Regulatory Pathways Supporting Development and Approval of Vaccines formulated with Novel Adjuvant: Regulatory Considerations and Challenges



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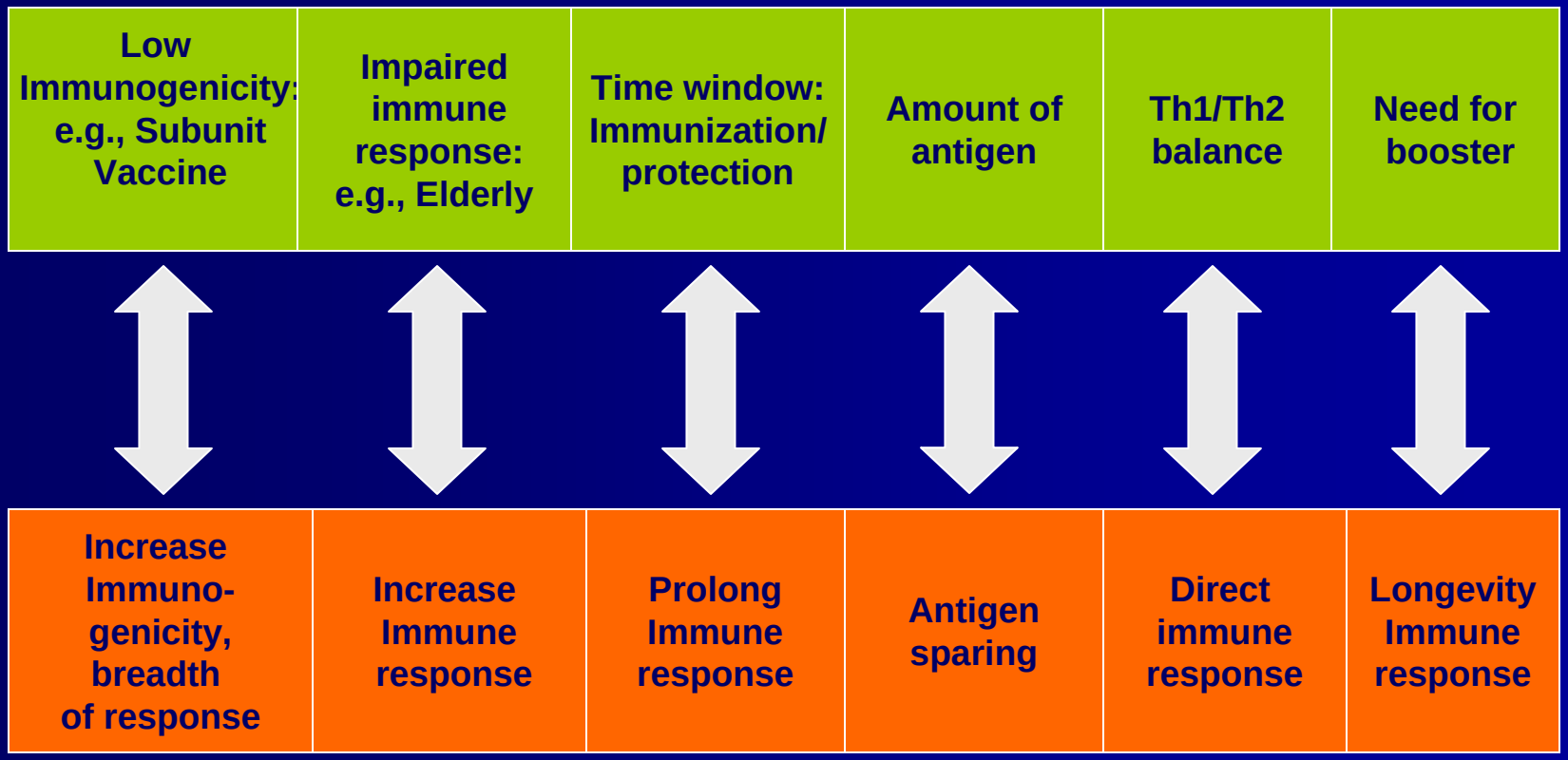
Reasons for Including Adjuvants in Vaccines



