Standardization for Preclinical Evaluation of Influenza Vaccines in Animal Models - *WHO activities*

2nd WHO Integrated Meeting on development and clinical trials of Influenza vaccines that induce broadly protective and long-lasting immune responses, 5 – 7 May 2014, Geneva

Tiequn ZHOU, Technologies Standards and Norms/WHO
WHO Norms and Standards for Biologicals

Standardization of influenza vaccines

- Available WHO standards specific for influenza vaccines
- WHO Guidelines on nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (recent project)
WHO and Standards Setting

- Setting norms and standards and promoting their implementation are WHO core functions ([http://www.who.int/about/role/en/index.html](http://www.who.int/about/role/en/index.html)).

- WHO has played a key role for over 60 years in establishing the WHO Biological Reference Materials necessary to standardize biological materials as well as developing WHO guidelines and recommendations on the production and control of biological products and technologies.

- WHO is committed to support countries to ensure that 100% of vaccines used in national immunization programmes are of assured quality.
**WHO Norms & Standards for Biologicals**

**Global written standards**

- **Global measurement standards**
  - >250 global measurement Standards are available

**Regulatory research**
- Scientific evidence
  1) Standardization of assays
  2) Further development and refinement of QC tests
  3) Scientific basis for setting specifications

**Facilitate implementation of standards into regulatory and manufacturers' practice**

**www.who.int/biologicals**
WHO Global Written Standards for Biologicals

- **International** technical specifications that help define safe & efficacious vaccines, available on: [http://www.who.int/biologicals/vaccines/en/](http://www.who.int/biologicals/vaccines/en/)

- Based on wide **scientific consultation and international consensus**

- Provide guidance for National Regulatory Authorities and manufacturers on assuring the **quality, safety and efficacy** of vaccines

- Used by Member States as the basis for **national legislation** for the regulation of such products

- Used by WHO as the basis for the **pre-qualification** procedure for vaccines procured by UN agencies

- Facilitate **international harmonization** of vaccine evaluation and licensure

- **Living documents** may be revised in response to scientific advances
Consultations/meetings involving all stakeholders (e.g. regulators, manufacturers, researchers) to review up-to-date evidence, identify key issues and reach consensus

Draft guidelines developed and circulated extensively for comments, via emails, WHO website and F2F meetings (involving meeting participants, Expert Advisory Panel for biologicals, regulators, industry, academia)

Final draft must be considered by the WHO Expert Committee on Biological Standardisation (ECBS) which meets annually (http://www.who.int/biologicals/WHO_ECBS/en/)

WHO International Measurement Standards for Biologicals

- International Standards (IS) and WHO Reference Reagents (RR)
  - Use in calibration of immune response assays in clinical trials
  - Use in quality control testing of vaccines (licensure/lot release)
  - Use in development, evaluation, standardization and control of products in industry, by regulatory authorities and also in biological research, academic and scientific organizations

- Tools for the comparison of results from different laboratories globally

- Support harmonization of international regulations of biologicals

- Facilitate development of vaccines, diagnostics and therapeutics

- Recognized by other international standards setting bodies (e.g. World Trade Organization, International Standards Organization)

Available WHO Standards Specific for Influenza Vaccines

- Recommendations for the production and control of influenza vaccine (inactivated), WHO TRS No. 927, Annex 3 (2005)
- Recommendations to assure the quality, safety and efficacy of influenza vaccines (human, live attenuated) for intranasal administration, WHO TRS No. 977, Annex 4 (2009)
  - H1N1 specific update, May 2009
  - H7N9 specific update, May 2013

Standardization for Preclinical Evaluation of Influenza Vaccines in Animal Models

- WHO Guidelines on Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines, established in 2013
Nonclinical Evaluation of Vaccines

- Nonclinical testing is a **prerequisite** to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product characterization, proof of concept/immunogenicity studies and safety testing in animals conducted prior to clinical testing of the product in humans.

  - Provide guidance to NRAs and vaccine manufacturers on the nonclinical evaluation of vaccines by outlining the international regulatory expectations in this area. Nonclinical evaluation refers to all in vivo and in vitro testing performed before and during the clinical development of vaccines.
  - Scope covers both prophylactic and therapeutic vaccines for infectious disease indications

http://www.who.int/entity/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf
Adjuvanted Vaccines (1)

- **Adjuvants** have been used for decades to enhance the immune response to vaccine antigens. Possible benefits of administering antigens in conjunction with adjuvants include:
  - √ induction of long-term protection and long-term memory
  - √ better targeting of effector responses
  - √ reduction of the antigen amount (dose-sparing) and/or the number of vaccine doses needed for a successful immunization
  - √ optimization of the immune response for populations with poor responsiveness

