Vaccines and Biologics: Meeting Product Development Needs to Better Address Bioterrorism

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Presentation at the American Enterprise Institute

6/27/2002

Major Issues in Vaccine Development (for BT): I.

- Financial Disincentives
  - **Uncertainty of markets in many cases**
  - **Low prices generally paid for preventive measures**
    - **Applied to large populations, high up front costs (e.g. potential cost of universal vaccination) drive low unit costs**
    - **Well individuals/constituencies; do not see selves as ill, unwilling to pay high price as for intervention, risk averse**
    - **Hard to compete for resources within companies/industry**
  - **Complex products, lack of predictability of new entities, safety requirements/expectations**
  - **Need for expensive facilities, in-process controls**
  - **Need for large clinical trials if potential for wide use**
  - **Other factors: advocacy groups, mistrust of government & industry, product liability**

Major Issues in Vaccine Development for BT: II.

- Scientific Difficulties
  - **multiple possible approaches**
  - **few historical (or recent) precedents for BT agents**
  - **difficult to establish efficacy, immunological surrogates often unclear**
  - **potential for genetic variability/manipulation of antigenic determinants**
  - **large immunocompromised (and chronic disease) populations complicate live vaccine approaches**
- Urgent perceived needs (sometimes *disease du jour*) and often transient resources vs. long product development cycles

Approaches to Speed Product Availability or Licensure

- Early and frequent consultation between sponsor, end user (if different) and FDA
- Availability for emergency use under IND
- Fast track and accelerated approval processes
- Priority review
- Approval under “Animal Rule”
- Careful attention to risk:benefit and risk management issues
- Incentives (existing: orphan, new: push or pull)

Early and Frequent Consultation

- Improves communication process
- Improves quality of laboratory, clinical studies and manufacturing
- Reduces misunderstandings and likelihood of unwelcome “surprises”, multiple review cycles
- Improves efficiency of product development
- Very resource intensive for FDA
- Product teams at CBER being used for this purpose for priority BT product development and review (e.g. smallpox, anthrax vaccines)

Availability Under IND

- **Can allow rapid access to treatment with products which may fill an emergency need but not have completed requirements for licensure (312.34)**
  - Acceptable basic safety data to assure no unreasonable risk
  - Reasonable scientific basis (vs. proof) for efficacy
  - Likely risk:benefit ratio should be favorable
    - expect with relatively non-toxic product and life threatening or serious disease w/o satisfactory alternate treatment
  - Informed consent, IRB review, collection of safety/effectiveness data when used

Pros and Cons of IND Approach

- Pros
  - Clarity that a treatment is not a standard licensed therapy equivalent to routine prescription drugs
    - Efficacy may be untested, safety database may be limited
    - Empowerment of individual/legal protection
    - Respect for autonomy, government not forcing treatment
  - FDA trusted as arbiter of information and of process
- Cons
  - Potentially Cumbersome
    - Need to define and enumerate uses, populations, product issues
    - Difficult to consolidate multiple usages
  - Connotation of “Experimentation”
    - informed consent, IRBs,
    - complexity/length of forms etc.
    - difficult to deploy in emergency/in field

IND Approach: Making it Work

- Simplification, flexibility for CT/BT issues
  - "streamlined" or "emergency use" INDs
- Rapid turnaround/active assistance from FDA
- Clarity and language of consent process
  - Why it is "investigational", differentiation from research aimed at product approval, clear risk/benefit
  - Shortened documents, multiple media possible
- Potential for waivers of informed consent may be considered under 50.24
  - Life-threatening, no satisfactory avail. Rx., potential for direct benefit, data are needed to assess S&E, ***IC not feasible***, public disclosure/discussion etc.
- Work towards licensure, wherever feasible

Priority Review

- Product is a significant advance (drugs)
- For serious or life threatening illness (biologics)
- 6 month complete review of license application
- Recent example: pneumococcal conjugate vaccine

Fast Track/Accelerated Approval

- Serious or life-threatening illness and provide meaningful therapeutic benefit over existing Rx.
  - Allows for rolling submission of licensure materials
- Accel. approval: utilize likely surrogate endpoints for clinical benefit (314.510, Subpart H)
  - E.g. CD4 cells for treatment of HIV, known protective antibody level for vaccine or IG , clinical markers (BP)
  - Post-licensure studies required (usually ongoing) to demonstrate effects on disease outcomes
  - Restrictions on use possible, promotional controls
  - Potential problems with obtaining controlled data
  - Withdrawal if agreements violated or not S&E

Animal Rule

- Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances
- Expected to provide meaningful therapeutic benefit over existing therapies
- Human efficacy trials *not feasible or ethical*
- Use of animal efficacy data scientifically appropriate

Animal Rule II.

