The Role of Research in Supporting Regulation of Biologicals: Building Bridges from Biomedical Discovery to Innovative Products

Jay S. Epstein, M.D.
CBER, FDA
Biologicals are Complex Products Critical for Public Health, National Preparedness & 21st Century Medicine

- Blood Derivatives
- Whole Blood
- Blood Components
- Devices
- Tissues

- Vaccines
- Somatic Cell & Gene Therapy
- Allergenic Extracts
- Xenotransplantation
Role of Research in Supporting Regulation of Biologicals

- Establish reference materials and standards
- Monitor product purity and potency
- Investigate product failures
- Conduct risk assessments
- Establish scientific basis for policies
  - Remove obstacles to product development
  - Facilitate rapid innovation
Regulatory Research at CBER, FDA

- Model of “Critical Path” Research
- Model of the “Research-Regulator”
- Examples of challenges and solutions
Figure 8: Problem Identification and Resolution During the FDA Product Review Process


Use Within Review Process

Guidance and Standards → Development of Public Standard → Public Input (Advisory Committees, Scientific Meetings and Workshops)
Figure 4: The Critical Path for Medical Product Development

Basic Research ➔ Prototype Design or Discovery ➔ Preclinical Development ➔ Clinical Development ➔ FDA Filing/Approval & Launch Preparation

Critical Path

Market Application ➔ Approval
CBER Research On the Critical Path

- **Science led FDA: Preserve a global gold standard and leader**
  - Good science informs policy and guidance for sponsors
  - Good science creates a predictable regulatory pathway and supports innovative products reaching people

- **Are products safe?**
  - Predictive safety tests prior to human use
  - Disease models, toxicology tests

- **Are products effective?**
  - Biomarkers, surrogate endpoints

- **Are products of high and consistent quality?**
  - Manufacturing innovations
  - Potency and purity testing
CBER’s Model of Research-Regulators

- CBER researchers fully integrated into the regulatory process under a “Researcher-Regulator” model
  - Review INDs and BLAs
  - Development of Policy and Guidance Documents
  - Meeting with Sponsors and Advisory Committees
  - Participation in Pre-license and Biennial Inspections
  - Evaluation of Adverse Drug Reactions and Risk Assessment
  - Performing research relevant to product evaluation of safety, efficacy, manufacturing: Developing/evaluating scientific tools & knowledge
The Added Value of CBER Research

• Innovators create scientific tools that are typically applicable to their specific products and not shared with others in industry

• CBER research-regulators are expert in biological product development AND standard scientific disciplines..expertise not often seen in standard biomedical discovery research arenas

• CBER staff see the successes, failures, and missed opportunities across whole classes of exciting and innovative products and want to help

• CBER Guidance documents that are based on science can provide a clearer, more predictable regulatory path

• CBER plays a convening and coordinating role for scientific needs across sponsors
Critical Path Research Management: Yearly Process

- Priorities
  - Reviewer meetings
  - BLA/IND application analysis
  - Critical and ongoing public health needs
  - Scientific Gaps/Needs analysis
  - Stakeholder input
  - FDA Advisory Committees
  - Leadership input

- Research Proposals
  - Priority evaluation
  - Scientific quality evaluation
  - Funding approval
  - Budgets set
  - Outcomes reported

- Outcomes Evaluated
  - Impact on regulatory challenges
  - Impact on facilitation of safe and effective products
  - Resolution of public health crisis
  - Preparedness for public health needs
  - External peer reviews of productivity
Examples of CBER Critical Path Investment Opportunities


- Better characterization of biological products & links to standardized clinical/lab efficacy and safety outcomes
- Appropriate toxicology approaches for complex biological products
- Improved manufacturing for biological products
- New assays, standards, biomarkers, surrogates for complex biologics safety, efficacy and quality
- Multipathogen and rapid detection methodologies
- Methods & validation of pathogen inactivation for blood, cells, tissues and other products
- Improving longevity/storage of biological products
- Enhanced clinical trial design-analysis
Vaccine Research Priority: Pandemic Influenza