“Novel” Adjuvants: Examples

- Monophosphoryl lipid A (MPL)
- CpG oligodeoxynucleotides
- Modified bacterial toxins
- Oil-in-water emulsions and surfactant-based
  - MF59 (Novartis)
  - AS03 (GSK)
- Adjuvant systems (GSK)
  - AS01: QS-21 + MPL + liposomes
  - AS02: QS-21 + MPL + oil-in-water emulsion
- Human endogenous immunomodulators
  - IL-12
  - IL-2

Investigational Vaccines combined with Novel Adjuvants

- CBER has seen an increase of IND submissions for products formulated with novel adjuvants.
- Numerous clinical studies under IND are underway with vaccines containing such adjuvants as:
  - Mineral salts
  - Oil-emulsion and surfactant-based adjuvants,
  - Particulates
  - Microbial (natural and synthetic) derivatives

Licensed Vaccines Containing Adjuvants

USA

- Al salts in many vaccines
- MPL as MPL/$AlOH_3$: AS04
  - Cervarix (human papilloma virus vaccine)

Europe

- Al salts in many vaccines
- MPL as MPL/$AlOH_3$: AS04
  - Fendrix (hepatitis B vaccine)
  - Cervarix (human papilloma virus vaccine)
- MF59
  - Focetria (pandemic influenza vaccine)
  - Fluad (seasonal vaccine)
- AS03
  - Pandemrix (pandemic influenza vaccine)

US: Criteria for Vaccine Approval

- 351 of the Public Health Service Act
  - Data must show that the product is safe, pure and potent
  - Manufacturing facility meets standards designed to ensure continued safety, purity and potency

Only those vaccines that are *demonstrated to be safe and effective,* and that *can be manufactured in a consistent manner* will be licensed by the FDA

Development Strategy for Adjuvanted Vaccines

Pre-clinical data supportive of initiating clinical studies

Human clinical data adequate to support the proposed indication and use

Post-licensure pharmacovi-gilance plan

Safe, effective, high quality product of known stability that can be consistently & reproducibly manufactured

Product-related data and testing plans adequate to support the manufacturing process

Manufacturing process ensuring quality product and consistency of manufacture

Facility data: compliance w/cGMPs, manufacturing controls, QA/QC

Regulatory Considerations: Adjuvant

- 610.15 Constituent Material
  - *a) Ingredients, preservatives, diluents, adjuvants*

    "All ingredients…shall meet generally accepted standards of purity and quality.
  - "An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product."
- Adjuvants are not licensed alone, but as a specific adjuvant/antigen formulation
  - Adjuvants are not active ingredients as defined in 21 CFR 210.3 (b) (7) and thus, adjuvants added to preventive vaccines are not licensed separately.
  - It is the adjuvanted vaccine formulation, *in toto*, that is tested in clinical trials and licensed.

CBER/NIH Public Adjuvant Workshop

- Dec 2 & 3, 2008: CBER/NIH Public Workshop: “Adjuvants and adjuvanted preventative and therapeutic vaccines for infectious diseases indications”
  - Objectives:
    - To assess the scientific knowledge base regarding vaccine adjuvants
    - To facilitate the development of a research agenda to improve the safety and efficacy assessments of adjuvanted vaccines for the treatment and prevention of disease
  - Nonclinical & clinical roundtable discussions
  - Transcripts available at http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm095698.htm

FDA Review is Product-based

- No “one size fits all” regulatory approach
- Dependent on characteristics of specific product
- Preclinical studies designed to support use of specific products
- Clinical trial design depends on objectives & endpoints/outcomes to be measured
- Supported by science, framed by regulations

