Regulatory Perspective on Development of Preventive Vaccines for Global Infectious Diseases

National Institute of Allergy and Infectious Diseases (NIAID)

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Outline

- Impact Global Infectious Disease Vaccines
- Global Vaccine Development Issues
  - IND studies
  - Non-IND studies
- Framework/Standards
  - Ethics/Good Clinical Practice
  - Study Conduct
- Applicable Regulations
- Mechanisms for Approval

Public Health Impact

- Need for expedited pathways
  - Emerging and re-emerging diseases
  - Pandemic strains of influenza
  - New vaccines of local and global importance
  - Bioterrorism agents
  - Vaccine shortages

Limitations & challenges in conducting vaccine studies only in US

- Epidemiology may limit ability to conduct efficacy studies in US
- Interest and enrollment in studies may be limited if alternative therapeutic options are available in US (but which may not be available ex-US)
- Duplication of development for worldwide registration
- Perceived inability to use non-US data could potentially delay the introduction of medically important new vaccines to the US population

Perspectives on IND vs. non-IND Studies

- **IND studies**
  - Prospective dialogue: acceptable trial design, potential issues
  - Formal pre-submission meetings: preview clinical and CMC data
    - phase 3 plans, proposed basis for licensure, eBLA format
  - Malaria, HIV, TB vaccines: regulatory guidance
- **Non-IND studies**: Risk that study results may not satisfy U.S. regulatory requirements
  - Additional studies needed, delayed filing of BLA
  - Potential for differing views between sponsor/CBER regarding : efficacy endpoint(s), safety evaluation (e.g. surveillance methods and timepoints, pre-specified adverse events), acceptability of statistical analysis plan

Underlying Ethical Principles

- Research must meet local and international ethical standards
- ICH E6: Good Clinical Practices (GCP)
- Other Documents (CFR etc.)

