Public Workshop: Adjuvants and Adjuvanted Preventive and Therapeutic Vaccines for Infectious Disease Indications

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December 2 & 3, 2008
Bethesda, MD

INTRODUCTION

- **The goal in vaccine development is to:**
  - **provide the safest vaccine**
  - **provide maximal efficacy**
  - **require the least amount of**
  - **antigen, and number of doses**

INTRODUCTION (CONT'D)

- Interest in vaccine adjuvants and new delivery systems has significantly increased over the past decade.

- New technological advances in vaccine development present significant challenges to National Regulatory Authorities including the US FDA, however, these products may present opportunities for advancing the public health.

- FDA must be in a position to develop new scientific and regulatory criteria to facilitate the development of new vaccines, including those with novel adjuvants for safety and effectiveness.

BACKGROUND

- **Presently, adjuvants are not licensed separately from the vaccine with which they are formulated.**
  - **Currently, only aluminum containing adjuvants are used in U.S. licensed vaccines.**
- **The individual vaccine/adjuvant combination that is licensed, necessitates case by case evaluation.**
  - **This leads to difficulties in the developing guidelines that would apply to all situations.**

Adjuvants: Challenges

- **Safety concerns**
  - **Evaluating benefit vs. risks**
- **Lack of universality**
  - **adjuvants are currently not considered the active ingredient in prophylactic vaccines**
  - **immune responses obtained with one antigen/adjuvant cannot be extrapolated to another antigen or even to the same combination given by different routes**

Adjuvants: Challenges (cont'd)

- There are also challenges evaluating manufacturing and clinical outcomes of vaccines made with novel adjuvants
  - Scale-up
  - Consistency of manufacturing from lot to lot
  - Stability
  - Determination of clinical endpoints for assessing safety and efficacy?

Workshop Objectives

- Mechanism of action of adjuvants
- Identification of scientific gaps
- Approaches to non-clinical safety evaluation for adjuvanted vaccines
  - Criteria for selecting the appropriate ROA, doses, schedule
  - Animal models
  - Alternate methods
- Clinical experience WRT safety

Roundtable 1: Nonclinical Issues

- Current approach to adjuvant toxicology testing
  - Is it sufficient to test only the highest 1X human dose of the vaccine/adjuvant combination and adjuvant alone?
  - Should dose-ranging studies be conducted on the adjuvant alone?
  - Should other parameters, such as cytokine levels or other biomarkers (e.g., CRP, fibrinogen) be assessed?
  - Are other aspects of the current study design such as route of administration and regimen appropriate ?

Roundtable 2: Clinical Issues

- What type of clinical studies are needed to:
  - Detect age-specific differences in adjuvant responses?
  - Provide long-term safety information?
  - Provide dose-ranging data on adjuvants as well as antigens?
- What clinical studies can be designed that will incorporate safety information obtained from preclinical data?

Summary

- The development and evaluation of novel adjuvants present unique challenges
- Use of adjuvants in vaccines may provide opportunities to improve public health
- Nonclinical safety assessment:
  - Product - CMC, characterization
  - Pharm/tox testing
- Clinical safety evaluation of adjuvanted vaccines is critical
  - risk vs. benefit

BACKUP SLIDES

Roundtable 1: Nonclinical Issues

- Is it sufficient to test in only one animal species?
- What constitutes a “relevant” animal model?
  - Species-specificity of the innate immune response
  - Species-specificity of the antigen/adjuvant
- Should toxicology studies be conducted in specific animal models to support the safety of adjuvants in special populations (elderly, pediatric, immunosuppressed, etc.)?

Roundtable 1: Nonclinical Issues

- **What immunologic parameters should be evaluated?**
  - **Vaccine antigen specific responses**
  - **Adjuvant specific responses**
- **How can *in vitro* assays be incorporated into nonclinical safety assessments?**
  - **E.g., cell based assays to supplement animal studies**

Roundtable 1: Nonclinical Issues

- **Is it adequate to assess only the combination when assessing a combination adjuvant (e.g., oil-in-water emulsion plus QS-21, and MPL) or should dose-ranging toxicity studies be conducted on each separate component as well?**

Roundtable 1: Nonclinical Issues

- What other toxicity testing should be conducted?
- E.g.,
  - Should the tendency to cause/exacerbate autoimmune or inflammatory disease be evaluated, if useful animal models exist?
  - Genotoxicity studies?
  - Chronic toxicity studies?

Roundtable 1: Nonclinical Issues

- Should additional animal studies be required to evaluate long term effects of adjuvants ?
- e.g.,
  - Exposure over multiple years (such as adjuvanted influenza vaccines) ?
  - Exposure to multiple types of adjuvants either concurrently or over multiple years?
  - If so, at what stage of clinical development should these studies be required?