Microbial (natural and synthetic) derivatives

Mineral Salts

Oil Emulsions

Immunoadjuvants

Licensure Pathways for Adjuvanted Vaccines

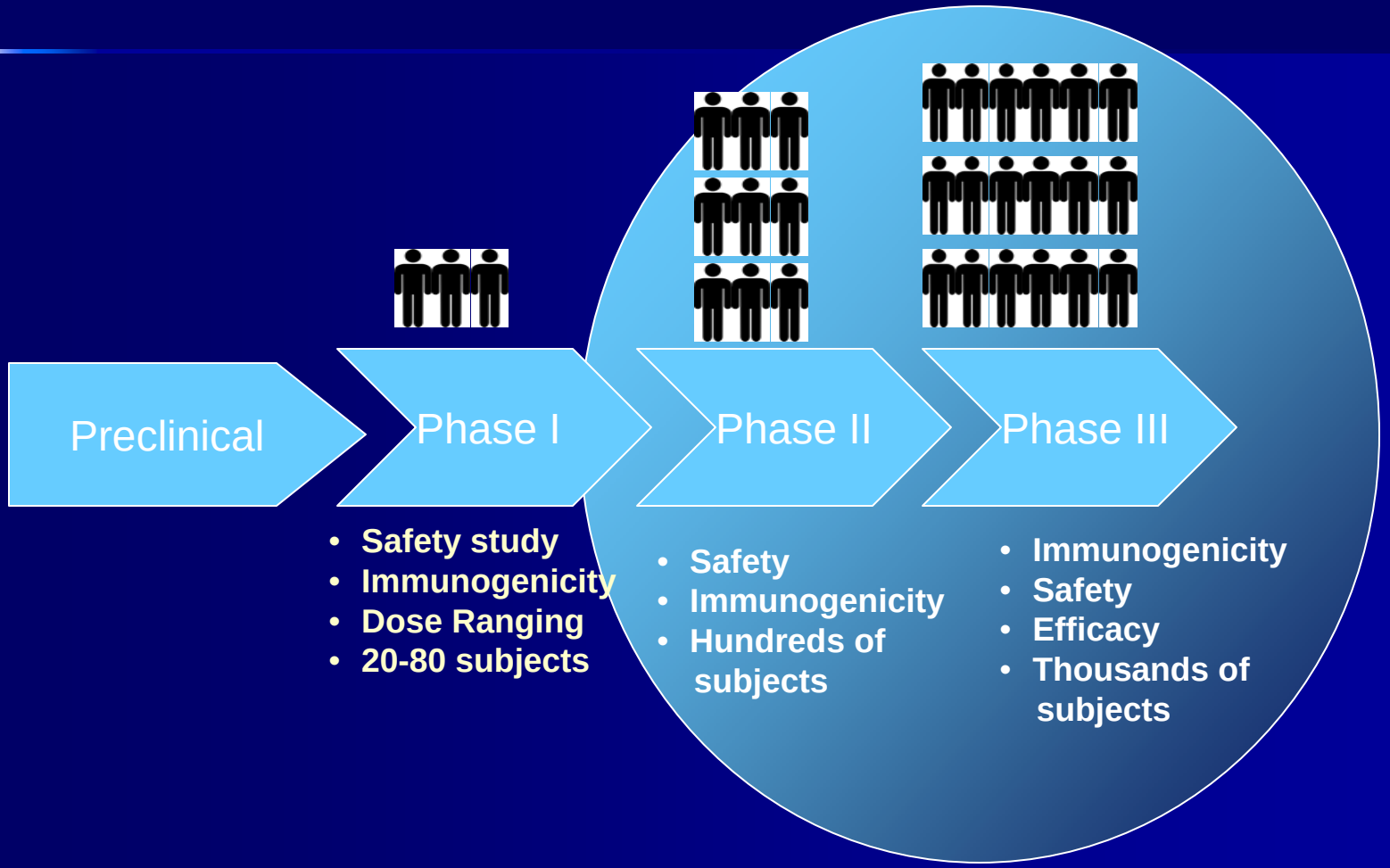
....the same as for unadjuvanted vaccines!

- Traditional approval
  - Efficacy based on clinical endpoint, e.g.
    - Prevention of disease
    - In some cases inferring effectiveness from immunogenicity
- Accelerated approval
  - Efficacy based on surrogate endpoint reasonably likely to predict clinical benefit
  - Confirmatory post-marketing study to verify clinical benefit
- (Animal rule)
- Demonstration of safety is required for all pathways

Special considerations

- Justification for use of the adjuvant
- Safety evaluation

Development of Adjuvanted Vaccines



Earlier Stages

Later Stages

Adjuvanted Vaccines: Preclinical Safety

- Codified in 21 CFR 312.23(a)(8)
- Current recommendations & guidance:
  - Local tolerance and repeat dose toxicity testing
    - Usually conducted prior to clinical trials
    - To identify and characterize potential local and systemic adverse effects
    - Histopathology of full tissue list (WHO guidance) for novel adjuvants
  - Reproductive toxicity testing
    - Conducted in parallel with Phase 3 clinical trials for products intended for females of childbearing potential

    or

    - Conducted prior to studies enrolling pregnant women

WHO Consultation on Nonclinical Evaluation of Adjuvanted Vaccines (Sept. 2011)

