Fast-Tracking Biodefense Vaccine and Therapeutic Testing and Approval: An Urgent Challenge

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CBER Roles and Products

- Roles:
  - Facilitate Product Development
  - Facilitate Product Availability
  - Help assure product integrity
  - Related research and regulatory activity
- Relevant Products
  - Vaccines, Ig, Blood and blood products, cell and tissue therapies
    - 133 active IND/IDE/MF/ 561 amendments
    - 93 CT research projects for unmet needs

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 and Bioshield proposal
- 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 and efficiency of laboratory and clinical studies
- 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)
- Simplification, flexibility for CT/BT issues
- Potential for waivers of informed consent may be considered under 50.24
- Work towards licensure, wherever feasible
- Rapid turnaround/active assistance from FDA
  - recent examples in smallpox, anthrax, botulism

Pros and Cons of IND Approach

- Pros
  - Clarity that a treatment is not a standard licensed therapy equivalent to routine prescription drugs
  - FDA trusted as arbiter of information and of process
- Cons
  - Potentially Cumbersome
    - Especially in emergency e.g. witnessed, written consent
  - Connotation of “Experimentation”

CT INDs : Making it Work

- Simplification, flexibility for CT/BT "streamlined" or "emergency use" INDs
- Rapid turnaround/active FDA assistance 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*

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, Accel. Approval

- Serious/life-threatening: meaningful therapeutic benefit over existing Rx.
- Allows for rolling submission
- Accel. approval:
  - utilize 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), histology (recent Fabrys approval)
  - Post-licensure studies required (usually ongoing) to demonstrate effects on disease outcomes
  - Restrictions on use possible, promotional controls
  - Potential problems obtaining controlled data
- Withdrawal if agreements violated/not S&E

Other Potential Approaches to Unlicensed Products

- **Presidential/Secretarial decisions in emergencies**
- **New classification/quasi-regulatory schemes**
  - **CT specific provisional labeling and/or IND approach (cf. *Bioshield*)**
  - **Any new (or existing) approaches need to deal with:**
    - **Clear cut public discussion/understanding ahead of time**
    - **Potential to affect confidence in safety of drugs/vaccines**
  - **Would require legislation**
    - President's *Project Bioshield* Proposal: EUA

Emergency Use Authorization Proposal in *Bioshield*

- EUA – the nuts and bolts
  - An emergency must be declared by the Secretary of Homeland Security (civilian) or Secretary of Defense (military)
  - The Secretary of HHS must issue the EUA
  - The product must be for an agent that can cause a serious or life-threatening disease or condition; no effective approved product available
  - The product's known and potential benefits must outweigh its known and potential risks (a new challenge to define standards)
  - The product's use and/or distribution may be limited
  - The authorization will be time limited and can be terminated

Emergency Use Authorization II.

- EUA – the nuts and bolts (continued)
  - Certain information to the user/consumer is mandatory
    - the significant risks and benefits of the product
    - option to refuse /alternatives
  - Certain information about the emergency use must be collected and made available (additional requirements optional)
  - Civil money penalties will be imposed on persons who violate the provisions related to the EUA

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.

- **Still need human clinical data:**
  - **PK/immunogenicity data**
  - **Safety in population(s) representative of use**
    - **Civilian use often includes pregnancy, children, elderly**
- **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**

Potential Incentive Approaches for Product Development

- **Existing:**
  - **Expedited regulatory pathways**
  - **Orphan status; < 200k patients; 7 yr exclusivity**
- **Other possibilities**
  - **Push: direct financial rewards, tax credits, exclusivity, partnerships, R&D assistance (e.g. basic, proof of principle, pilot lot production, clinical)**
  - **Pull: known markets, longer term contracts, prices proportional to public health benefit, dual uses (nonBT)**
  - **Liability protection**
- President's *Bioshield* Proposal
  - **New indefinite spending authority for critical countermeasures**
  - **$ 1 b FY04; SP, anthrax, bot; $ ~6 b over coming years**

Bioshield Procurement

- The Basics:
  - The Secretary of Homeland Security identifies threat
  - The Secretary of HHS assesses countermeasure needs and availability
  - HHS Secretary identifies countermeasures that should be included in stockpile
  - Presidential approval of procurement recommendations
  - Congressional notice of Presidential decision
  - Contract terms
    - Payment conditioned/staged on substantial delivery into EUA stockpile and subsequent licensure
    - Can be terminated for non-delivery

Procurement Authority

- The Specifics for Existing Countermeasure Procurement
  - Must be approved or likely to be within 5 years
  - Reasonable grounds to believe that sufficient amounts can be produced and delivered within 5 years
  - No significant commercial market for the countermeasure

CBER BT Research: Focus-Product Development Success

- ***Generally aim to meet otherwise unmet needs with regulatory implications***
  - Better determine potency
  - Immunogenicity/protection, disease models, correlates
  - Assuring safety (e.g. cell lines, adventitious agents)
  - Make regulation more scientific, less "defensive"
  - Benefit multiple companies across industry
- Maintain staff "cutting edge" expertise needed for dealing with evolving biotechnologies
- Scientific expertise and confidence foster objectivity
  - Reduces risks of reflexive over- or under-protectiveness

CBER Research in BT: II.

- **Examples of current studies on threat pathogens**
  - Smallpox**: animal models of vaccine neurovirulence, assay for immune response**
  - Anthrax**: Improved immunologic assays**
  - VIG**: Identification of protective isotypes, assays of commercial IGIV for activity**
  - Tularemia**: correlates of immunity for IC pathogens**
  - Yellow fever/VEE**: protective env antigens**
  - Botulinum toxin**: cellular trafficking of toxin, mechanisms of neutralization**
  - MDR TB**: identify attenuated vaccine candidates**
  - General**: stimulation of innate immunity/adjuvants**

Risk/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**
- 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*
- BT a moving target, no predictable epidemiology;
  - witness post-anthrax experience, extension of military products to broader, less well, populations
- The public expects safe (and effective) and products, especially vaccines given to well individuals, and looks to FDA for protection.
- Preserving confidence in medical products, and in public health leadership, is critical.
  - When things go "wrong" (or even if someone just thinks they did); few will remember the crisis or good intent

What FDA Cannot Do

- Provide monetary or tax incentives
- Assure that anyone makes a product
- Product development (conflict of interest)
- Provide indemnification or compensation
- Guarantee absolute safety
- Guarantee efficacy based on non-human data or based on non-BT experience

What FDA Can Do

- **Encourage sponsors to make needed products and facilitate their development**
- **Perform research that facilitates product development, safety and improves regulation**
- **Provide intensive & early interactions and regulatory priority where appropriate**
- **Increase confidence in efficacy of products**
- **Reduce likelihood of serious adverse events**
- **Partner with other agencies, health systems to improve product use & monitoring**
- ***These approaches highly relevant to many CBER products, especially evolving technology to meet critical public health/medical needs***

Recent and Ongoing CBER Actions

- Meetings to encourage developing new products
- Early interactions w/ sponsors; facilitate partnerships
- Collaboration and rapid turnaround on INDs
- Proactive trips to examine facilities
- Participation in multiple interagency and interdepartmental teams.
- Expedited approval of key product(s) apps.

•INDs/IDEs/MFs:

-2001 New-14, Amend.- 435
-2002 New-25, Amend.- 533

•License/License Supplement – 3

•"Site Visits": 18 manufacturing, 4 pre-approval (US/global)

Thanks!

Contact us:

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- ***Questions/comments now or later?***
- ***As a new CBER Director, your opportunity, and my need, for you to help us move forward collaboratively and meet our national needs.***

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