ADVAC ALUMNI MEETING DURING SAGE

WHO perspective on Human Challenge Trials in Vaccine Development and Licensing

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23rd October 2018

WHO standards and other services to facilitate regulatory oversight of vaccines in developing countries

- Facilitating registration (regulatory standards – Guidelines, Recommendations and measurement standards)
- Prequalification and emergency assessment procedures
- Collaborative procedures and joint assessments
- Vaccine safety initiatives

WHO norms and standards for biologicals

Global written standards

Total 93 docs (Recommendations/ Guidelines)
General docs that apply to vaccines & BTP: 10
General documents that apply to all vaccines: 12
Vaccine specific: 63
BTP specific: 8

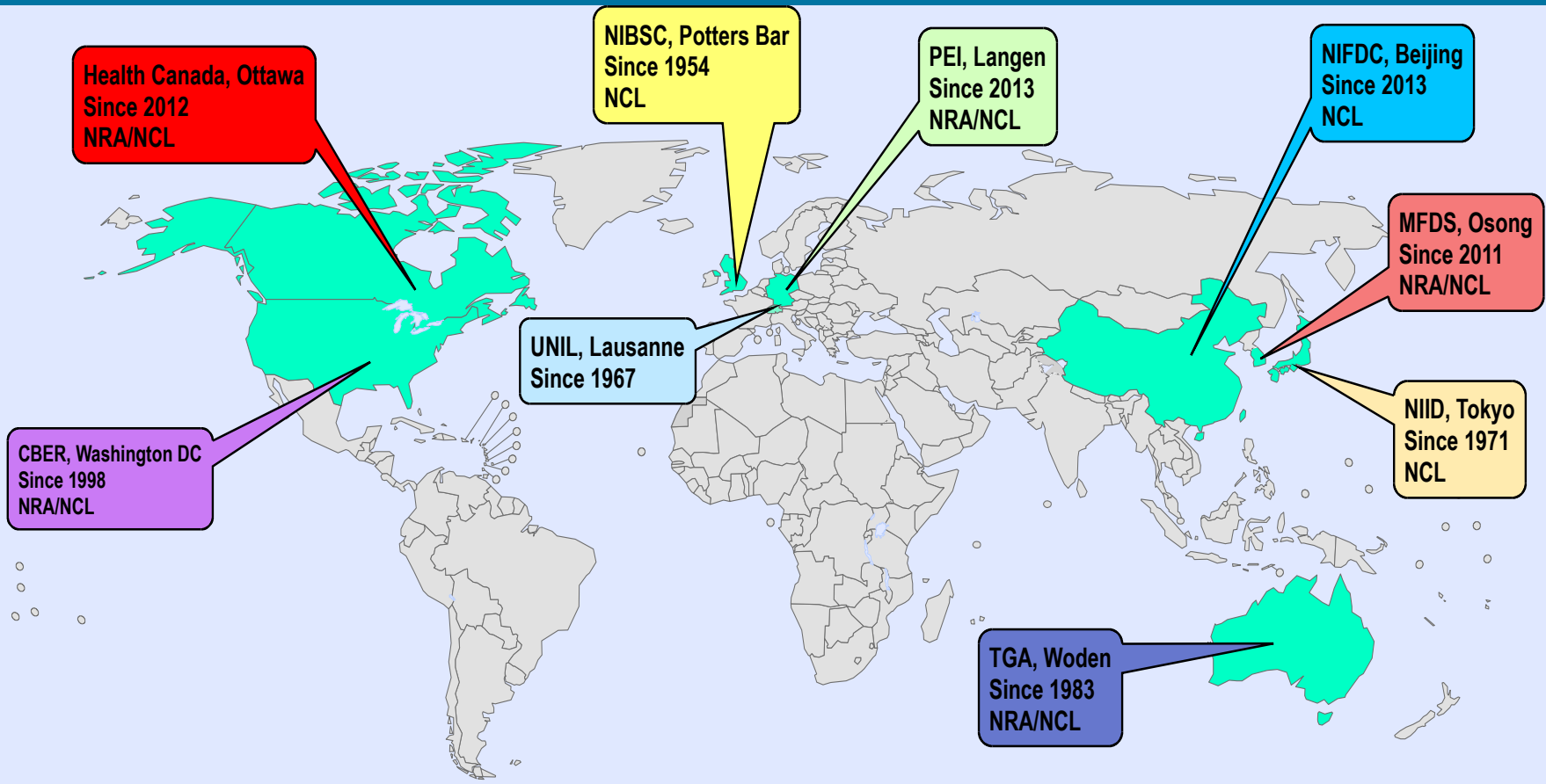
Scientific evidence

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

Global measurement standards

Measurement standards: essential elements for development, licensing and lot release

