



United States Department of

Health & Human Services

Office of the Assistant Secretary for Preparedness and Response (ASPR)



Botulism

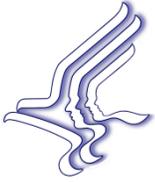
Medical Countermeasures

Biomedical Advanced Research and Development Authority (BARDA)

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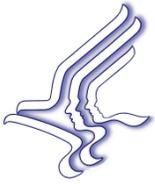
HHS/ASPR/BARDA



Roadmap



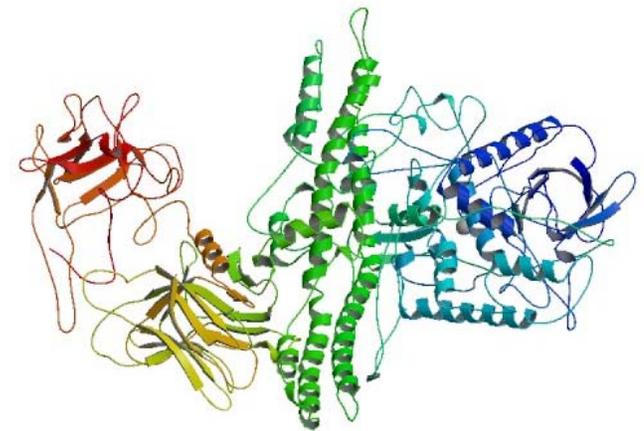
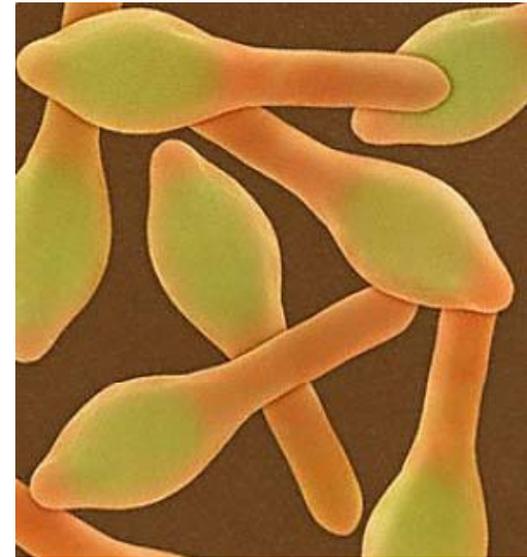
- **Botulism and the current state of vaccines and therapeutics**
- **Development of heptavalent botulinum antitoxin**
- **Licensure under the Animal Rule**
- **Future directions**
- **BARDA funding**

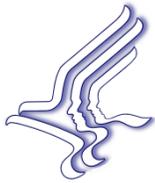


Botulism



- **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

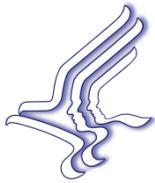
- In development by DoD

- **Licensed**

- BabyBIG

- Human polyclonal antibody therapeutic against botulinum neurotoxin Serotypes A/B
 - Available through the California Department of Public Health





USG Strategy

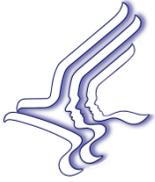
- **Establish requirements**

- 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.**

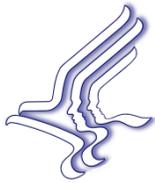


USG Strategy



- **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



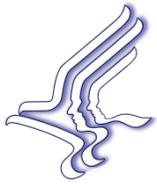
Project BioShield



- 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

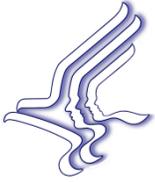
CANGENE





hBAT Immunization and Plasma Collection





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



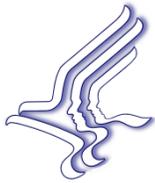
- **Clinical trials with botulinum toxin are not feasible**
- **Safety demonstrated in humans**
- **Efficacy demonstrated in animal models**
 - NOT “Two Animal Rule”
 - Small animal model for “statistical data”
 - Large animal model for bridging correlates or surrogates
 - Models must be accepted before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



Lessons Learned from Animal Model Development



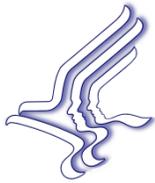
- A well characterized natural history study of the disease is critical.
- The disease progression in animals should correlate with disease progression in humans – identify the gaps early in animal model development
- MCM requirement is for a treatment indication thus identification of an FDA approved 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



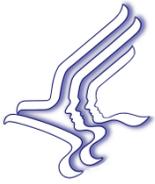
- **Address gaps in the portfolio**
- **Human/human compatible product**
- **Small molecule antitoxins against multiple serotypes**
- **Special populations**
- **Administration and storage**
 - Antitoxins administered as IVs – concept of operations
 - Improved formulation, alternate administration routes, 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
- **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

