PREPARING FOR HIV VACCINE LICENSURE: US PERSPECTIVE

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Workshop on Vaccine–induced seropositivity
(VISP/VISR)
March 13-14 2013
Correlate(s) of protection not fully established (humans and animals)

Animal model limitations

Genetic/immunologic diversity of pathogen

Vaccines must induce durable immunity

Safety issues (real and perceived)

Clinical development for diverse populations
STAGES OF REVIEW AND REGULATION

Clinical Investigational Plan

Phase 1
Safety Immuno-genicity

Phase 2
Immuno-genicity
Safety
Dose
Ranging

Phase 3
Efficacy
Safety
Immuno-genicity

IND

Phase 4
New population (pediatrics)
Accelerated to Traditional approval
Safety
Efficacy

BLA
Data to support approval; Inspection

BLA Supplement
Post-approval Changes:
New Indications
Dosing
Manufacture
Equip./Facilities

IND = Investigational New Drug Application; BLA = Biologics License Application
PHASE 2 CLINICAL TRIALS

- Safety and immunogenicity
- Up to several hundred subjects per trial
- Often randomized & controlled
- Likely to include subjects at high risk for infection: some breakthrough infections expected in the face of VISP

Vaccine-elicited immune responses:
- Humoral vs. Cellular; *Longevity*
  - Algorithm to rapidly confirm infection during the trial must be in place.
  - Vaccine specific?
EXPANDED PHASE IIb CLINICAL TRIALS: Desired Outcomes (proof-of-concept)

- Confirmative data for vaccine dose (vector, antigens, adjuvant), and formulations
- Obtain safety and immunogenicity data using the candidate vaccine in the target populations in which efficacy trials will be performed (at risk)
- Double-blind, placebo controlled, predicted to observe infections in the control group.
- Up to thousands participants
- Early evidence of vaccine activity (or even efficacy) against one or more HIV clades: Possible information on correlates of protection
- Results should be used for designing pivotal efficacy trials with verifiable primary end points
- VISP must be dealt with in order to identify breakthrough infections in a timely manner. Change or validate algorithm
FDA DISCUSSION
PRIOR TO VACCINE EFFICACY TRIAL

- Updated epidemiological data for HIV transmissions (incidence, endemic strains) for the intended target populations.

- Supporting safety & immunogenicity data (from Phase II & IIb trials):
  - predicted VISP frequency: in which type of diagnostics? How to distinguish from true infections?

- Pilot evaluation of efficacy endpoints
  - Statistical plan

- Plans for post licensure phase IV trials to collect long term clinical end points.
POSSIBLE CRITERIA TO MOVE VACCINES INTO EFFICACY TRIALS

Without *a priori* knowledge about correlates of protection against HIV-1 infection or disease progression:

- Levels of “relevant” immune responses could be used as criteria
- Clinically relevant surrogate end-point criteria are desirable
POSSIBLE IMMUNOLOGICAL CRITERIA TO MOVE VACCINES INTO EFFICACY TRIALS

Humoral responses:

 ✓ Breadth of neutralization using relevant panels of primary isolates from the intended geographical region.
 ✓ Higher Neut. titers than those observed during early seroconversion
 ✓ Sustained titers and/or rapid anamnestic responses post exposure
POSSIBLE CRITERIA TO MOVE VACCINES INTO EFFICACY TRIALS

Cytotoxic T cell responses:

- Breadth of epitopes recognized in multiple HIV genes (present in isolates from the intended geographical region?)

- Functional robustness (multiple cytokines, high CTL activity). Level of responses should be similar to Long Term Non Progressors (LTNP)

- Evidence of Sustained “central memory” and rapid anamnestic responses post exposure
In preparation for Phase III HIV Vaccine Trials: Validated assays for virologic, clinical, and immunological end-points should be in place

- Assays to detect vaccine-elicited responses
- Vaccine product potency assays (for lot release and stability)
- Statistical plans based on several possible trial outcomes and verified end-points
- Assays to identify HIV infections in vaccine recipients (licensed);
  - Anticipated %VISP; Differential diagnostics?
- Sensitive viral load assays
- Patient’s consent forms: anticipated adverse reactions including long term VISP
DEFINING EFFICACY: POTENTIAL INDICATIONS FOR LICENSURE

- Protection from infection (strong)
- Prevention of disease (strong)
- Control viral loads and delay of ART (soft)
- Reduced transmission (soft)
PHASE III CLINICAL EVALUATION

- Confounders of Pivotal Studies
  - Sub-populations
  - Unanticipated drops in infection rates
  - Higher than expected rates of withdrawals and loss to follow up
  - True clinical benefit may require long follow up
  - Uncommon / Rare adverse events
  - Post marketing surveillance essential

- Phase IV studies likely to be needed for all prophylactic HIV vaccines
Licensed vaccine: *Product Insert*

- HIGHLIGHTS OF PRESCRIBING INFORMATION
- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS

- WARNINGS AND PRECAUTIONS
  - *Adverse reactions during/post vaccination*
  - *Vaccine associated AE; HIV infections; VISP*
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Dose
Ranging

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Immunogenicity

BLA
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Efficacy

Post approval Commitments
Safety
Infections
VISP

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Additional post-licensure safety authority

The FDA Amendments Act of 2007 (FDAAA 2007) gives CBER authority to:

- Require postmarketing studies and clinical trials
- Require sponsors to make safety related labeling changes
- Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)

Who is responsible?
- Vaccine manufacturer / sponsor
- Local health authorities
Post-marketing Studies

- Additional information about a product’s safety, efficacy, or optimal use
- Conducted after FDA has approved a product for marketing
- Required of versus Agreed to by a sponsor
- Described in the approval letter
- Much longer duration compared with Phase III or Phase IV studies
- Much larger number of vaccinees, expanded populations, geographical areas
How to deal with VISP before and after licensure?

- Breakthrough infections in the face of VISP are expected from Phase II – Phase IV
- The algorithm for confirmation of true infections is likely to change during product development
- Tests to differentiate VISP from true infections are essential and could be developed in parallel with product development:
  - Site of testing
  - Role for licensed vs. not licensed tests
  - Platform: Serological (vaccine specific), nucleic acid (PCR), other
- Post marketing: HIV Diagnostics may differ from those used during pre-licensure studies (cost, simplicity, point-of-care). VISP needs to be addressed