Risk Research Gaps Identified

- More sensitive animal models
- Positive controls for animal studies
- Better understanding of the impact of DNA size, quantity (dose response), route of administration (oral, SC, IV, ID, IM), and configuration (linear, circular, chromatin)
- Validation of DNA inactivation methods

Vaccine Cell Substrates - 2004

DNA Consensus Recommendations

- The one theoretical risk that may be specific to the DNA of CCLs is the potential for a dominant, activated cellular oncogene to be transmitted in a biological product and then to cause a tumor in recipients of that product.
- The risk of residual cell substrate DNA can be reduced to negligible levels when a DNA-inactivating method or a nucleic acid fragmentation method is used in the manufacturing process, and data are available to validate these methods, and to demonstrate the consistency of the manufacturing process.

Vaccine Cell Substrates - 2004

DNA Consensus Recommendations (cont'd)

- WHO should establish a working group to recommend studies designed to answer specific questions relating to theoretical risks associated with residual cellular DNA. Such studies should be supported by appropriate government agencies:

Vaccine Cell Substrates - 2004

DNA Study Recommendations

- Platform studies to address the risk of oncogensis by residual cellular DNA in appropriate models, including the use of relevant positive controls
- Dose-response studies to determine the relationship of DNA dose to biological activity
- Studies to determine whether there is less risk from DNA derived from non-tumorigenic continuous cell lines than from those that are tumorigenic

Vaccine Cell Substrates - 2004

DNA Study Recommendations (Cont'd)

- Risk reduction strategy studies to determine the impact of reducing the size of DNA fragments to various lengths, and to assess the effect, if any, of the configuration of the DNA (naked DNA, chromatin DNA, etc.) on risk.

Vaccine Cell Substrates - 2004

DNA Study Recommendations (Cont'd)

- Agreement among major regulatory agencies and WHO should be reached on levels of cellular DNA that can be considered risk-free.
- WHO could facilitate reaching a consensus on this point and should be encouraged to do so by undertaking a review of the DNA issue, as was done by the 1986 Study Group and the 1994 ECBS, when sufficient new data become available to warrant such a meeting.

Status of DNA Consensus Recommendations

- WHO has agreed to coordinate resolution of the DNA issue
- WHO discussion with advisory groups has occurred and a proposal will be presented to the 2004 ECBS
- If ECBS approves, a Working Group will be established to agree on details of studies that are needed, and on which organizations might be best equipped to conduct them
- Consideration may be given by some government agencies to provide financial support for some of the studies

Summary

- Long and productive history of collaboration between WHO and IABs
- Future activities
  - Resolution of remaining cell substrate issues
  - Followup in other areas
    - Cell and gene therapy
    - Comparability
      - Manufacturing changes
      - “Generic” biologicals
    - Safety
      - Antibodies to recombinant proteins
      - Emerging blood borne diseases

The Future of IABs

- Continue to provide assistance to WHO and regulatory authorities
- Expand membership and participation in Asia and South America
- Work with other professional organizations such as the Japanese Society of Biologics and JAACT to identify issues that could benefit from discussion in a scientific conference

Thank You!

- Dr. Takao Hayakawa
- Dr. Toru Kawanishi
- Japanese Biologics Forum
- Japanese Society of Biologics