- Vaccines with aluminum-based adjuvants have been extensively used in immunization programs worldwide with well-established safety profile. Along with the evolving knowledge in vaccine adjuvants, the number of vaccines containing **novel adjuvants** being evaluated in clinical trials has increased (licensed or under development)
  - Such as: HPV, malaria, HIV, TB, and **new generation influenza vaccines**
Importance of adjuvants' use in vaccines that of global health importance (e.g. pandemic influenza response, global polio eradication) to increase global vaccine supply and meet global demand was recognized by WHO Strategic Advisory Group of Experts on Immunization (SAGE)

The use of adjuvants in influenza vaccines is of particular interest to: 1) develop pandemic influenza vaccines as they can increase production capacity through dose sparing; 2) increase protection in subjects with poor immune response to conventional influenza vaccines

- First adjuvanted vaccine for H5N1 avian influenza was approved in US in 2013
- Examples of adjuvants used in influenza vaccines: virosomes, oil-in-water emulsions
- Manufacturers are developing adjuvanted influenza vaccines (pandemic)
Adjuvanted Vaccines (3)

- However, the development and evaluation of adjuvanted vaccines present regulatory challenges; in particular nonclinical evaluation of adjuvanted vaccines is crucial for proceeding to clinical trials.

- Existing WHO *Guidelines on nonclinical evaluation of vaccines (WHO TRS 927, Annex 1)* provide valuable general guidance; however, they provide limited information specifically related to new adjuvants and adjuvanted vaccines.

- Vaccine manufacturers and regulators have requested WHO to provide *internationally harmonized* guidance on the nonclinical evaluation of adjuvanted vaccines to facilitate vaccine development & licensure, *e.g. the type of information and extent of data that are required to support proceeding to clinical studies with adjuvanted vaccines and to their eventual licensure.*
In the above context, in 2011 WHO initiated the project to develop Guidelines on nonclinical evaluation of adjuvants and adjuvanted vaccines

- WHO Consultation on the Nonclinical and Preclinical Evaluation of Adjuvanted Vaccines, 7-8 Sep 2011, Rockville, Maryland, USA
  - Attended by experts from academia, NRAs/NCLs, and industry involved in the research, manufacture and approval of adjuvanted vaccines (including influenza vaccines) from countries around the world
  - Reviewed scientific information and available data, discussed and identified major issues to be addressed in an international Guideline, agreed on an Outline

- Drafting Group consisting of experts from NRAs was set up by WHO to prepare series of drafts

- The drafts of the Guidelines were circulated among experts who are involved in the subject from worldwide countries (academic institutions, industry, NRAs/NCLs) for comments

- Attended by around 50 representatives and experts from academia, industries, and regulatory authorities from worldwide countries
  - experts with special expertise on influenza vaccines also attended
- Reviewed the draft Guidelines, reached consensus and proposed improvements

Revised draft has gone through two rounds of public consultation on WHO Biologicals website to invite public comments

Final draft was reviewed and adopted, with a number of amendments, by the Expert Committee on Biological Standardization (ECBS) at its 64th meeting in Oct 2013; published on WHO website:

http://www.who.int/entity/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf?ua=1
Content of the Guidelines (1)

Introduction, Background, Scope

1. General Considerations

2. Definitions

3. Manufacturing and quality considerations for the nonclinical and clinical evaluation of vaccine adjuvants and adjuvanted vaccine
   3.1 Production, characterization and quality assurance of lots to be used in nonclinical pharmacology studies
   3.2 Production, characterization and quality assurance of lots to be used in nonclinical toxicology studies and first-in-human clinical trials
   3.3 Information required for later-stage clinical trials

4. Rationale for the use of the adjuvant
   4.1 In vivo proof-of-concept studies
   4.2 In vitro supporting studies
5. Considerations for selection of the animal species for nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines
   5.1 Selection of animal species for nonclinical pharmacology studies
   5.2 Selection of animal species for nonclinical safety studies
   5.3 Limitations of animal studies

6. Nonclinical safety assessment in animals
   6.1 General remarks
   6.2 Toxicity studies of vaccine adjuvants and final adjuvanted vaccine formulations
   6.3 Additional considerations

7. Considerations for first-in-human clinical trials

Appendix 1: Examples of classes of adjuvants

Appendix 2: Tissue samples to be collected for a repeated-dose toxicity study

Authors, References
Introduction

- This document provides guidance to national regulatory authorities (NRAs) and manufacturers on the nonclinical and initial clinical evaluation of vaccine adjuvants and adjuvanted vaccines by outlining the international regulatory expectations in this area. It should be read in conjunction with the existing guidelines on nonclinical and clinical evaluation of vaccines published by the WHO.

