Botulism
Medical Countermeasures

Biomedical Advanced Research and Development Authority (BARDA)

Melissa Willis, Ph.D.
Project Officer, Antitoxins/Therapeutics
HHS/ASPR/BARDA
Roadmap

• Botulism and the current state of vaccines and therapeutics
• Development of heptavalent botulinum antitoxin
• Licensure under the Animal Rule
• Future directions
• BARDA funding
Botulism

• Agent
  — Botulism caused by neurotoxins secreted by Clostridium botulinum

• Botulism clinical manifestations and timelines
  — Symptoms start 6 to 36 hours after exposure (eyes, mouth)
  — Paralysis progresses to limbs, death from paralysis of respiratory system

• Incidence
  — ~145 naturally occurring cases in the U.S. per year
Botulism Therapies and Vaccines

• Advanced Development
  – hBAT
    • Equine despeciated polyclonal antibody therapeutic
  – Bivalent vaccine against A/B
    • In development by DoD

• Licensed
  – BabyBIG
    • Human polyclonal antibody therapeutic against botulinum neurotoxin Serotypes A/B
    • Available through the California Department of Public Health
USG Strategy

• Establish requirements
  – BoNT Antitoxin - against serotypes A-G to treat symptomatic individuals.
  – A single heptavalent product
  – A combination of antitoxins that neutralize all serotypes
  – FDA approved, rapid, serotype-specific diagnostic

• Fulfillment of requirements
  – Acquisition of products via Project BioShield contracts
  – Development of products via Advanced Research and Development contracts
  – Review portfolio as requirements change

• Requirements are reviewed on a regular basis and do change over time.
USG Strategy

• Acquisition Strategy
  — Near term- fulfill requirements with technologies immediately available, acquisitions based on fit between technology and concept of operations (antibody-based antitoxins)
  — Mid-term- The ideal next generation product would be a fully human/human-compatible product that can be used for treatment. It would have an extended shelf life and should be stable at room temperature.
    • Diagnostic
  — Long term- A product which can inhibit both circulating and bound BoNT
    • Preferably a small molecule that has an extended shelf life, is stable a room temperature, and neutralizes multiple serotypes
Project BioShield

• Heptavalent botulism antitoxin (A-G)
• Cangene Corporation – 2003 CDC, 2006 BARDA
• Equine polyclonal antibody preparation against serotypes A-G neurotoxins
• Single use vials
• Intravenous administration
• Despeciated IgG
• Key Deliverables
  – 200,000 doses to SNS
  – BLA
Status of the hBAT Product

• Administered under CDC held IND
• Product has been shown to be safe in clinical studies
• hBAT has demonstrated efficacy in two treatment animal models
• As of March 13, 2010, hBAT became the only botulinum antitoxin available in the United States for naturally occurring non-infant botulism
• 70 people have been treated with hBAT (10 days – 82 years old) since 2008
Animal Rule Licensure

- Clinical trials with botulinum toxin are not feasible
- Safety demonstrated in humans
- Efficacy demonstrated in animal models
  - NOT “Two Animal Rule”
  - Small animal model for “statistical data”
  - Large animal model for bridging correlates or surrogates
  - Models must be accepted before pivotal studies possible
    - Model reflects the disease in humans
    - Treatment predicts human response
- Identify human dose
  - Evaluate repeat-dose safety
Lessons Learned from Animal Model Development

• A well characterized natural history study of the disease is critical.

• The disease progression in animals should correlate with disease progression in humans – identify the gaps early in animal model development.

• MCM requirement is for a treatment indication thus identification of an FDA approved trigger for treatment is essential.

• The development program is going to require a LOT of animals – IACUCs should know this ahead of time.
Future of Botulism Antitoxins

• Address gaps in the portfolio
• Human/human compatible product
• Small molecule antitoxins against multiple serotypes
• Special populations
• Administration and storage
  — Antitoxins administered as IVs – concept of operations
  — Improved formulation, alternate administration routes, storage without cold-chain
• Keep in mind TRL requirements: must have active IND and initiated clinical trial
Engaging BARDA in Your Development Plan

- **TechWatch** – request a meeting with program and regulatory staff at [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)

- **Broad Agency Announcements – Advanced Research and Development**
  - BAA open all-year round
  - Discuss with program and regulatory staff before submitting a proposal
  - Funding is typically for one year with multiple one-year options
  - Contracts are driven by well-designed development plans with go/no go milestones and decision points

- **Project BioShield**
  - Reserved for very late-stage products
  - Companies with licensed products with an interest in broadening label claims are highly encouraged to contact us
Interfacing with BARDA

• **www.phe.gov**
  – Program description, information, news, announcements

• **www.medicalcountermeasures.gov**
  – Portal to BARDA
  – Register, request a meeting
  – Tech Watch

• **www.fedbizopps.gov**
  – Official announcements and detailed information about all government contract solicitations