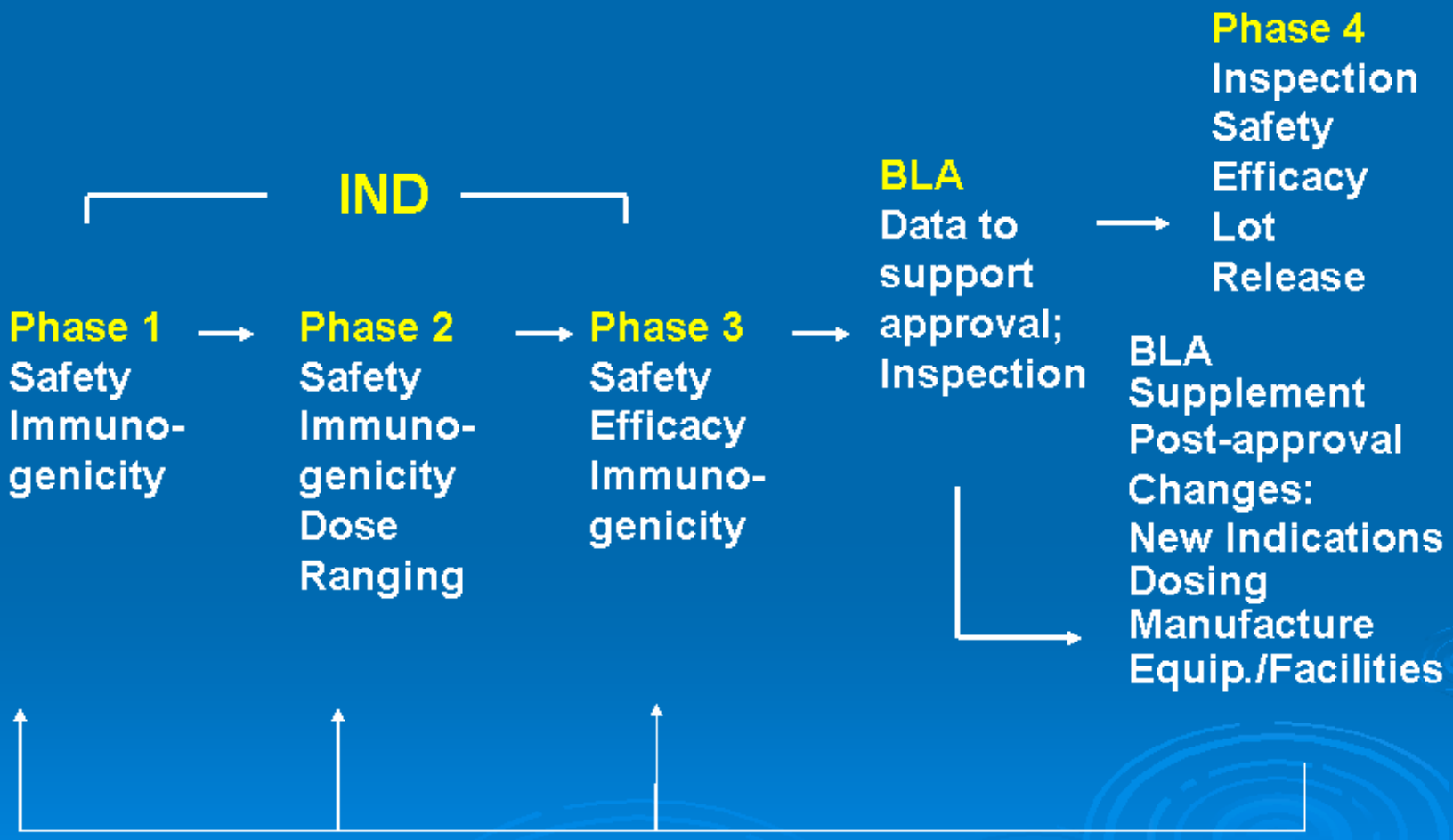
Study Conduct

- **Consult FDA early and discuss:**
  - Disease to be prevented/treated
  - Subject selection; Choice of control group
  - Key clinical trial design parameters
    - Endpoints; dose & dosing; duration; concomitant meds/vaccines
  - Safety assessment methodology
  - Standard of medical care/practice
  - Clinical data in relevant demographic groups that are often under-represented in US clinical trials
  - IND vs. non-IND studies
    - Rationale
    - Compliance with 21CFR §312.120

What is regulatory path forward to U.S. licensure for a vaccine targeted to disease or conditions not endemic in the U.S.?

- Same path as for disease endemic in U.S.

Stages of Vaccine Review & Regulation



IND =Investigational New Drug Application; BLA=Biologics License Application

Does CBER use a different standard for evaluating vaccine products meant solely for the foreign market versus U.S. market?

- No, the same standards apply.
- The following slides will review points related to efficacy and safety in clinical product development.

Vaccine Efficacy

- There are 3 approaches for showing vaccine efficacy:
  - Clinical endpoint
  - Immune response endpoints, if accepted by FDA (e.g., Hib vaccines, Hepatitis B vaccines)
  - “Animal Rule”, if certain criteria are met

Clinical Endpoint Efficacy Studies

- Clinical trials demonstrating preventive efficacy for clinical endpoints provide the greatest scientific rigor for evaluating vaccines
- Prospective, controlled, randomized
- Primary endpoint: prevention of disease
- Usually necessary in situations when
  - Vaccine is novel
  - First of its kind administered to target population
  - No accepted immune response correlate of protection

- Example: NCKP efficacy trial of the heptavalent pneumococcal conjugate vaccine: ~ 38,000 infants
  - Prevention of invasive pneumococcal disease

Assessment of Efficacy

- Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (May 1998)
  - Two efficacy trials are the “standard”
  - One trial can be adequate if result is compelling, which is often the case for vaccine efficacy trials
  - Robust data, e.g., multi-center

Statistical Considerations for Pooling Clinical Trial Data

- Prospectively defined statistical analysis plan
- Similarities in
  - Primary outcome
  - Adverse event definitions (e.g., intussusception)
  - Eligibility criteria
  - Dose, dosing regimen, concomitant vaccines administered
  - Baseline status of study population
  - Duration of follow-up
  - Medical practice (e.g., availability of ER)
  - Management and documentation of withdrawals, drop-outs
- Results from studies are in general agreement, not contradicting each other
- Variation in study design and conduct that might introduce bias or imprecision in individual estimates of treatment effect.
- Differences in background incidence rates that may cause differences in variance estimations (if applicable)

Correlate of Protection

- Generally, a laboratory parameter that has been shown to be associated with protection from clinical disease
  - Adequate and well-controlled trials
- An immunological correlate of protection is most useful if clear qualitative and quantitative relationships can be determined

Correlate of Protection (cont.)

