Beyond Efficacy: The Full Public Health Impact of Vaccines in Addition to Efficacy Measures in Trials

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A USA PERSPECIVE ON REGULATORY REQUIRMENTS FOR VACCINE EFFICACY

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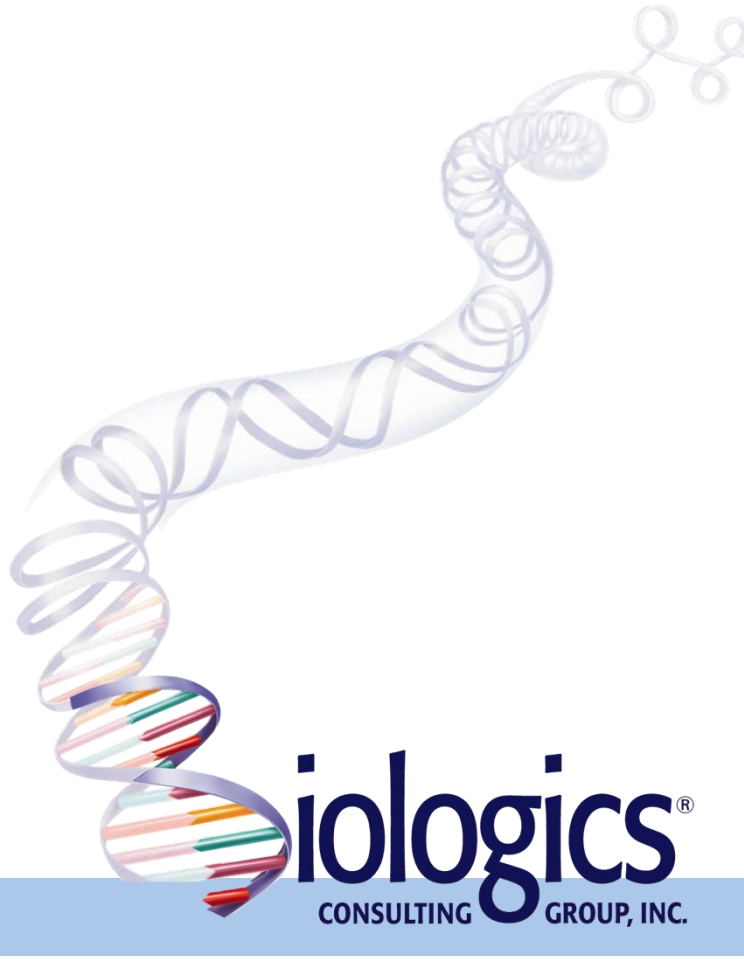

Disclosure

I am responsible for the oversight and management of Biologics Consulting Group Inc., which provides advise to the regulated industry, government and non-government organizations on matters related to the development, evaluation and marketing authorization of human medical products, including vaccines.

Presentation Outline

- Legislative history of safety and efficacy
- Regulatory considerations for vaccine efficacy
  - advantages and disadvantages
- Use of serological assays to evaluate vaccine effectiveness
  - Meningococcal and Pneumococcal Conjugate vaccines
- Expedited regulatory pathways to licensure
- Summary
- Conclusion

Introduction: Legislation

The Food, Drug and Cosmetic Act of 1938

- Required premarket notification.
- ***Required a demonstration of safety for approval***.
- Basis of refusal:
  - (a) did not include ALL tests reasonably applicable to show whether drug is safe when used under proposed labeling
  - (b) testing shows drug unsafe or do not show that it is safe
  - (c) information submitted or any other information available are insufficient to determine whether safe
  - (d) labeling is false or misleading in any particular

Introduction: Legislation

Keyfauver Harris Amendments 1962

- Required FDA to actively grant approval before a drug could be marketed.

- Requirement to study drugs under an Investigational New Drug Application (IND); informed consent

- ***Effectiveness requirement: Substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use.***

Biologics (Vaccines)

- In 1972, FDA review of the safety and effectiveness of all previously licensed biologics.
- FDA required ***proof of effectiveness*** consisting of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)).
  - e.g., serological response data where a previously accepted correlation with clinical effectiveness exists.
- ***No statutory or regulatory requirement to demonstrate a specific level of vaccine efficacy or threshold of protection.***

Biologics (Vaccines)

- Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, ***licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).***

Vaccine Efficacy: Regulatory Perspective

- The ability of a vaccine to bring about the intended beneficial effects on vaccinated individuals in a defined population under ideal conditions of use.
- Regulatory authorities evaluate the potential *benefits of an effective vaccine, against the potential risk of adverse events* following immunization with a vaccine.
- The highest standard for demonstrating efficacy of a vaccine is a *prospective, randomized, blinded, well-controlled study*.
- The absolute protective efficacy of a vaccine is usually defined as the reduction in the chance of developing the disease after vaccination relative to the chance when unvaccinated as determined in a prospective randomized controlled study.

