Regulatory Considerations for Determining Vaccine Efficacy

U.S. FDA Perspective

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Panel Discussion Points:

- Should regulators and public health authorities take into account high baseline incidence of disease when evaluating “modest % efficacy” vaccines?

- What are some considerations for defining an acceptable threshold of protection from both regulatory and policy perspectives?

Guidance for Industry: General Principles for the Development of Vaccines against Global Infectious Diseases (2008)

- Focus on development of vaccines targeted against infectious diseases or conditions endemic in areas outside the US
- Provides general recommendations for regulatory pathways in the development of vaccines against global infectious diseases
  - FDA can license vaccines to protect against infectious diseases or conditions not endemic in the US
- The regulations are the same as for vaccines licensed for use in the US
- Clinical data from trials conducted outside the US can be used in support of US licensure
- Principles are supported by legislation
  - Food & Drug Administration Amendment Act [FDAAA] 2007, Addition of Section 524 to the FD&C Act)
  - Importance of having products to treat and prevent tropical diseases that disproportionally affect poor and marginalized populations and for which there is no significant market in developed nations

  - http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074762.htm

Examples of Vaccine Candidates against Global Infectious Diseases: Vaccine Efficacy

- HIV-1 vaccine candidate (ALVAC/AIDSVAX)
  - Randomized multi-center, double blind, placebo-contr., prime/boost trial in >16, 000 subjects 18-38 yrs. in Thailand
  - ITT: VE 26.4% (95% CI - 4.0, 47.9)
  - PP : VE 26.2% (95% CI - 13.3, 51.9)
    - *N. Engl. J. Med. 2009; 361:2209-20*
- Malaria vaccine candidate (RTS,S/AS01)
  - Randomized contr. double-blind trial in children 5 to 17 months of age in 7 African countries (incidence of first episodes of clinical malaria in the first 6,000 children)
  - ITT: VE 50.4% (95% CI 45.8, 54.6)
  - PP: VE 55.8% (97.5 CI 50.6, 60.4)
    - *N. Engl. J. Med. 2011; 365:1863-75*
- Dengue vaccine candidate (CYD-TDV), recombinant, live attenuated, tetravalent chimeric vaccine
  - Randomized controlled phase 2b trial in 4000 children 4-11 yrs. of age in Thailand
  - VE: 30.2% (95% CI -13.4, 56.5)
  - VE was serotype dependent
    - *Lancet 2012; 380:1559-67*

Applicable Law

- 351 of the Public Health Service Act
  - Data must show that the product is safe, pure and potent
    - Potency has been interpreted to include efficacy

- No statutory or regulatory requirement to demonstrate a specific level of vaccine efficacy or threshold of protection

Regulatory Consideration for Determining Vaccine Efficacy (VE)

Considerations affecting threshold or criteria for acceptable VE

- Incidence & severity of disease/condition being prevented
- Target population
- Availability of other therapies or control measures
  - Safety and effectiveness of alternative available therapy
- Safety profile of the candidate vaccine
  - e.g., frequency, severity and sequelae of adverse events

Factors affecting observed VE

- Trial design and size
- Endpoints
- Clinical case definition
  - Specificity of diagnostic methods employed

Regulatory Consideration for Determining Vaccine Efficacy (cont.)

Desire for high specificity of case definition

- Low specificity dilutes VE estimates
  - (*see Lachenbruch PA, 1998, Controlled Clinical Trials 19:569*)
  - Vaccine efficacy estimates derived from vaccine trials depend on case definition
  - Described in labeling
    - e.g., rotavirus vaccine (Rotateq)
    - Case definition: Gastroenteritis caused by serotypes contained in the vaccine
      - VE: against any grade of severity: 74% (66.8, 79.9%) in ITT and 60% (51.5, 67.1) in PP
      - VE against severe gastroenteritis: 98% (88.3, 100.0) in ITT and 96.4% (86.2, 99.6) in PP

How much better than placebo?

- Addressed by a confidence interval (e.g. 95% CI on VE)
- LB of the CI should be acceptably better than 0

Regulatory Consideration for Determining Vaccine Efficacy (cont.)

Licensure of vaccine with "modest % efficacy" (e.g., 20-60%) may present challenges for the development of second generation vaccines for the same indication, e.g.,

- Ethical challenges to conduct placebo-controlled trials
- Evaluation of 2nd generation vaccine relative to first vaccine licensed
  - Superiority trials (new vaccine better by a pre-defined clinically acceptable margin)
    - Specifying superiority margins that are too wide: classifying superior vaccines as non superior
  - Non-inferiority trial (new vaccine stays within a pre-defined acceptable margin)
    - Specifying margins that are too wide: classifying inferior vaccines as non inferior
    - Specifying margins that are too narrow potential for rejecting the new vaccine that may provide clinical benefit

Regulatory Consideration for Determining Vaccine Efficacy (cont.)

Considerations for vaccine efficacy trials

- Reliance on a single adequate and well controlled efficacy study to support approval in cases where
  - Well-designed multicenter study provided reliable and statistically strong evidence of a meaningful clinical benefit (e.g., effect on severe disease, significant morbidity)
  - Single trial sufficient to demonstrate VE **IF** VE acceptably high based on LB of the CI
- More than one study may be necessary to substantiate findings
  - e.g., especially if LB close to 0 (greater likelihood of a Type 1 error)

Regulatory Consideration for Determining Vaccine Efficacy: Summary

- No regulatory requirement for a specific VE threshold or particular endpoint, regulatory acceptance of "modest efficacy" would depend on
  - Pre-specification of endpoints and VE criteria
  - Confidence interval around the VE point estimate (esp. lower bound)
  - Severity & incidence of disease to be prevented
  - Safety profile of the candidate vaccine
  - Available alternative therapy or control measures
- Possible epidemiological modeling that suggests what "modest" levels of VE could impact public health
- Public consultation with advisory bodies
  - e.g., at planning stage for defining clinical endpoints and VE criteria
  - e.g., during review of Biologic License Application to discuss safety and efficacy data
- Approved use reflects population for which there is substantial evidence of efficacy