- Animal endpoint clearly related to desired benefit in humans
- Selection of an effective dose in humans
  - Kinetics, pharmacodynamics and/or other relevant data
- Still need human clinical data re: safety in population(s) representative of use
    - Civilian use often includes pregnancy, children
- Approval subject to post-marketing studies, any needed restrictions on use
- Potential limitations:
    - Where there is no valid animal model of disease
    - Confidence may be an issue, even in valid models

General Thoughts about Risk and Benefit for CT Products

- **Risk:benefit differs and is assessed by FDA for each product & potential use**
  - **Treatment**: For CT related products which have impact on otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty (but desirable to reduce)
  - **Prophylaxis**: If given to well individuals before event or, post-event, to individuals who may not be at risk, balance shifts
- **For lethal disease, *lack of efficacy is a safety issue***
  - Ill-placed confidence
  - Something is not always better than nothing
  - Acceptance of an ineffective therapy may inhibit development or use of a more effective one, potentially costing lives
- All such products:
  - **Need for honest and effective/efficient (*vs. legalistic*) risk communication process**, which may be quite challenging in unanticipated emergency settings

Regulation and BT Products: What is the value added?

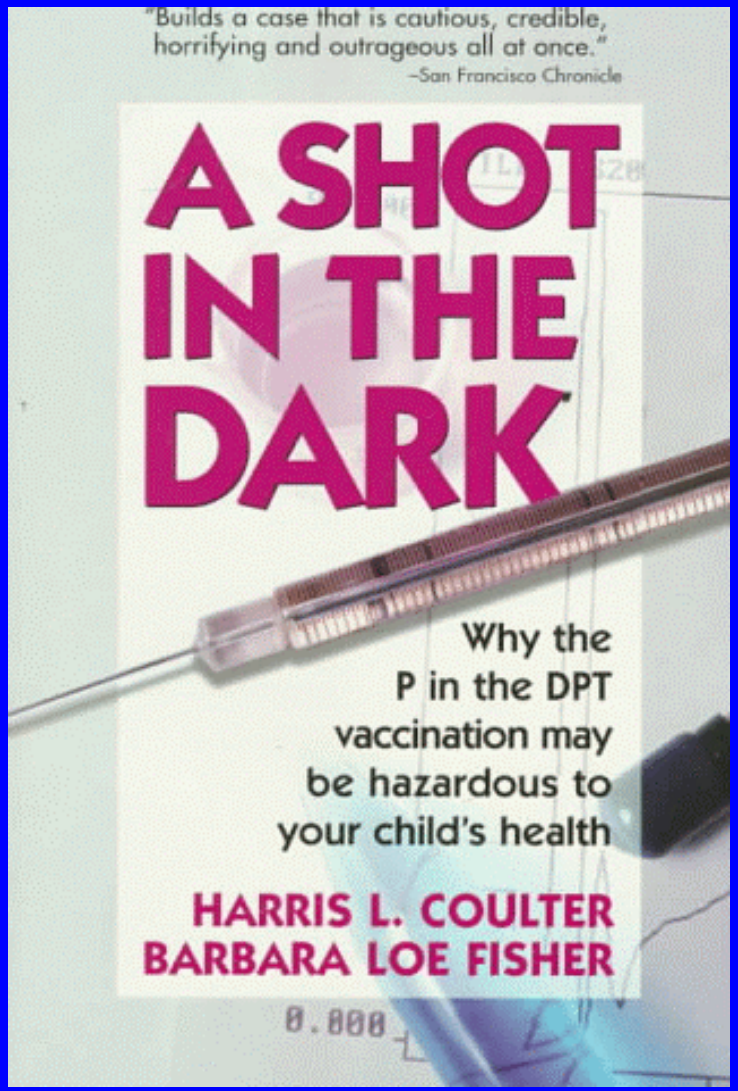
- As for other medical products (but perhaps even more important): need for consistent and objective protection of the public's safety ***and need for trust***
  - Heat of the moment(s): sense of emergency and national crisis;
    - dangers of decisions made in panic mode
  - Almost all parties (even sister agencies, academia) can become invested in product development and availability, financially and/or emotionally
  - Need to identify where speed and innovation do not compromise safety or effectiveness
  - When things go "wrong" (or even if someone just thinks they did), few will remember the crisis