- To summarize the scientific information, available data, and outcomes of past scientific meetings on adjuvants
- To discuss regulatory considerations for nonclinical evaluation of adjuvanted vaccines
- To initiate the process of drafting a WHO guidance document for the nonclinical evaluation of adjuvanted vaccines
- To globalize and harmonize recommendations for nonclinical safety evaluation for adjuvants & adjuvanted vaccines across regulatory agencies

Clinical Development of Adjuvanted Vaccines: Early vs. Late Stage

- During the early phase clinical trials (Phase I/II)
  - Determine the safety of the product in a small number of subjects
  - Optimal dose
  - Dosing schedule

- During later phases of clinical trials (Phase II and III)
  - Determine the product's immunogenicity, effectiveness, and safety in the target population.
  - Results from such trials may support an application for licensure

Phase 1 and 2 Studies of Vaccines Containing Novel Adjuvants:

- Perform initial trials in limited number of healthy adults (ages 18 – 50)
  - Specifically exclude individuals with history of autoimmune disease
- Ideally, establish minimum dose needed to achieve adequate immunogenicity (adjuvant dose-finding)
- Assess safety of adjuvanted vaccine
  - Extensive safety monitoring for local/systemic AEs, conservative stopping rules

Pre-IND meeting with FDA encouraged

Phase 3 Studies of Vaccines Containing Novel Adjuvants

- Objectives:
  - Demonstrate clinical benefit of the adjuvanted vaccine
  - Expand knowledge of safety
    - Most safety data come from efficacy trial(s)
    - Usually best opportunity for randomized safety data
- Size: Large enough to meet objectives
  - Often thousands or tens of thousands
- Endpoints:
  - Clinically meaningful efficacy case definition
  - 1° and 2° endpoints prospectively specified in protocol
- Design
  - Typically double-blind, rand. controlled
- Surveillance and Monitoring Plans
- Statistical Plan
  - Outlined prospectively in protocol

Special Considerations:
Safety Evaluation of Adjuvanted Vaccines

- Must have assurance that the product is safe before licensure for widespread use in healthy individuals
- Safety requirement for vaccine licensure (21 CFR 600.3(p))
  - Relative freedom from harmful effect
  - Taking into consideration the character of the product in relation to the condition of the recipient
- Definition of safety implies a risk/benefit evaluation

Special Considerations:
Novel Adjuvant Systems & Components

- Range of properties that invoke complex immune responses
- Mode of action of adjuvants not always known
- Animal models that predict safety and efficacy of a adjuvant-antigen combination not available
- Safety concerns, e.g., unpredictability of potentially occurring rare serious adverse events

Special Considerations:
Safety Evaluation of Adjuvanted Vaccines

- Use of adjuvant may increase potential for:
  - Excessive amounts of pro-inflammatory & pyrogenic mediators (IL-6, TNFa, IL-8, IL-1b, PGE2)
  - Organ specific toxicity (local inflammation; cell death; immune-based)
  - Severe local reactogenicity (increased vascular permeability, cellular infiltration, fluid accumulation)
  - Break-down of self tolerance: e.g., induction of Th17 cells; host factors (autoreactive cells, HLA)
  - Combined toxicities due to interactions between vaccine and adjuvant induced mechanisms

Special Considerations: Safety Evaluation of Adjuvanted Vaccines *September 2011: Finland*

NATIONAL INSTITUTE
FOR HEALTH AND WELFARE

Association between Pandemrix and narcolepsy confirmed among Finnish children and adolescents

1 Sep 2011

An association between Pandemrix and narcolepsy among children and adolescents in Finland is confirmed

In its final report, the National Narcolepsy Task Force confirms the tentative conclusion published in its Interim Report last January that the Pandemrix vaccine used in the winter of 2009–2010 contributed to the increased incidence of narcolepsy observed among 4–19-year-olds in Finland. According to the report, the increased risk associated with vaccination amounted to six cases of narcolepsy per 100 000 persons vaccinated in the 4–19 age group during the eight months following vaccination. This was 12.7 times the risk of a person in the same age group who had not been vaccinated. No increased incidence of narcolepsy was observed among children under the age of four or among adults over the age of 19.

In all the cases examined, narcolepsy associated with Pandemrix vaccination has been identified in persons who carry a genetic risk factor for narcolepsy. Because of this very strong association with the genetic risk factor which regulates immune responses, narcolepsy is considered an immune-mediated disease.