- Example of licensed vaccines with an identified correlate of protection:
  - Hepatitis B, *Hemophilus influenza type b*
- However, identification of correlate not a requirement for licensure
- Examples of licensed vaccines without an identified immune correlate of protection:
  - Acellular pertussis, Typhoid, Tuberculosis (BCG)
- Immune correlate(s) useful for interpreting trials with immune response endpoints,
  - E.g., “bridging studies”

Animal Rule

- Evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or practical.
- Applies to new drugs or biologics that are intended to treat or prevent life-threatening or serious conditions.

New Drug and Biological Products; Evidence Needed to Demonstrate Efficacy of New Drugs When Efficacy Studies are Not Ethical or Feasible. 21 CFR 601.90-95, 21 CFR 314.600-650. Final rule published FR 67:37988-98; May 31, 2002.

Animal Rule

- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
- The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allow for the selection of an effective dose in humans.

Animal Rule

- FDA may approve a product for which :
  - Human safety has been established.
  - Animal Rule requirements are met.

This rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations.

Animal Rule

- All studies subject to the Animal Rule must be conducted in accordance with pre-existing requirements under the GLP (21 CFR 58) and the Animal Welfare Act (7 U.S.C. 2131)
- GLP will be required for the definitive/pivotal animal studies (not necessary for pilot studies). If it is in the label, the study must be conducted according to GLP.

Animal Rule

- Potential for Animal Rule Applications:
  - Smallpox, Anthrax, Botulism, Plague, Tularemia, Ebola
  - Each product will be reviewed on a case-by-case basis

Safety Monitoring

- Goals:
  - Protect subjects by monitoring local, systemic, and potential end-organ toxicity
  - Identify major toxicity
- Clinic visits
  - Symptom review, diary cards
  - Clinical exam
- Laboratory studies
  - Hematologic
  - Chemistries: e.g., hepatic, renal (U/A), endocrine
  - Others? Per pre-clinical toxicology study, previous experience with similar vaccines, etc.

Safety Monitoring

- Safety:
  - Items to be assessed/time schedule
    - (Well organized summary in a table)
  - Active post-vaccination monitoring
  - Monitoring tools
    - Submit to IND with protocol
      - Case Report Forms (CRFs)
      - Diary cards
      - Toxicity grading scales
      - Scripted interviews
    - Other (e.g., photo of vaccination sites)

Safety Monitoring

- Toxicity Grading Scales
  - Define grades for specifically monitored parameters (clinical and laboratory AEs)
  - Based on healthy volunteers
- Stopping rules
  - Provide specific criteria
  - Based upon Toxicity Grading Scale
  - Address grade 3 (severe) or grade 4 (serious) adverse events
- 21 CFR 312.32: IND Safety Reports
    - Proposed Rule March 14, 2003 FR
      - AE relationship to product cannot be ruled out

How can CBER assist developing countries with regulatory authorities in development of critical vaccines for their country?

- Submit an IND
- Product review
- Pre-clinical toxicology and testing
- Clinical protocol design and statistical analysis
- Sponsor's discretion to share FDA advice with local National Regulatory Authority (NRA)

What are the advantages for submitting an IND if a sponsor has no intent to market its vaccine in the U.S.?

- FDA may provide input on factors such as:
  - Endpoint development
  - Evaluation of safety
  - Clinical trial design
  - Statistical Analysis Plan
  - Product manufacturing
  - Quality testing
  - Assay validation

Does the FDA have a process whereby scientific advice and guidance on clinical product development can be given to a sponsor who may not plan to ultimately license a vaccine in the US?