WHO COLLABORATING CENTERS IN THE AREA OF VACCINE RESEARCH AND STANDARDIZATION



Data Source: World Health Organization

World Health Organization

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Concept of WHO Guidelines

1) Provide key principles for evaluation of biologicals as a basis for setting national requirements;

2) Leave space to NRAs to formulate additional/ more specific requirements;

3) Living documents that will be developed further in line with the progress in scientific knowledge and experience

4) Assist with the implementation of the guidelines into regulatory and manufacturers practices through:

- **Global, regional and national workshops involving regulators, manufacturers and other relevant experts**
- **Trainings, advisory groups**

5) Consider guidance issued by other bodies – intention to complement them, not to create a conflict.

Revised Guidelines on clinical evaluation of vaccines (TRS 1004, annex 9)

- Introduction
- Scope
- Glossary
- Vaccine Clinical Development Programs
- Immunogenicity
- Efficacy and effectiveness
- Safety
- Authors and Acknowledgements
- References

Scientific and regulatory considerations for HCT, TRS 1004, annex 10 (1)

- Not all diseases are suitable for "challenge-protection studies"
- Regulatory framework
- Quality and safety of pathogenic challenge strain
- GCP
- Various purposes for HCT in vaccine development:
  - Often a type of efficacy indicating study
  - Better understanding of pathogenesis of , and immunity to, the organism to guide decisions on immune responses that a vaccine might need to elicit in order to protect against disease

Scientific and regulatory considerations for HCT, TRS 1004, annex 10 (2)

Various purposes for HCT in vaccine development (cont.):

- Proof of concept
- to identify potential ICP and other elements which will be then validated in an efficacy study
- Down or up selection of vaccine candidates
- Provision of a basis for licensure (rare case)
- Post-licensure studies to explore waning immunity, need for booster or duration of protection
- other

Scientific and regulatory considerations for HCT, TRS 1004, annex 10 (3)

World Health Organization

Study design of human challenge trials:

- the purpose of the study is influencing study design
- Different models according to the purposes and study design
- Challenge organism
- Usefulness for positive or negative prediction

Operational aspects

- Relevant committees
- Qualified investigators
- Protocol
- Special facilities to prevent spread of challenge organism
- High level of control

Scientific and regulatory considerations for HCT, TRS 1004, annex 10 (4)

- **Some key ethical considerations:**
  - Minimize risk to subjects and maximize benefits
  - Review by an independent ethics committee
  - Informed consent
  - Other issues and references to more detailed sources of information

Quality and safety of challenge strains

- **Strain characterization:**
  - **Details like patient isolate, passage history etc**
  - **Phenotype**
  - **Genotype**
- **Purity**
- **Potency**
- **Stability**
- **Safety**

Challenges identified by DCVRN

- Outcomes of survey of DCVRN representatives
  - HCT have not been conducted in their countries
  - WHO guidelines for regulators recognized as a standard
  - Need for further assistance from WHO
- The following concerns were noted: safety of participants, risks of spreading challenge organism to the environment, availability of suitable care for (infected) participants, coercive (excessive) payments for participation, public perceptions of unsafe or unethical conduct
- The need for Phase-3 studies to confirm HCT results

Challenges in the international context

- Lack of expertise and experience for reviewing HCT
- Responsibilities for oversight of HCT are not defined at the national level:
  - Unclear role of various expert groups/ committees
  - Lack of understanding role of regulators in HCT
- Infrastructure, CT sites, inspections
- Lack of trust in "experimental studies"
- Risk benefit analysis, RMP
- Lack of publicly available data due to lack of CT registration but also selected data for publication

Way forward

- **Implementation workshops**:
  - At the global and regional level are very much needed
  - Case studies and review of examples
  - Topics of particular interest:
    - Immune response to vaccines
    - Quality of challenge strains
    - Design of HCT
    - Data from HCT in the context of licensing
    - HCT as part of development of vaccines for PHE

Acknowledgements

1. Rebecca Sheets and other authors of the report of the 1st IABS conference held in Oct 2014
2. Drafting group on clinical evaluation of vaccines – M. Powel (MHRA, UK), J. McEwen (TGA, Australia), V. Moorthy (WHO)
3. Participants of WHO consultation held in July 2014: meeting report published in Vaccine 2015; 33 (17):1999-2003

Thank you

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