In approximately one quarter of those who developed narcolepsy following Pandemrix vaccination, the THL Immunology laboratory found antibodies binding to the AS03 adjuvant component of the vaccine. Adjuvants containing squalene have not previously been reported to induce the production of antibodies. The significance of this preliminary observation will be the subject of further research.

Tests on viral antibodies indicated that less than 10 per cent of the children and adolescents who developed narcolepsy had been infected with swine flu. Swine flu infection thus does not appear to play a significant role or be in joint effect with the Pandemrix vaccine in the onset of narcolepsy.

Only Finland and Sweden have confirmed increased incidence of narcolepsy

Special Considerations: Safety Evaluation of Adjuvanted Vaccines (cont.)

- The safety of the adjuvanted vaccine formulation must be demonstrated in adequate and well-controlled prelicensure safety studies
- Longer follow-up than is typical for non-adjuvanted vaccines
  - Typically 12 months following vaccination
  - Follow-up for vital status, SAEs, new-onset medical conditions, “adverse events of special interest”
  - Examination for potential autoimmune related adverse events
  - Potential for other inflammatory mediator-related events

Special Considerations:
Safety Monitoring of Adjuvanted Vaccines

- AEs of “special interest”
  - Focus on autoimmune/autoinflammatory diseases
  - Examples
    - Neuroinflammatory disorders (e.g., optic neuritis, transverse myelitis)
    - Musculoskeletal and connective tissue diseases (e.g., RA, SLE, Wegener’s)
    - GI disorders (e.g., Crohn’s disease, ulcerative colitis)

Assessing Safety of Vaccines containing Novel Adjuvants: Analytical Approaches

- Specific inquiries regarding symptoms consistent with autoimmune and neuroinflammatory diseases
- Consider targeted laboratory screening assessment (e.g., CRP, fibrinogen, ANA, ANCA, Rheumatoid factor)
- Maintain banked serum specimens where possible
- One-year clinic safety follow-up suggested
- Suggested comparisons (early in clinical development):
  - Adjuvanted vaccine vs. saline placebo
  - Adjuvanted vaccine vs. unadjuvanted antigen

Special Considerations:
Safety Evaluation of Adjuvanted Vaccines

- No requirement to compare the safety of the adjuvanted to the unadjuvanted vaccine formulation in comparative phase 3 safety studies
- Safety information submitted to the Biologic License Application may include the safety experience obtained from domestic or foreign trials
- Safety experience with the same adjuvant formulated with other vaccine antigens may also contribute to the adjuvant's safety evaluation

Special Considerations:
Justification for use of the Adjuvant

- Manufacturers should provide a rationale for the use of adjuvant in their vaccine formulation whereby supportive data may be derived from
  - Preclinical studies (e.g., in *vitro assays* and/or proof-of-concept studies in animal models)
  - Early clinical immunogenicity trials comparing adjuvanted vs. unadjuvanted vaccines to include
    - evidence of enhanced immune response,
    - antigen sparing effects,
    - or other advantages
  - Data from use of adjuvant with related vaccine antigens
  - If available, information about the presumed mechanism of action of the adjuvant

Special Considerations:
Justification for use of the Adjuvant

- Manufacturers are not required to demonstrate the “added benefit” of an adjuvant in comparative phase 3 efficacy trials
  - no *à priori* requirement for comparative phase 3 efficacy studies, however, such studies may be requested by the agency on a case-to case basis,
    - e.g., if serious safety concerns have been identified

Risk Benefit Balancing

- Risk/benefit balance potentially more tolerant of AEs:
  - For vaccines targeting serious diseases
  - Where no vaccine currently exists
- Risk/benefit balance potentially less tolerant of AEs:
  - If adding adjuvants to currently existing, effective vaccines (e.g., for dose-sparing)
  - If targeted diseases are low-grade, self-limited

Summary

- Regulatory pathways supporting development and approval of vaccines formulated with novel adjuvant are the same as for unadjuvanted vaccines
- Efficient planning of the development pathway for an adjuvanted vaccine requires careful attention to preclinical testing, study design, dosing decisions, and safety monitoring
- Although manufacturers are not required to demonstrate the “added benefit” of adjuvanted *vs* unadjuvanted vaccines in clinical comparative phase 3 studies, manufacturers should provide a justification for including an adjuvant in the vaccine
- Demonstration of safety of the adjuvanted vaccine can be challenging given special safety considerations

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