

Emerging Strategies to address Antimicrobial Resistance – Should Vaccines play a role in combating antimicrobial resistance (AMR)? The Regulatory Perspective

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Vaccines may affect antimicrobial resistance by:

- Providing immunity against infectious agents that may develop resistance/are resistant to antimicrobial therapy
- Preventing disease conditions that are frequently treated with antibiotics and may contribute to the development of AR in other organisms (e.g.: otitis media, viral respiratory disease)
 - However, usually not specifically developed against a particular AMR strain(s) of a pathogen

FDA's Pre-licensure Expedited Programs for Serious Conditions

- Designation of drug as FAST TRACK product

(Sec 506(b) FD&C Act, added FDAMA of 1997, amended FDASIA 2012)

- Treatment of serious or life threatening disease or condition AND *nonclinical or clinical data* demonstrate the potential to address unmet medical need
- Provides opportunities for frequent interactions with review team

- Breakthrough Therapies (BT)

(Sec 506(a) FD&C Act, added FDASIA 2012)

- Treatment of serious or life threatening disease or condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies
- Sponsor may request a designation as a breakthrough therapy concurrently with, or any time after, submission of an IND
- FDA makes a determination whether such designation will be granted within 60 days of the request
- Benefit is increased interaction with FDA to expedite the development and review of the application

- Difference between BT and Fast Track

- BT designation not contingent on the *potential* to treat an unmet medical need, but requires *evidence* of substantial improvement over current treatments
- Designations are not mutually exclusive

Licensure Pathways

- “Traditional” Approval
- Accelerated Approval
- [“Animal Rule”]

- Priority review designation
 - Prescription Drug user Fee Act of 1992

Demonstration of clinical safety required for all pathways

Demonstration of effectiveness required for all pathways; differences in approach among pathways

Accelerated Approval and Animal Rule-- specific “eligibility” criteria and associated requirements

“Traditional” Approval

Pre-licensure clinical studies provide evidence of effectiveness based on:

- Protection against clinical disease
- Immunologic response, in some cases
 - scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
 - facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease

Examples of Traditional Approval: Pevnar 7 and Pevnar 13

- Pevnar 7
 - Efficacy against invasive pneumococcal disease (IPD) based on randomized double-blind clinical endpoint efficacy study (endpoint: prevention of invasive pneumococcal disease due vaccine serotypes)
 - Priority review application
 - Efficacy against otitis media based on randomized double-blind clinical endpoint efficacy trials (endpoint: prevention of OM due to *S. pneumoniae* serotypes contained in the vaccine)
- Pevnar 13:
 - Effectiveness against IPD inferred from NI comparative studies to Pevnar 7
 - Pevnar 13 elicited anti-polysaccharide binding and functional opsonophagocytic (OPA) antibodies, as measured by ELISA and OPA assays, respectively
 - Pevnar 13 for infant indication granted fast track

Accelerated Approval (21 CFR 601.41)

- For a serious or life threatening disease or condition AND generally provides meaningful advantage over available therapies AND
 - Demonstrates an effect on *a surrogate endpoint that is reasonably likely to predict clinical benefit* OR
 - On a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit
 - Requirement to confirm clinical benefit post approval
- Difference Accelerated approval vs Breakthrough therapy:
 - Breakthrough Therapy designation is focused on expediting the review and approval process, rather than relying on endpoints that may be reasonably likely to predict clinical benefit as the basis for approval

FDASIA (Sec 901) Enhancement of accelerated patient access to new medical treatments

- FDASIA (901(b)) provides that
 - Evidence to support that an endpoint is reasonably likely to predict clinical benefit to include “... epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.” FDA should take into account “...the severity, rarity, or prevalence of the condition...” in considering whether to grant accelerated approval
- FDASIA
 - Expands the scope of available endpoints that can be used to demonstrate a product qualifies for accelerated approval.
 - Reinforces regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options
 - Facilitates somewhat broader use of accelerated approval

Expedited Programs for Serious Conditions

- Prevnar 13
 - Granted Accelerated Approval [21 CFR 601.41]:
 - Granted priority review
 - Prevnar 13: active immunization for prevention of pneumococcal disease in adults 50 years of age and older caused by vaccine serotypes
 - “meaningful therapeutic benefit” for protection against *pneumococcal pneumonia* or pneumococcal pneumonia combined with IPD
 - “Surrogate endpoint”: opsonophagocytic antibodies
- Trumenba & Bexsero (Meningococcal group B vaccines)
 - Designated Breakthrough Therapy & granted Accelerated Approval
 - Granted priority review
 - “Surrogate endpoint”: serum bactericidal antibody levels induced by the vaccine, as measured by serum bactericidal activity assays
 - Confirmatory studies: breadth of coverage of vaccines against diverse meningococcal group B strains that represent a range of genetically diverse menB variants in the US.

Summary

- Pre-licensure expedited programs are available for regulatory review of vaccine products
 - FDA has used expedited programs such as Breakthrough therapy for vaccines meeting the requirements
- Licensure pathways are available that facilitate earlier access of vaccines to the end user
 - FDA has used accelerated approval provisions for vaccines meeting the requirements in order to provide earlier access to these products
 - Priority review timelines applied
- FDASIA 2012 expands the scope of endpoints used for accelerated approval and reinforces regulatory flexibility regarding evidence required to support product approval for serious or life threatening disease or conditions