Regulatory Aspects of TB Vaccine Development: Preclinical Safety Assessments Toxicology/Adjuvants

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Workshop on Regulatory Aspects of TB Vaccine Development
Rockville, MD
December 9, 2003

Objectives

- Key components/regulatory requirements
- Safety concerns
- Safety assessments
  - Prior to Phase 1 clinical trials
    - General guidance for preclinical animal safety study
  - In parallel with clinical development
    - To address specific safety concerns depending on clinical indication
- Challenges

Definition of Vaccine

- **"…a heterogeneous class of medicinal products containing antigenic substances capable of inducing specific, active and protective host immunity against an infectious agent or pathogen"**
  - **Preventive TB vaccines**
    - **Prime an immune response to initial infections**
  - **Postexposure & Therapeutic TB vaccines**
    - **Prevent infection from progressing to disease in those previously exposed to *M. tuberculosis***

Key Components in Non-clinical Safety Evaluation

- Product characterization
- Manufacturing process
  - Starting materials
  - In-process controls for intermediates
  - Validated process procedures
  - Consistency in manufacture
  - Lot release
    - Adequate specifications
    - Purity, potency, identity
  - Stability

- *In vitro* studies
- Animal studies
  - Immunogenicity
  - Pyrogenicity testing
  - General safety testing
  - Neurovirulence testing
  - Reversion to virulence
  - Biodistribution studies
  - Integration studies
  - Freedom from virulent mycobacteria

  - Safety studies

Regulatory Requirements

- **21 CFR 312 – IND regulations**
  - **312.23(a)(8) – Pharmacologic and Toxicologic Studies**
    - **"…adequate information about the pharmacological & toxicological studies… *in vivo* or in *vitro studies* should be conducted on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations."**

Potential Safety Concerns Associated with TB vaccines

- Inherent toxicity of the vaccine
- Toxicity of impurities/contaminants
- Toxicity due to interaction of components
- Toxicity linked to the immune response induced

Preclinical Safety Studies: General Principles

- Risk/benefit considerations
  - Target population, ROA, available clinical data, mechanism of action, product features
- Design based on best available science
- Adequate to identify toxic effects
- Need for balance in interpretation of data

Preclinical Safety Studies for TB Vaccines: Goals

- To demonstrate the safety, purity and potency of a vaccine
- To support entry into clinical trials, where human safety is ultimately evaluated
- Maximize the benefit-to-risk of vaccine development
- Determine a safe dose
- Identify any potential or unknown toxicities

Preclinical Testing Programs are Product Specific

Unique safety concerns need to be addressed using adequate *in vitro* and *in vivo* tests and methods specifically tailored to the particular product category, e.g.

- **Live attenuated BCG strains & live vectors**
  - **Assays demonstrating sufficient attenuation and lack of reversion to wild-type**
- **DNA vaccines**
  - **Tissue distribution, persistence, expression, integration**
- **Vaccines formulated with adjuvant**
  - **Safety evaluation of adjuvant**

Preclinical Safety Study: Study Design

- Dedicated stand alone toxicity studies *or*
- Combination safety/activity study
  - Control arms
- ROA (mimic clinical route)
- Total number of doses equal or exceed number of clinically administered doses
  - "N plus 1" *vs.* "n = 1" ?
  - Episodic dosing, if applicable

Preclinical Safety Study: Study Design

- **Maximum human dose (1x)**
  - **In general, no need for dose response**
    - **Possible exceptions (e.g., adjuvants)**
  - **Volume**
    - **Same as administered to humans (1x)**
    - **Scale based on mg/kg, if 1x dose not feasible**

Preclinical Safety Study: Parameters Monitored

- Local/systemic events
- Immunogenicity
- Clinical observations (general health, body weight and food consumption, injection site, limb use impairment)
- Serum chemistries including liver and renal function tests (ALT, AST, creatine kinase, BUN)
- Hematologic analysis (CBC and differential)
- Injection site histopathology
- Terminal procedures (necropsy, organ description, weights, histopathology on tissue including evaluation of immune organs)

Preclinical Safety Study: Effects on the Immune System

- Characterization of the immune response
  - Changes in immune parameters are expected
  - Parameters to be evaluated include white blood cell count, bone marrow, lymphoid tissue histopathological examination
  - Tiered testing approach
    - In some cases specific immune investigations may be necessary
    - Hypersensitivity reactions

Adjuvanted Vaccines

- Demonstrate adjuvant effect in non-clinical immunogenicity study
- Evaluate relevant vaccine/adjuvant formulations in preclinical safety studies:
  - Vaccine product with and without adjuvant in preclinical studies
  - Antigen/adjuvant formulation intended for clinical use
- If novel adjuvant, safety assessment program for adjuvant may be developed

Nonclinical Safety Studies for TB Vaccines: Goals

- To further demonstrate the safety, purity and potency of a vaccine
- Assess potential safety concerns that may have arisen during clinical development, e.g., clinical trials, changes in product manufacture, etc.
- Assess potential safety concerns derived from what is known about the disease, other TB vaccines, patient population
- Safety/toxicity evaluation in appropriate animal models

Animal Models: Challenges

- **A species that develops an immune response after vaccination, such as antibodies**

  …*however*, mechanisms underlying the control of *M. tuberculosis* infection not fully understood

  CMI critical to define "relevant species"

- **Ideally, species should be sensitive to the pathogenic organism or toxin (challenge)**

  …*however*, animal models, e.g. mouse, guinea pig & rabbits have different sensitivities to TB infections

- **One relevant animal species in general sufficient**

  ***…however*, data suggest that certain animal species respond differently to specific *M. tuberculosis* antigens suggesting that for some vaccine testing in multiple animal models may be required**

Administrative Procedures

- Discuss pre/nonclinical evaluation program with CBER prior to or during pre-IND meeting
  - Provide adequate information on product manufacture and clinical plan
- Submit toxicity protocols supporting Phase 1 clinical trials for CBER review prior to initiation of animal studies
- Submit toxicity study report to original IND
- Discuss with CBER early in product development the need for additional safety assessment to address specific safety concerns

Summary

- Preclinical safety study may be needed to support proceeding to Phase 1 clinical trials
  - Case-by-case approach
  - Includes safety evaluation of adjuvant
- Pre/Nonclinical testing strategies depend on particular TB vaccine and target population
  - Approaches to pre/nonclinical toxicity assessment for TB vaccines are evolving.
  - Discussions needed to reach consensus on non-clinical testing strategies and animal models to address the safety of TB vaccine candidates for specific target populations