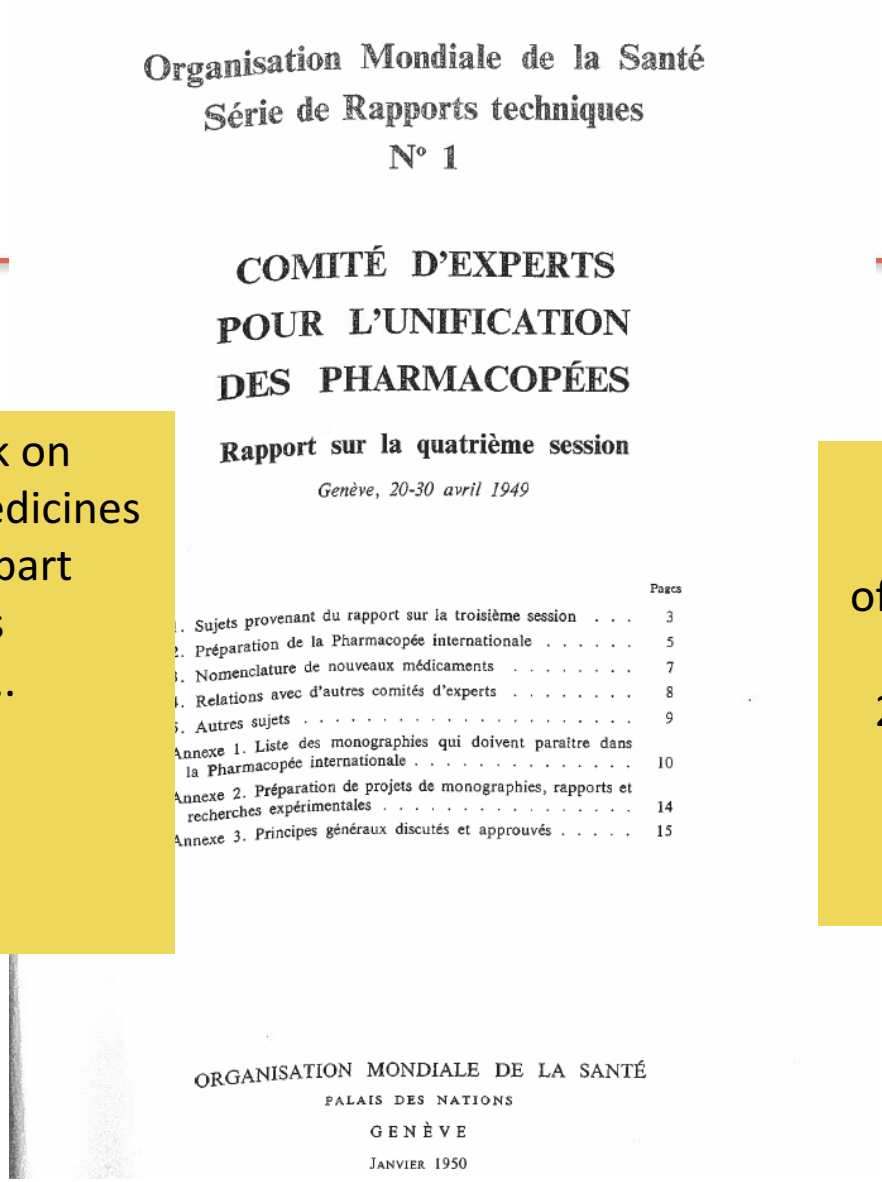
Outcomes of 2016 ECBS

WHO written and measurement standards to support the regulation of vaccines

Prof K Cichutek, Chair, ECBS

World Health Organization



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COMITÉ D'EXPERTS
POUR L'UNIFICATION
DES PHARMACOPÉES

Rapport sur la quatrième session

Genève, 20-30 avril 1949

ORGANISATION MONDIALE DE LA SANTÉ
PALAIS DES NATIONS
GENÈVE
JANVIER 1950

WHO's normative work on biologicals, diagnostics, medicines and vaccines has been part of our core business since the very start….

WHO Technical Report Series Number 1

We continue the good work of our predecessors….