- There is substantial diversity among vaccine adjuvants and adjuvanted vaccines and their nonclinical and clinical testing programmes will depend on product-specific features and their clinical indications. Therefore, the text is written in the form of guidelines instead of recommendations. “Guidelines” allow greater flexibility than “Recommendations” with respect to specific issues related to particular adjuvanted vaccines.
The goal of this document is to provide consistent and harmonized guidance on nonclinical testing approaches to support the use of candidate adjuvanted vaccines in all stages of clinical development and ultimately for marketing authorization of the product.

This document covers adjuvanted vaccines used in both prophylactic and therapeutic indications against infectious diseases.

- Therapeutic vaccines (e.g. against cancer) have a different benefit/risk ratio and therefore are not included in the scope. However, some principles outlined in this document may be applicable to adjuvanted therapeutic vaccines for other indications as well (e.g. cancer).
For the purposes of this document, the term “adjuvant” includes formulations that contain one **individual adjuvant** as well as **adjuvant combinations** that contain multiple adjuvants.

- No vaccine adjuvant is authorized in its own right, but only as a component of a particular adjuvanted vaccine

This document **does not deal** with carrier proteins that are covalently linked to polysaccharide antigens in conjugate vaccines. Also, the immune enhancing properties that are intrinsic to certain vaccine antigen preparations, such as the naturally occurring adjuvant activity of whole-cell pertussis vaccines, are not considered “adjuvants” within this document.

* A list of examples of classes of adjuvants is provided as an Appendix.*
Scope (3)

- This document provides guidance related to the evaluation of new adjuvants and adjuvanted vaccines, to include:
  - unlicensed adjuvanted vaccines;
  - antigens and adjuvants that have been included in licensed vaccines, but for which the production process has undergone significant changes;
  - previously licensed products that have undergone major formulation changes (e.g., a change in adjuvant or addition or removal of one of the components);
  - previously licensed products given by a new route of administration

- For the purposes of these guidelines, a novel adjuvant is defined as an adjuvant that has not been included in a licensed vaccine. Considerations specific to the evaluation of novel adjuvants are provided where appropriate in this document.
Key Issues (1)

- **Product characterization** (antigen, adjuvant and adjuvanted vaccines) and consistent manufacturing process, QC specifications are critical to assure the consistent safety and effectiveness of adjuvanted vaccines
  - Guidance provided on these aspects for lots to be used in nonclinical pharmacology/toxicology studies and FIH clinical trials

- **Rational for the use of adjuvant**: Manufacturers should provide scientific rationale supporting the benefit of adding the adjuvant and the choice of specific adjuvant(s)
  - Considerations may include: the immune response desired, effects on the magnitude/ breadth and/or the type of immune response to specific antigens and on the safety profile
  - Special example of influenza: "adjuvants are used in antigen dose-sparing strategies with the aim of increasing the availability and supply of vaccines—for example, under emergency situations of an influenza pandemic"
Key Issues (2)

- **Selection of animal species**
  - Guidance provided on how to select the animal species for nonclinical pharmacology and nonclinical safety studies (e.g. the rationales, principles to be considered, the number of species to be used)
  - Acknowledge the limitations of animal studies
    - The limitations to predict human immune responses and local/systemic adverse effects in animals
    - It is highlighted that there is a lack of animal models to screen adjuvants/adjuvanted vaccines for induction of autoimmunity or hypersensitivity
    - Insufficient knowledge about suitable animal models for neonates and elderly populations
    - Further research is encouraged to fill the gaps
Key Issues (3)

- **Nonclinical safety assessment in animals**
  - Valuable tools to help define an acceptable adjuvant/antigen ratio and a safe dose, as well as to identify unknown or potential adverse effects that should be taken into consideration for further product development or to be monitored in future clinical trials.
  - Detailed guidance provided on animal toxicity study design (types and timing of studies), observation and interpretation of study results.

- **Considerations for first-in-human (FIH) clinical trials**
  - Provides guidance on the points to consider when transitioning from nonclinical to clinical testing - an important area that was not specifically covered in other WHO guidance documents.
    - Use and limitations of non-clinical data; demonstration of the "added-benefit" of the adjuvant and study arms to be included; study population; defining the starting dose; safety monitoring and evaluation; etc.
For Detailed Information

Please consult:

"WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines," adopted by ECBS in Oct 2013, available on:

http://www.who.int/entity/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf?ua=1

Note: "A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series."
WHO Biological Standardization

- **WHO Biologicals:** [http://www.who.int/biologicals/en/](http://www.who.int/biologicals/en/)

- **Webpage for nonclinical evaluation of vaccines:**

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