Vaccine Efficacy: Advantages and Disadvantage

- Advantages: rigorous control for biases afforded by randomization, as well as prospective, active monitoring for disease attack rates and careful tracking of vaccination status
  - often there is, at least for a subset of the study population, laboratory confirmation of the infectious outcome of interest and a sampling of vaccine immunogenicity

- Disadvantages: complexity and expense of performing trial, especially for relatively uncommon infectious outcomes for which the sample size required is driven upwards to achieve clinically useful statistical power

Regulatory Acceptance of Moderate Efficacy

- The US FDA has not defined a specific threshold for vaccine efficacy or a particular endpoint; however, regulatory acceptance of moderate efficacy depends on a number of considerations

Regulatory Consideration for Determining Vaccine Efficacy (VE)

- Considerations affecting threshold or criteria for acceptable VE
  - Incidence and 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

Regulatory Consideration for Determining Vaccine Efficacy (VE)

- Factors affecting observed VE
  - Trial design and size
  - Endpoints
  - Clinical case definition
  - Specificity of diagnostic methods employed

Regulatory Consideration for Determining Vaccine Efficacy

- 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

Regulatory Consideration for Determining Vaccine Efficacy (cont'd)

- Evaluation of second 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 remains 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

Vaccine Efficacy

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

Correlate of Protection

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

Using data from serologic assays to evaluate vaccine effectiveness

- Meningococcal Conjugate Vaccines
  - Anti-polysaccharide IgG antibody assay
  - Serum bactericidal activity (SBA) assay
  - Meningococcal anti-PS antibody measured by ELISA does not always correlate with functional antibody measured by complement-mediated SBA

U.S. Licensed Meningococcal Vaccines

Menomune 1981 (>2 yo). (A, C, Y, W-135) PS vaccine, licensed based on efficacy data for A and C only. Not enough disease in W-135 and Y. W-135 and Y were based on 4 fold rise of SBA in 90% of vaccinees.

Menactra - Quadravalent (A, C, Y, W-135) PS *conjugate*

- 2005: 11-55 yo
  - 4-fold rise rSBA non-inferiority to Menomune
- 2007: 2-10 yo
  - % ≥ 1:8 hSBA non-inferiority to Menomune
- 2011, 9-23mo
  - % ≥ 1:8 hSBA (no comparator)

Menveo - Quadravalent (A, C, Y, W-135) PS *conjugate*

- 2010: 11-55 yo
  - % ≥ 1:8 hSBA non-inferiority to Menactra
- 2011: 2-10 yo
  - % ≥ 1:8 hSBA non-inferiority to Menactra

MenHibrix – (C and Y) and Hib Conjugate Vaccine

- 2012: 6 wks – 18 mo
  - % ≥ 1:8 hSBA (no comparator);
  - Hib: non-inferiority to US-licensed monovalent Hib

Using data from serologic assays to evaluate vaccine effectiveness

- Pneumococcal Conjugate Vaccines
  - ELISA – Serotype specific IgG
    - Infants
      - IgG antibody levels are associated with protection from invasive pneumococcal disease
      - Good correlation between IgG and pediatric serum OPA titers
    - Older children and adults
      - Not considered to be an appropriate endpoint.
  - Opsonophagocytic Antibody (OPA) Assay
    - OPA measures functional antibodies which play a critical role in protection against pneumococcus; directed at capsular antigens

US Licensed Pneumococcal Vaccines

Pneumovax 23 (1983**)** Multivalent (23) polysaccharide vaccine.

- 50 years of age or older, and persons aged ≥2 years who are at increased risk for pneumococcal disease.
- Efficacy of PS vaccines evaluated in several clinical trials

Prevnar - 7 valent polysaccharide *conjugate* vaccine

- Clinical endpoint efficacy trials:
  - 2000: infants and toddlers against invasive disease caused by *S. pneumoniae* vaccine serotypes
  - 2002: infants and toddlers against otitis media caused by *S. pneumoniae* vaccine serotypes
- VRBPAC 2001 - advised that for new pneumococcal vaccines effectiveness could be inferred from non-inferiority studies using ELISA to measure GMT. Immunologic endpoint trial.

