FDA/CBER's Role in Facilitating Development of and Access to Medical Countermeasures

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Biological Products Regulated by CBER

- Blood, blood components and derivatives
- Vaccines (preventive and therapeutic)
- Allergenics
- Cell and Gene Therapies
- Tissues
- Xenotransplantation
- Related Devices (including IVDs)

It’s Not Been Business As Usual!

- CBER has adapted to challenges through extraordinary efforts and proactive measures.
- Many more meetings to encourage/speed development of new products.
- Collaboration and rapid turnaround in product review.
- Inspections of manufacturing facilities earlier in the process.
- Careful attention to risk/benefit and risk management issues.
- Critical Path research to assist in more efficient, rapid development and availability.

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 or Emergency Use Authorization (EUA).
- Priority review
- Fast track
- Accelerated approval
- Approval under “Animal Rule”

Product Development Path, Milestones and Usual Recommended Meetings

Pre-IND Meeting:

-Manufacturing

-Lot Release

-Animal safety & immunogenicity

-Phase 1 protocol

End-of-Phase 2 Meeting:

-Phase 3 protocol(s)

-Phase 1 & Phase 2 data

-Animal efficacy protocols & data (if "animal rule" used)

-Update on manufacturing & lot release

Pre-BLA Meeting:

-Clinical data summary: Safety & Efficacy data

-Manufacturing, etc.

-Outline of BLA

Risk Management

IND = Investigational New Drug Application
BLA = Biologics License Application

Early and Frequent Consultation

- Improves communication process.
- Improves quality of laboratory and clinical studies.
- Reduces misunderstandings and likelihood of multiple review cycles.
- Improves efficiency of product development.
- Very resource intensive: CBER teams for priority BT product development/review (e.g., smallpox, anthrax vaccines).

Product Use Under IND

- Facilitated implementation of protocols under IND for use of investigational products in an emergency.
  - Contingency Use IND
  - Informed consent required per regulations
  - Potentially cumbersome for wide-spread use
- Project BioShield allows EUA in specified circumstances, rather than use of investigational product under IND.

Emergency Use Authorization (EUA) in *Project Bioshield*

- **Secretary of HHS can declare an emergency after Secretary of Defense, Homeland Security, or HHS determines an emergency (or potential for) exists.**
- **Secretary of HHS can authorize use of an unapproved product or unapproved use of an approved product if:**
  - **Agent can cause serious or life-threatening disease or condition;**
  - **No adequate and sufficiently available approved alternative;**
  - **Product's known and potential benefits must outweigh known and potential risks; and**
  - **The product may be effective.**
- **EUA is granted for up to 1 year, or until termination of declaration or revocation; can be renewed.**

EUA – Conditions of Authorization

- **Inform health care workers or recipients, if feasible:**
  - **Product authorized for emergency use;**
  - **Significant known and potential risks and benefits, extent to which unknown;**
  - **Alternatives; and**
  - **Option to accept or refuse the product.**
- **Appropriate conditions for monitoring and reporting AEs, record keeping and reporting.**
- **Can be additional conditions on use, e.g., who may distribute or administer, collection and analysis of information.**

Fast Track

- Granted during IND process.
- Applies to development program for a specific indication.
- Product must be for serious or life threatening condition and demonstrate potential to address unmet medical need.
- If granted, allows for a rolling submission of BLA.

Priority Review

- Granted at time of BLA submission.
- Product eligible if provides significant improvement:
  - In safety or effectiveness of treatment, diagnosis, or prevention of serious or life threatening disease (biologics).
  - Compared to marketed products in treatment, diagnosis, or prevention of disease (drugs).
- 6 month complete review of license application.
- Most CT products expected to qualify.

Accelerated Approval

- Product eligible if it provides a meaningful therapeutic benefit over existing treatments for serious or life-threatening illness.
- Efficacy based on surrogate endpoints likely to predict clinical benefit (314.510, 601.40).
- Post-licensure studies required (usually ongoing) to demonstrate effects on outcomes.
- Restrictions on use or distribution possible.
- Potential problems obtaining controlled data.
- Withdrawal if agreements violated/not S&E.
- Can approve through regular mechanisms with validated surrogate.

Animal Rule

- **To 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 benefit over existing therapies.**
- **Human efficacy trials *not feasible or ethical.***
- **Use of animal efficacy data scientifically appropriate.**
- **Does not apply if approval can be based on efficacy standards elsewhere in FDA regulations.**

Animal Rule (cont.)

- **Still need human clinical data:**
  - **PK/immunogenicity data, and**
  - **Safety in population(s) representative of use.**
    - **Civilian use often includes pregnancy, children.**
- **Approval subject to post-marketing studies and/or restrictions on use.**
- **Please work closely with FDA on planning animal studies before starting them.**
- ***Potential limitations:***
    - **Where there is no valid animal model of disease;**
    - **How to predictably bridge animal data to humans; and**
    - **Confidence may be an issue, even in valid models.**

Risk/Benefit for CT Products

- **Risk/benefit differs and FDA assesses for each product & potential use.**
  - **Treatment: For otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty.**
  - **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:***
  - **Something is not always better than nothing;**
  - **Accepting ineffective therapy inhibits development/use of more effective one.**
- **All such products:**
  - **Need honest and effective risk communication; may be challenging in emergencies**

New Guidance

- **Guidance for Industry: Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms (2007)**
- **Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (2007)**
- **Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines (2007)**
- **Draft Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases (2006)**

More Guidance/Regulations

- **Direct Final Rule: Revision of the Requirements for Live Vaccine Processing (21 CFR 600.11) (2007)**
- **Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (2007)**
- **Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007)**
- **Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (2006)**

Regulation and CT Products: What is the value added?

- Proactively facilitating development, licensure, and availability of new countermeasures by developing new pathways to speed development and enhance the assessment of safety.
- As for other medical products: need consistent and objective protection of public health.
- BT a moving target, no predictable epidemiology.
- Public expects safe and effective products, especially vaccines given to well individuals, and looks to FDA for protection and reassurance.
- Preserving confidence in medical products, and in public health leadership, is critical.

Thanks!

- **CBER's CT page:** http://www.fda.gov/cber/cntrbio/cntrbio.htm
- **OCTMA phone – (301) 827-2000**
- **Manufacturer's assistance:** http://www.fda.gov/cber/manufacturer.htm
- **C. Kelley phone – (301) 827-0636** cynthia.kelley@fda.hhs.gov