Update on Vaccine Regulation: Expediting vaccine development

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Challenges in vaccine development

- High cost of development relative to typical profits
- US markets are often dependent upon ACIP recommendations
- Clinical endpoint studies may not always be feasible pre-licensure
- Need to identify endpoints and regulatory pathways to facilitate development for product sponsors
- The public reasonably demands safe, effective vaccines that meet a high standard
  - Low tolerance for error
  - Human subjects protections are also critical

Licensure of Vaccines

Section 351 of the Public Health Service Act, 42 USC 262:

- Licensure on the basis of a demonstration
  - that the biological product … is safe, pure, and potent; and
  - the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; ….
- 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
- Biological product must be "applicable to the prevention, treatment or cure of diseases or injuries of man" (21 CFR 610.3)

CBER-sponsored or Co-sponsored Scientific Meetings

- Recent meetings to discuss scientific data that could support development of regulatory pathways for vaccines against specific pathogens included:
  - 4/14 Workshop on Regulatory Issues Related to Dengue Virus Vaccines
  - 9/13 Workshop on Immune Correlates of Protection for Tuberculosis Vaccines
  - 6/12 Universal Influenza Vaccines
  - 1/12 The Development and Evaluation of Human Cytomegalovirus Vaccines
  - 9/11 The Development and Evaluation of Next-Generation Smallpox Vaccines
  - 4/11 Neisseria Meningitidis Serogroup B Vaccine, VRBPAC meeting to discuss study endpoints

Refocusing the Vaccines IND Process

- Engage sponsors in addressing key issues earlier in the regulatory cycle
- Especially important for vaccine CMC discussions
  - Delayed CMC discussions may reduce likelihood of first cycle approvals, because CMC issues will need to be resolved during BLA review
- Separate clinical and CMC meetings can assure that all issues are discussed
  - Routinely offered pre-BLA
  - May also be useful at end of phase II
- Increased discussion of longer-term strategies earlier in the review process

Regulatory programs to expedite vaccine development & licensure

- Fast track
- Breakthrough
- Accelerated approval
- Priority review

Definition of Serious Condition

- A disease or condition is associated with morbidity that has substantial impact on day-to-day functioning, and
- Drug must be intended to have an effect on a serious aspect of a condition

Definition of Available Therapy

- Approved or licensed in the U.S. for the same indication
- Is relevant to current U.S. standard of care (SOC)
  - When a drug development program targets a subset of a broader disease population, the SOC for the broader population, if there is one, generally is considered available therapy for the subset
  - SOC will evolve- FDA will determine what constitutes available therapy at the time of the relevant regulatory decision
- A drug granted accelerated approval based on a surrogate or clinical endpoint and for which clinical benefit has not been verified is not considered available therapy
- Accelerated approval (restricted distribution) or approval with a REMS is considered available therapy only if study population for new drug is eligible to receive the drug

Definition of Unmet Medical Need

- A condition not addressed adequately by available therapy
- Will consider a range of potential advantages, for example
  - Has an effect on a serious outcome of the condition that is not known to be influenced by available therapy
  - Ability to address an emerging or anticipated public health need (e.g., drug shortage)
- Exists if the only available therapy was approved under accelerated approval based on a surrogate or an intermediate clinical endpoint and the clinical benefit has not been verified

Fast Track Designation

- Criteria
  - Serious condition
  - Nonclinical or clinical data demonstrate the potential to address unmet medical need
- Features
  - Actions to expedite development and review
  - Rolling Review

Breakthrough Therapy Designation

- New designation created by FDASIA
- Criteria
  - Serious condition
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints
- Features
  - All of Fast Track features
  - Organizational commitment

Accelerated Approval Pathway (21 CFR 601, Subpart E)

- Criteria
  - Serious condition
  - Meaningful advantage over available therapies
  - Demonstrates an effect on either:
    - A surrogate endpoint- a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit
    - An intermediate clinical endpoint- a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM
- Feature
  - Approval based on an effect on a surrogate or an intermediate clinical endpoint
  - Subject to confirmatory study

Priority Review Designation

- Criteria
  - Serious condition
  - Demonstrates potential to be a significant improvement in safety or effectiveness
- Features
  - Filed marketing application reviewed in 6 months (compared to 10 months for standard review)

What about vaccines that do not meet formal criteria for breakthrough therapy?

