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?

- 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 disproportionately affect poor and marginalized populations and for which there is no significant market in developed nations

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)

- **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)

- **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
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
RegulatoryConsiderationforDeterminingVaccineEfficacy(cont.)

Licensureofvaccinewith“modest%efficacy”(e.g.,20-60%)maypresentchallengesforthedevelopmentofsecondgenerationvaccinesforthesameindication,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 \textbf{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