- The established IND process provides a mechanism by which FDA can offer scientific advice and recommendations.

Has CBER licensed vaccines targeted against diseases not in the U.S.?

- Yes:
  - Typhoid
  - Japanese Encephalitis
  - H5N1 influenza
- Section 351 of the Public Health Service Act and Section 505(b) of the Food Drug and Cosmetic Act do not limit approvals for products to treat, mitigate, diagnose or prevent conditions or diseases found only in the U.S.

Does CBER accept surrogate endpoints for clinical trials of vaccines against diseases or conditions not found in the U.S.?

- Yes.
- Surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence
  - November 2001 VRBPAC recommended CIN 2/3 and AIS or worse as surrogates for cervical cancer in HPV vaccine clinical trials

Mechanisms to Facilitate Product Development of Vaccines with High Public Health Impact

- Accelerated Approval
- Fast Track
- Priority Review

Accelerated Approval

- FDA may grant accelerated approval based on determination that the effect of the surrogate endpoint is reasonably likely to predict clinical benefit (21 CFR 314.510 and 610.41).

Accelerated Approval

- Surrogate endpoint –was defined as a "laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, and survives and that is expected to predict the effect of therapy."(57 FR **13234 - 13235**, 4/15/92)
- Codified in Modernization Act of 1997
- 2001 VRBPAC discussed preventive HPV vaccine surrogate endpoints

Fast Track

- The fast track programs are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.
- Set forth in Section 112(b) of the Food and Drug Modernization Act of 1997, Section 506.
- This designation applies to the combination of the product-specific indication for which it is being studied.
- Guidance for Industry: Fast Track Development Programs-Designation, Development and Application Review – 11/18/98 (http:www.fda.gov/cber/guidelines.htm)

Fast Track

- Fast track adds to existing programs, such as accelerated approval, the possibility of a rolling submission for a marketing application.
- An important feature of fast track is that it emphasizes the critical nature of close early communication between the FDA and Sponsor to improve the efficiency of product development.
  - Fast track allows for an end-of-phase 1 meeting and other meetings (e.g., end- of -phase 2, pre-BLA) are strongly recommended.
- Fast track is intended to facilitate and get an approved product to market expeditiously

Priority Review

- Products regulated by CBER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a serious life-threatening disease.
- Priority review – 6 month review of entire BLA from the time the last section is submitted (instead of 10 months)
- A fast track product would ordinarily meet either criteria for a priority review.
- Examples include 7-valent pneumococcal conjugate vaccine and HPV vaccine

Would CBER grant priority review to a BLA submitted for a vaccine indicated for a disease not endemic in the U.S.?

- Yes if appropriate criteria are met.

Does CBER require that pivotal studies for vaccine licensure be conducted in the U.S. population?

- No.

Foreign Clinical Data from Supportive and Confirmatory Trials

21 CFR §312.120, 314.106: Foreign data

- Study design and conduct applicable to U.S. population and relevant to U.S. medical practice
- Qualified clinical investigators
- Data validation via on-site inspection or other appropriate means
- Conformance with ethical principles

In addition, demonstration of effectiveness

- §314.126 Adequate and well-controlled studies

E5: Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data

- Framework for evaluating the impact of ethnic factors on a drug's effect.
  - i.e. efficacy & safety at a particular dose.
- Regulatory & development strategies:
  - To permit adequate evaluation of the influence of ethnic factors.
  - To minimize duplication of clinical studies.
  - To expedite the drug approval process.

ICH E5: Acceptability of Foreign Clinical Data

Bridging study: supplemental study performed in the new region (e.g. U.S.) to provide clinical data on efficacy, safety, dosage and dose regimen

- Bridging studies for efficacy
  - Bridging study using **immune response** endpoints
- Bridging studies for safety
  - When a bridging study for efficacy is too small or of insufficient duration, a separate safety study may be needed

Considerations for Foreign Trials

- Efficacy (and Immunogenicity) differences between populations may result from differences in factors such as genetics, nutritional status, & background infections
  - e.g., OPV in developed vs. developing countries
- Obtain safety and immunogenicity data using candidate vaccine in specific population in which efficacy trial will be performed
- Case definition
- Adequate sample size
- Schedule (changes)

Foreign Trials of Preventive Vaccines

- Examples where foreign field trials may play an important role in vaccine development in the future (U.S.)
  - Vaccines where epidemiology precludes or limits efficacy trials in U.S. e.g.,
    - Malaria, ETEC, Cholera
- Past examples where foreign field trials played an important role in vaccine development
    - E.g., DTaP, oral polio, typhoid Vi PS, Hep A

Does CBER require all foreign studies be under IND for license applications?