2016 report will be WHO Technical Report Series Number 1004

WHO written regulatory standards for vaccines adopted by 2016 ECBS

- Guidelines on **Clinical Evaluation of Vaccines**: Regulatory Expectations (*Revised*)
- Guidelines on Regulatory Preparedness for Non-Vaccine producing countries in response to **Pandemic Influenza** Emergency *(New)*
- Labelling information of **inactivated influenza vaccines for use in pregnant women** *(New)*

WHO guideline on **clinical evaluation of vaccines**

TRS 1004 Annex 9 (2017)

Key messages

- ✓ Explains upfront the very variable nature of the clinical development programme depending on the type and novelty of the vaccine content and the nature of trials that may serve as pivotal
- ✓ Addresses issues that have commonly arisen during TRS preparation and questions repeatedly put to WHO
- ✓ Becomes the new standard for PQ evaluation of vaccine clinical trials

Contents

(see spare slides for more details)

WHO guideline on regulatory preparedness for provision of Marketing Authorization of human pandemic influenza vaccines in non-vaccine-producing countries

NEW

TRS 1004 Annex 7 (2017)

Need for Guideline

- This guideline was requested by Member States to set up, in advance of a pandemic, a regulatory process for pandemic influenza vaccines.
- This process should enable countries to decide on appropriate regulatory actions, and
- Expedite the licensing/approval and lot release of influenza vaccines in response to a pandemic emergency.
- Several consultations and public comments during 2014-16

Background

- Each Member State has national legislation and policies on the regulation of medicines
- During the inter-pandemic phase each member State should;
  - Develop a national pandemic influenza preparedness plan
  - Develop a national deployment and vaccination plan for pandemic influenza
  - [These are specified in other WHO Guidance documents]
- These plans should acknowledge the NRA responsibility for control of pandemic vaccines and medicines

National regulatory preparedness

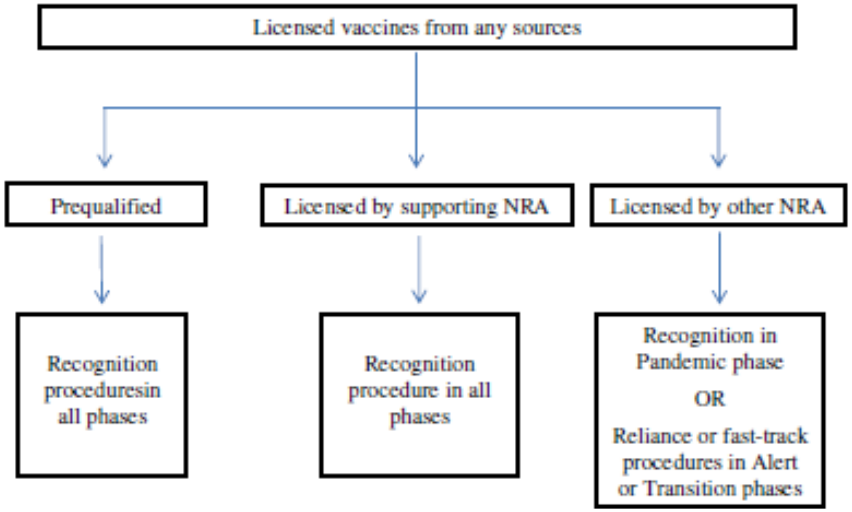
- The new guideline provides guidance on regulatory preparedness
  - NRA contact point for communications
  - Public Communications plan on basis for decisions
  - Allocation of resources when pandemic is declared
  - Appoint Task Team for evaluation of pandemic vaccines and medicines
  - Set up procedures to interact with deployment agency
  - Prepare procedures for expedited license and lot release including reliance / recognition of supporting NRA decisions or WHO prequalification (PQ)
  - Prepare systems for post-marketing safety surveillance in cooperation with deployment agencies

Reliance on the decisions and expertise of other national regulatory authorities (NRA)

- The NRA should select and establish links with suitable supporting NRAs in inter-pandemic period
  - Rely on assessment reports or advice to make decisions
  - May recognize supporting NRA decision and adopt this
- Enter into WHO collaborative procedure for licensing PQ vaccines (Requires time and MoU)

Other features of the Guideline

- Decision-tree for choosing a regulatory pathway



- Final-review, Quality control and Lot-release advice
- Post marketing surveillance outline-plan
- Appendices
  - Checklist for regulatory preparedness
  - Example of a possible seasonal strain change procedure

Labelling Information of Inactivated Influenza Vaccines for Use in Pregnant Women

NEW

TRS 1004 Annex 8 (2017)

Background

- **WHO Strategic Advisory Group of Experts on Immunization (SAGE)**
  - WHO Position Paper 2012 (Vaccines against influenza)
    - recommended the immunization of pregnant women with trivalent IIV at any stage of pregnancy.
    - also recommended that pregnant women should have the highest priority for countries considering the initiation or expansion of immunization programmes for seasonal influenza vaccination.
  - Requested WHO to develop a process and plan to improve maternal immunization (2013).