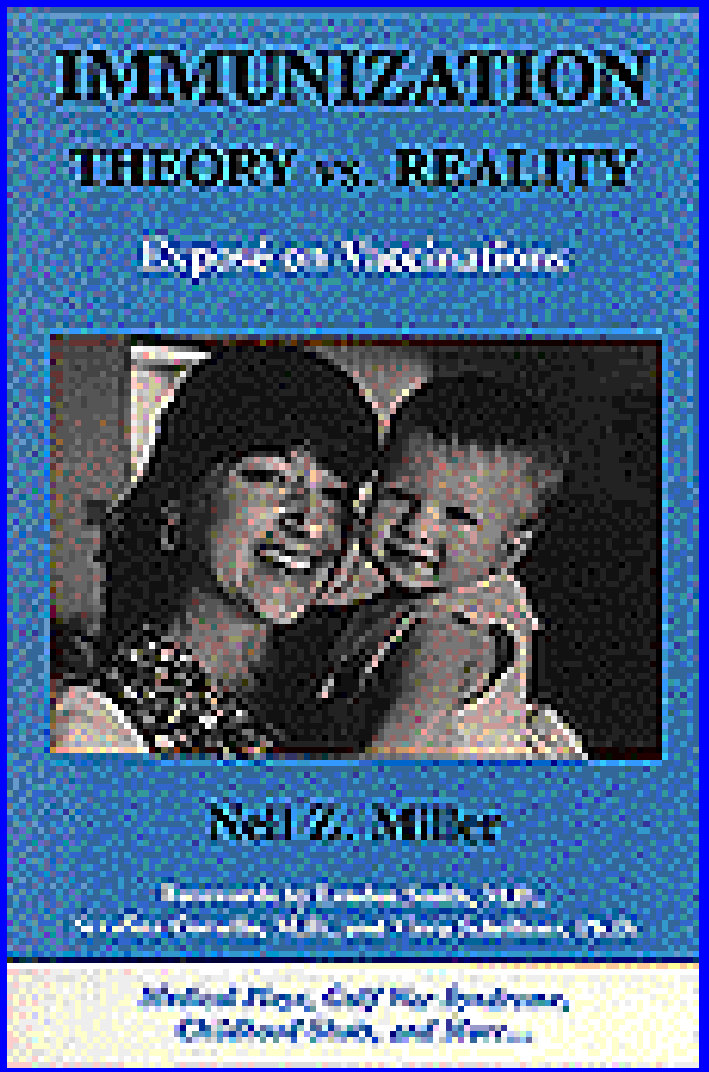

GO ON IN, IT'S SAFE!


SPECIAL INVESTIGATION
LIFE
The Tiny Victims of Desert Storm
Has Our Country ABANDONED THEM?

Why Regulate BT Products cont?

- BT is not one disease of predictable epidemiology
  - Recent examples from CBER:
    - AVA for anthrax, previously given to limited populations, raises important safety concerns if & when given to hundreds of thousands in the military or US population
    - Live SP vaccines, most safety experience from pre-HIV era
    - Environmental tests used to direct treatment decisions; sensitivity, specificity unknown or unsatisfactory
- The public expects safe (and effective) products, especially vaccines given to well individuals, and looks to FDA for protection.
- Preserving confidence in vaccination, in general, in other medical products, and in public health and government is critical in meeting ongoing threats.


"Builds a case that is cautious, credible, horrifying and outrageous all at once."
–San Francisco Chronicle
A SHOT IN THE DARK
Why the P in the DPT vaccination may be hazardous to your child's health
HARRIS L. COULTER
BARBARA LOE FISHER


IMMUNIZATION
THEORY vs. REALITY
Expose on Vaccinations
Neil Z. Miller

What FDA Cannot Do

- Provide monetary or tax incentives
- Assure that anyone makes a product
- Sponsor, manage or directly assume burden of product development (conflict of interest)
- Provide indemnification to manufacturers
- Discuss commercial confidential information/trade secrets, even in response to complaints/debate
- Guarantee absolute safety
- Guarantee human efficacy based on non-human data such as animal studies or surrogate endpoints
- Guarantee efficacy in BT setting based on non-BT experience

What FDA Can Do

- Encourage sponsors to make products needed for public health priorities such as BT
- Perform research that ultimately facilitates product development and safety and improves the quality of regulation
- Provide intensive & early interactions and regulatory priority where appropriate
- Increase confidence in likely efficacy of products primarily approved based on surrogate/animal data
- Reduce likelihood of serious adverse events
- Partner with other agencies, health systems to improve monitoring of such products when used

Recent and Ongoing CBER Actions

- **Promoting results-oriented culture, creative approaches**
- **Meetings to encourage interest in developing new products**
- **Early interactions w/ sponsors**
- **Collaboration and rapid turnaround on INDs**
- **Proactive trips to examine facilities**
- **Participation in multiple interagency and interdepartmental teams.**
- **All lots of hard work.**

- **We welcome your ideas and input.....**
- **Thanks!**