- No.

Foreign clinical studies not conducted under IND

- FDA accepts such studies provided:
  - Relevant
  - Well-designed
  - Well-conducted
  - Performed by qualified investigators
  - Conducted in accordance with ethical principles acceptable to the world community
- Studies meeting these criteria may be utilized to support clinical investigations in the US and/or marketing approval

Can a sponsor submit a BLA without any expectation of marketing the vaccine in the U.S.?

- Yes but the absence of U.S. marketing intent does not affect user fees. If they meet certain criteria, the user fee may be waived.
- http://www.fda.gov/cder/about/smallbiz/pdufa.htm

Are population bridging studies needed if the safety and efficacy data to support licensure of the vaccine are derived from pivotal foreign studies?

- It depends on the indication being sought.

Types of Bridging Studies

To address:

- New population (foreign studies)
- Age group
- New product to standard of care
- New schedule
- Manufacturing changes

- If immune response/safety profile are similar, then efficacy can be inferred

Population Bridging Studies

- Clinical endpoint efficacy trial not possible in certain regions
  - Disease endemic in limited areas
  - Existing vaccines in some countries
- Approach: conduct clinical efficacy trial where disease rate is high, then “bridge” to US population with single-arm study in US

Population Bridging Studies (cont.)

- Not possible to randomize region, ethnic group
- Thus, not randomized but controlled
  - Compare immune/safety endpoints in region where clinical efficacy shown to those endpoints observed in US bridging study
- Try to keep comparison group similar
  - Demographic factors, e.g., age, gender
  - Medical practice, e.g., concomitant vaccines, schedule & route of administration
  - Conduct of trial, e.g., inclusion/exclusion criteria, surveillance for adverse events, timing of blood draws, etc.

Other Issues

- Co-administration
- Human Challenge Studies
- Adjuvants
- Pediatrics/PREA

Human Challenge Studies

- “Proof of Concept”
  - Malaria
- Demonstrate Efficacy
  - Cholera
- May not preclude the requirement for large phase 3 safety studies
- Discuss with CBER

Coadministered Vaccines

Consult early and discuss relevancy & FDA's concerns regarding:

- Pivotal data with use of US-coadministered vaccines on a US-schedule
  - Data only from non-US countries
  - Pooling US and non-US data, and sub-analysis by country
- Pivotal data with co-ad vaccine licensed in non-US countries that sponsor believes is the same as US-licensed vaccine (e.g., *Prevnar* in US vs. Prevenar ex-US)
- Pivotal or supportive nature of data with "US-like" coads (i.e., combination vaccines containing antigens also included in US-licensed vaccines)

Protection of Human Subjects: 21 CFR 50

- Subpart A: General Provisions
- Subpart B: Informed Consent
- Subpart C: [Reserved]
- Subpart D: Additional Safeguards for Children in Clinical Investigations

Pediatric Research Equity Act of 2003 (PREA)

- Applies to drugs & biologics (vaccines)
- Requires assessment of safety and effectiveness in all relevant pediatric subpopulations for certain applications, unless waived or deferred

Pediatric Vaccine Development

- ICH E11 provides regulatory guidance regarding pediatric research
- 21 CFR 50 directs IRBs regarding allowable research in children
- PREA requires assessments of drugs/biologics (vaccines) in all relevant pediatric populations

Summary

- CBER commitment to assist in the development of vaccines to prevent global infectious diseases even if the U.S. market may be limited and the primary target populations are in developing countries.
- The U.S. IND process can support this endeavor.

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