Problem statement
Label & Package Insert - influenza vaccines

- *A recent survey indicates that health care providers perceive package insert information as contradicting national immunization recommendations and this affects their decision whether to use inactivated influenza vaccine in pregnancy* (Lancet 2016)
- Prescribing information is cautionary
  - Most Flu vaccines are not INDICATED for use in Pregnant Women
  - Sections on use in pregnancy advise "**Caution" or "Use only if clearly needed"**
- WHY?
- BECAUSE: Pregnant women are not included in clinical trials
  - Thus no robust data on safety or efficacy is available
  - National requirements for cautionary statements for PW

Key issues addressed

- Labelling:
  - requirements for format and language are prescribed by regulation specific to the country where the product is licensed
  - Common principles include that Product Insert be based on available data, must not be misleading and must not contain implied claims for use
- Document of the new Guidelines focused on those sections relevant to use of vaccines in pregnancy, i.e.
  - Indications and Usage
  - Warnings and Precautions
  - Contraindications
  - Use in Specific Populations

Key messages conveyed

- IIVs are not contraindicated for use in pregnancy
- Indications and usages section specifies age range that includes women of childbearing age
  - Lack of statement specifically addressing product use in pregnant women does not preclude use of the vaccine in pregnancy
- Certain countries require information about use in pregnancy to be included under the "Warnings and Precautions" or "Contraindications" section
  - Reflect precautionary approach rather than known or suspected safety issue
- Programmatic recommendations (e.g. SAGE) for use of IIVs during pregnancy are consistent with labeling

WHO MEASUREMENT STANDARDS

ECBS 2016

- In total 11 measurement standards established; 6 for IVDs, 5 for blood products
- 14 new projects on measurement standards endorsed; 10 for IVDs, 4 for blood products

WHO Measurement Standards

- worldwide recognized tools in biological standardization
- among WHO priority tasks in R&D Blueprint

New WHO Reference Reagents

relevant to vaccine development and/or surveillance

- **Zika Virus RNA** - 1st International Standard for Nucleic Acid Amplification (NAT) based assays
- **Ebola VP40 Antigen** – 1st International Reference Panel for point-of-care tests
- **Dengue Virus types 1 to 4 RNA** - 1st International Reference Reagents for NAT based assays for each serotype
- **Hepatitis B Virus DNA** - 4th International Standard for NAT based assays

Spare slides

ECBS Blood Track – New Guidance Documents

- **Guidelines for the production, control and regulation of snake antivenom immunoglobulins**
  1st revision
- **Guidelines on management of blood and blood components as essential medicines** - new
- **Guideline on estimation of residual risk of HIV, HBV or HCV infections via cellular blood** - new
- **Manual for the preparation of secondary standards for IVD assays designed for infectious disease nucleic acid or antigen testing** - new

Content of the revised guideline on clinical evaluation of vaccines

1. **Introduction**

✓ Briefly explains reasons for the revision and the major changes

2. **Scope**

✓ Types of vaccines covered; guidance specific to vaccines intended to prevent a clinical infectious disease and/or the consequences of chronic infection

3. **Glossary**

✓ The definitions given apply to the terms used in this guideline. *They may have different meanings in other contexts.*

Vaccine clinical development programmes

4. Vaccine clinical development programmes

4.1 General considerations

- ✓ 4.1.1 Consultation with national regulatory authorities
- ✓ 4.1.2 Use of independent data monitoring committees
- ✓ 4.1.3 Registering and reporting clinical trials

4.2 Pre-licensure clinical development programmes

- ✓ 4.2.1 Preliminary trials
- ✓ 4.2.2 Pivotal trials

4.3 Post-licensure clinical evaluations

Immunogenicity

5. Immunogenicity

- ✓ 5.1 General considerations
- ✓ 5.2 Characterization of the immune response
- ✓ 5.3 Measuring the immune response
- ✓ 5.4 Determination and use of immunological correlates of protection

Immunogencity

5.5 Immunogenicity trials

- ✓ 5.5.1 Objectives
- ✓ 5.5.2 General considerations for trial designs

5.6 Specific uses of immunogenicity trials

- ✓ 5.6.1 Selection of formulation and posology
- ✓ 5.6.2 Using immunogenicity data to predict efficacy
- ✓ 5.6.3 Co-administration trials
- ✓ 5.6.4 Immunization of pregnant women
- ✓ 5.6.5 Changes to the manufacturing process
- ✓ 5.6.6 Clinical lot-to-lot consistency trials

Efficacy and effectiveness

6. Efficacy and effectiveness

6.1 General considerations for efficacy trials

6.2 Types of efficacy trials

- ✓ 6.2.1 Human challenge trials
- ✓ 6.2.2 Preliminary efficacy trials
- ✓ 6.2.3 Pivotal efficacy trials

6.3 Design and conduct of efficacy trials

6.4 Approaches to determination of effectiveness

Safety

7. Safety

7.1 General considerations

7.2 Assessment of safety in clinical trials

- ✓ 7.2.1 Safety outcomes as primary or secondary endpoints
- ✓ 7.2.2 Recording and reporting adverse events
- ✓ 7.2.3 Categorization of adverse events

7.3 Size of the pre-licensure safety database

7.4 Post-licensure safety surveillance