US Licensed Pneumococcal Vaccines (con't)*

Prevnar 13 – 13 valent polysaccharide conjugate vaccine

- **2010**: Licensed in 6 weeks through 5 years of age
  - Prevention of invasive disease caused by *S. pneumoniae vaccine specific* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F)
  - Prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F
  - The efficacy was inferred from comparisons to Prevnar 7 using IgG (ELISA) to measured the production of vaccine type (VT) functional antibody
- **VRBPAC 2005** – emphasized the need for clinical endpoint studies while acknowledging challenges, accelerated approval reasonable path
- **VRBPAC 2011**
  - IgG does not correlate with functional antibody for older children and adults. Therefore, IgG measurement was not considered to be an appropriate endpoint in these age groups. OPA - used as the "surrogate endpoint that is reasonably likely… to predict clinical benefit" of Prevnar 13 in adults
- **2012**: Licensed for ≥ 50 years of age for active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F *using the OPA as a surrogate endpoint (confirmatory trial)*

**Slide from C. Fiore (FDA/CBER/OVRR)*

Meningococcal Protein Vaccines for Serogroup B*

- No US licensed vaccine available at the time
- Broad range of endemic serogroup B isolates, *i.e.*, many antigenically diverse strains
- Experimental and epidemiologic data support complement-mediated bactericidal activity as the predominant mechanism of human protection from invasive meningococcal disease
- Performing hSBA assays against all disease causing strains is not possible. Therefore methods to assess how hSBA measured against a subset of strains can predict protection against other strains are being investigated

**Slide from C. Fiore (FDA/CBER/OVRR)*

US FDA Expedited Regulatory Pathways

- Fast Track: Program designation
  - Pneumococcal Vaccine,
  - HPV Vaccine
- Breakthrough Therapy: Program designation
  - Meninge B Vaccine
- Priority Review: Program designation
- Accelerated Approval: Approval pathway
  - Influenza vaccines
- Emergency Use Authorization: Approval Pathway

Fast Track Program

- Drug intended to treat a serious condition, and nonclinical or clinical data demonstrate the potential to address an unmet medical need or a product designated as a qualifying infectious disease product

- Actions to expedite development and review; rolling review

Breakthrough Therapy

- Drug intended to treat a serious condition and *preliminary* clinical evidence indicating the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over existing therapies

- Intensive guidance on efficient drug development; FDA organizational commitment; rolling review

Priority Review

- An application or efficacy supplement for a drug that treats a serious condition and if approved would provide a significant improvement in safety or effectiveness

- Shorter review clock (6 month review time versus 10 months for standard review

Accelerated Approval

- A drug that treats a serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit

- Approval based on an effect on a surrogate endpoint or intermediate clinical endpoint

Examples of Vaccine Labeling under Accelerated Approval

- Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. *The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.*

Emergency Use Authorization

- Authorization of the use of an unapproved product or the unapproved use of an approved product when an emergency or a potential emergency exists

- Allows introduction of drug, device or biological into interstate commerce by the Sec. of DHHS for use in an actual or potential emergency

Summary

- There is no regulatory requirement for “efficacy”; vaccines must be demonstrated to be safe and effective
- The FDA has no statutory regulatory requirement for sponsors to demonstrate a specific level of vaccine efficacy or threshold
- Licensure of vaccines with modest efficacy (e.g., 20-60%) may present challenges
- Vaccines can be licensed on the basis of immune response when correlate of protection is known
- Data from validated serological assays have been used to evaluate vaccines for licensure based on effectiveness
- Expedited regulatory pathways are available for vaccines meeting an unmet medical need.

Conclusion

- From the regulator's perspective as new vaccines are considered for licensure, two basic questions must be answered:
  - **How well does the candidate vaccine prevent the disease for which it is developed?**
  - **And is it Safe?**

THANK YOU!

BACK-UP SLIDES

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 controlled 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

**Slide Source: M. Gruber (FDA/CBER/OVRR)*

Priority Review Voucher

- The Tropical Disease Priority Review program provides for a voucher that is awarded at the time of approval of certain drugs that prevent or treat a tropical disease that subsequently can be redeemed for a priority review of an application for a drug for any indication submitted at a later time
- The PRV is intended to reduce two types of inefficiency:
  - accelerate approval of potential blockbuster therapies in the US, getting US patients access to these treatments more quickly.
  - motivates more treatments for neglected diseases.
- The PRV holder must pay the FDA an additional user fee ($2,562,000 in fiscal year 2015).
- The PRV is transferrable
- In the seven years existence of the voucher system no vouchers have yet been sold, and only one has been used (unsuccessfully).