- Even for vaccines that do not meet formal criteria for expedited programs, OVRR is committed to providing useful guidance with senior management involvement throughout the review cycle

Accelerated approval

- Traditionally, for vaccines, this has involved approval based on immune markers thought to be predictive of protection, e.g. antibody titer
- Intermediate clinical endpoints can be considered
- Novel approaches to confirming efficacy post-licensure may also be considered
  - Powerful new epidemiological techniques may have promise in this area
  - Under discussion

OVRR will consider strategies to obtain important information earlier in development

- Increased use of phase I/II studies to facilitate go/no-go decisions
- Other adaptive study designs
  - With appropriate statistical considerations
- Early studies to compare multiple formulations or candidates (e.g., exploratory IND)
- Early discussion of these or other novel strategies recommended

Summary

- New vaccines must meet regulatory requirements for safety and efficacy
- New programs are in place to help to expedite availability of novel products
- OVRR is committed to developing additional approaches that may help sponsors obtain the information they need in order to expeditiously develop safe and effective products
- We encourage both general and product-focused discussion of these issues

Update on Vaccine Regulation: Considerations for adjuvanted vaccines

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CMC Strategy Forum, Europe

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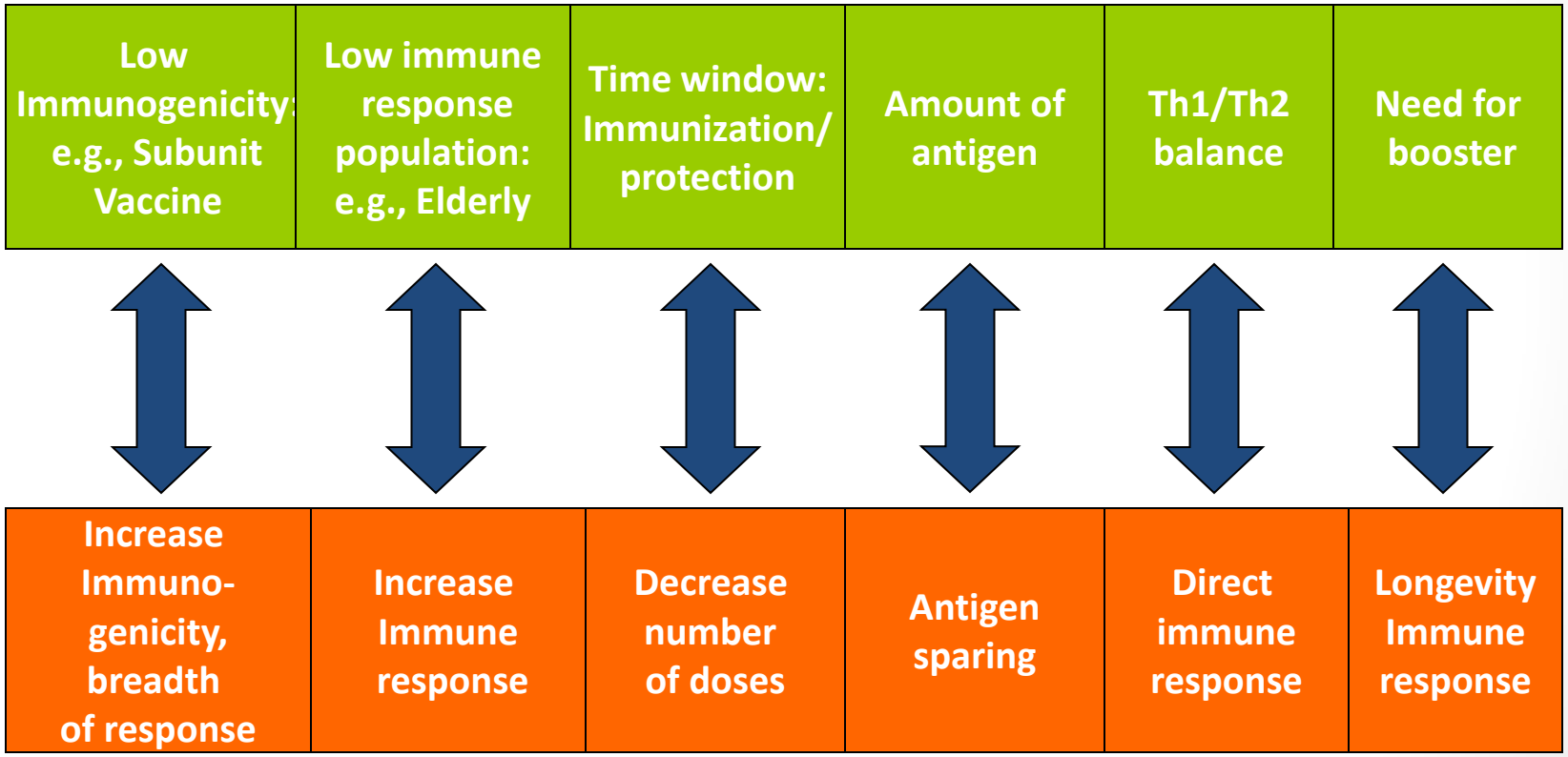
Reasons for Including Adjuvants in Vaccines



