



# United State Army Medical Material Development Activity (USAMMDA)

**Question to the Board: Utility of  
Pentavalent Botulinum Toxoid**

# Background



- Concerns of Human Subject Research Review Board (HSRRB), the Institutional Review Board of record for this Investigational New Drug (IND) contingency protocol, regarding the declining immunogenicity and potency testing for Pentavalent Botulinum Toxoid.
- FDA approval for use against serotype “A” only, under DoD IND #3732.
- CDC protocol IND#161 in place for laboratory workers and covers USAMRIID lab personnel

# Current DoD Strategies



- Current DoD strategies to counter this potential bioterrorist weapon include:
  - Pre-Exposure strategy
    - PBT IND 3732 (for A only)
    - rBotulinum Bivalent (A/B) in development – FY12
  - Post-Exposure strategy
    - DoD's He-BAT IND 10621
    - CDC products – Antitoxin, Aventis Pasteur BOT-AB, Antitoxin Type E, Antitoxin-Monovalent A, Antitoxin-Heptavalent A-G

# Pentavalent Botulinum Toxoid



- **The Product**

- Formalin-inactivated toxoid
- Potential protection against botulism caused by toxin serotypes A, B, C, D, and E
- Used in at-risk laboratory workers since 1959
- Potential protection 4 weeks after the initial 3 doses of the PBT (day 0, day 14, and 3 months)<sup>1</sup>
- Higher antitoxin titers after 12-month booster dose<sup>2</sup>

- **Manufacturing History**

- Two current lots PBP003 + PBP004
- Toxoids prepared in 1970+1971; some type A in 1984
- Monovalent adsorption to Alhydrogel in 1970+1971; some types A + E in 1990 + 1991
- Pentavalent Formulations in 1991 + 1992; plus reformulation 1995

- **Manufacturer**

- Michigan Dept of Public Health > Bioport Corp

# Stability Test Results



**Data Available from Original Test in 1993 until July 2005 (Lot PBP004 and May 2006 (Lot PBP003)**

**Chemical, Safety, and Sterility Assays:** Meets specification all time points

**Lot BPB003 Potency Tests:**

Mouse Neutralization Assay:

**Passed for Serotype A all time points;** Failed for Type B for Product stored in Germany failed in 2006; Failed for Type C since 2003; Failed for Type D since 2002; Failed for Type E in 1998 (passed in 1999 and failed thereafter)

Guinea Pig Challenge Assay

**Passed for Serotype A, B, and C all time points;** Failed for Type D since 2001; Failed for Type E in 1998 (passed in 1999 and 2003, and failed thereafter)

# Stability Test Results (cont)



## Lot BPB004 Potency Tests:

### Mouse Neutralization Assay:

**Passed for Serotype A all time points;** Failed for Type B since 1993; Failed for Type C since 2001; Failed for Type D since 2002; Failed for Type E in 2003 but passed in 2005.

### Guinea Pig Challenge Assay

**Passed for Serotype A, B, and C all time points;** Failed for Type D from 1999 to 2002, but passed in 2003 and 2005; Failed for Type E in 2002 and 2005 (passed in 2003).



## Animal Resistance to Challenge (PBT Lot PBP-003)

	<b>Per Cent Survival by Year</b>				
<b>Toxin serotype</b>	<b>1999</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004-5</b>
<b>A</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>
<b>B</b>	<b>91%</b>	<b>82%</b>	<b>73%</b>	<b>91%</b>	<b>100%</b>
<b>C</b>	<b>100%</b>	<b>82%</b>	<b>73%</b>	<b>100%</b>	<b>100%</b>
<b>D</b>	<b>64%</b>	<b>9%</b>	<b>18%</b>	<b>18%</b>	<b>27%</b>
<b>E</b>	<b>36%</b>	<b>27%</b>	<b>1%</b>	<b>55%</b>	<b>40%</b>

# New PBT Dosing (CDC)



- PBT doses at day 0, 14, 84, and 180 for primary series
- Booster at 360 days (1 year) and then yearly thereafter
- No titers
- No longer considered to offer potential protection as a pentavalent toxoid



- Potential protection against toxin serotype A
- PBT Lot PBP-003 passes potency tests to serotype B
- PBT still protective of 100% animals to serotype C

# Medical Considerations



- Takes six months to confer protective titers
- Lack of DoD vaccination plan or policy regarding the use of PBT to immunize the force
- Lack of available alternative therapies for the foreseeable future (FY13)

# Summary



- **Review of information provided**
- Current prophylactic treatment for botulinum toxin exposure is limited to Type A (possible efficacy against types B & C) – unmet need for Types B, C, D, E, F, & G
- New recombinant vaccines are years away and only address need for Type A and B.
- **Options we want the Board to consider**
- If the product has utility for FHP what population should have priority of use?



# BACK UP SLIDES