“Novel” Adjuvants: Examples

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

Examples of Licensed Vaccines Containing Adjuvants

US

- Al^{+++} salts in many vaccines
- MPL/$AlOH_3$: AS04
  - Cervarix (human papilloma virus vaccine)
- AS03
  - Q-Pan (H5N1) monovalent pandemic influenza vaccine

Europe

- Al^{+++} salts in many vaccines
- 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)

Regulatory Considerations: Adjuvants

- Adjuvants are not considered active ingredients
  - 21 CFR 610.15 Constituent Material (*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."
- It is the adjuvanted vaccine formulation, *in toto*, that is tested in clinical trials and licensed.

Regulatory Considerations: Adjuvants

- Of primary interest is the vaccine antigen induced immune response (enhancement thereof) in the presence of adjuvant
  - Safety evaluations
  - Evaluation of “added benefit” (justification for use of the adjuvant)
- From a regulatory perspective, ***if*** adjuvants would be considered active ingredients
  - Expectation that each active ingredient makes a contribution to the claimed effect(s)
  - Demonstration of claimed effect by conducting phase 3 clinical trials

Adjuvants: Special Considerations

- Exhibit range of properties that invoke complex immune responses
- Mode of action of adjuvants not always known or not fully understood
- Animal models that predict safety and efficacy of a adjuvant-antigen combination not available

Adjuvanted Vaccines: Preclinical Safety

- 21 CFR 312.23(a)(8)
- Current recommendations & guidance:
  - Repeat dose toxicity
    - 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 use in females of childbearing potential, *or*
    - Conducted prior to studies enrolling pregnant women
- WHO guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines published in 2013

When & how should the "added benefit" of the adjuvant be demonstrated?

- Manufacturers should provide a rationale for the use of adjuvant in their vaccine formulation, 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

When & how should the "added benefit" of the adjuvant be demonstrated?

- Because adjuvants are not considered active ingredients from a regulatory perspective manufacturers are not required to demonstrate the "added benefit" of an adjuvant in comparative phase 3 efficacy trials, e.g.,
  - Studies comparing vaccine antigen with and without adjuvant
- Thus, 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.,
    - Safety concerns have been identified
    - Superiority claims

Adjuvanted Vaccines: Clinical Safety

- The safety of the vaccine must be demonstrated in prelicensure safety studies
- 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 for Adjuvanted Vaccines: Safety Evaluation

- Suggested comparisons (early in clinical development):
  - Adjuvanted vaccine vs. saline placebo
  - Adjuvanted vaccine vs. unadjuvanted antigen
- Specific inquiries regarding symptoms consistent with autoimmune and neuroinflammatory diseases
- Longer post-vaccination follow-up than is typical for non-adjuvanted vaccines
  - Typically 12 months following vaccination
  - Follow-up SAEs, new-onset medical conditions, “adverse events of special interest”

Special Considerations for Adjuvanted Vaccines: Safety Evaluation

Duration of follow-up

- Some potential adverse events beginning after vaccination may not be recognized or diagnosed until much later
- Trade-off: Longer duration can increase identification of potential AEs, but may also increase noise
- Longer follow-up is often routinely obtained in efficacy studies, but increases the complexity where product is evaluated based on immunogenicity

Special Considerations for Adjuvanted Vaccines: Safety Evaluation

- Adverse events of “special interest” (AESI)
  - 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)

Special Considerations for Adjuvanted Vaccines: Safety Evaluation

- 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

Safety Evaluation of Adjuvanted Vaccines: Recent Discussions and Issues

- VRBPAC
  - CpG adjuvanted hepatitis B vaccine (Heplisav)
  - VRBPAC requested additional safety data
- VRBPAC
  - AS03 adjuvanted pandemic flu vaccine (Q-Pan)
  - VRBPAC members indicated safety database size was sufficient
- Potential association of Pandemrix and narcolepsy

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 any 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
- Evaluation of safety of an adjuvanted vaccine needs to include special safety considerations