• **Problem:** Inadequate vaccine manufacturing capacity and speed of response

• **Solution:**
  – Create scientific tools and Guidances to support innovations
    1. Pandemic influenza virus libraries & antisera with improved assays and testing
    2. Tests for tumorigenicity, infectious agent risks in new non-egg based technologies (e.g., recombinant and cell culture manufactured vaccines)
    3. Tests for vaccines that cross protect against changing strains
    4. Tests for vaccines with enhanced immune response (antigen-sparing technologies)
  – Intensive and early interactions with all stakeholders throughout development: Improved success

• **Outcomes:** Better vaccine, faster, to more people: save lives
Vaccine Research Priority: Meeting the Biodefense Vaccine Challenge

Vaccines against bioterror agents and emerging diseases

- **Problem**: When human testing is impossible or unethical, inability to test or predict effectiveness of many biodefense vaccines slows development

- **Solutions**:  
  - Better laboratory tests, including animal models to assess likely vaccine effectiveness without human trials: tularemia, smallpox, etc.

- **Outcomes**: Developing and using new laboratory tests and the "Animal Rule" to make needed vaccines more rapidly available
Vaccine Challenge: Need Smallpox Vaccine for Biodefense

- **Problem:** Vaccine development and human studies slowed by antiquated test for vaccine effectiveness (i.e., antibody response)
- **Solution:** CBER develops modern, high throughput test and provides to NIH and industry to facilitate rapid vaccine testing and availability
- **Outcomes:**
  - Emergency smallpox vaccine supply now available for every American
  - New vaccines under development using CBER assay
Blood Research Priorities

• Assure safety and availability of the blood supply
  – Improve safety for known transmissible agents (e.g. tests for malaria, Chagas disease)
  – Address new and emerging infections including bioterror agents (e.g. vCJD, HIV and HBV variants, smallpox)
  – Rapidly assess and act on new safety concerns and balance with availability (e.g. SARS, WNV, pandemic flu)
  – Prevent/resolve product shortages
  – Systems to model/track blood supply

• Facilitate development of needed new products
  – Cell based model to predict toxicity of blood substitutes
  – "Multiplex” microarray donor screening
  – Animal models and assays for validation of new immune globulin products, e.g., VIGIV
Challenge: Smallpox Vaccine Safety

- **Problem**: Smallpox vaccines can cause rare, fatal complications that need treatment with antiserum (VIG), but existing supplies inadequate (both amount and quality). Studies of VIG effectiveness cannot be done in humans.

- **Solution**: CBER develops novel mouse model that is adopted by NIH and industry and used in developing new VIG supplies.

- **Outcome**: VIG available to protect vaccinated people and save lives if smallpox emergency and mass vaccination occurs.

![Smallpox Vaccine Safety Graph](image.png)

- 4 long-term disease-free survivors.
Challenge: West Nile Virus and Blood and Tissue Safety

- **Problem:** WNV infections from transfused blood and transplanted tissues, identified by CDC/FDA
- **Solutions:** CBER coordinates unprecedented effort with CDC, NIH, blood and diagnostic industries to develop and implement testing
  - Provides guidance for approval pathway for WNV NAT donor screening test
  - Develops reference materials critical for test development
  - Implements nationwide WNV screening of blood donors using investigational NAT assays
  - Coordinates with CDC, NIH and blood banking establishments to collect and monitor data on WNV infection and evaluate testing.
- **Outcomes:** Prevention of distribution and transfusion of thousands of infected units of blood, preventing illness and death in blood recipients

Licensed NAT screening now available for blood, tissues and organs
Reducing the risk of transfusion-transmitted variant Creutzfeldt-Jakob disease

**Problem:** A new variant of Creutzfeldt-Jakob disease (vCJD or “mad-cow” disease) transmitted to recipients of blood transfusions from donors incubating vCJD in Britain.

**Actions:**
- Proactive FDA risk based “deferral policy” to restrict use of blood from donors at significant risk during vCJD outbreaks
- CBER evaluating methods for detection and decontamination of vCJD in medical products

**Outcomes:**
- Identified methods for decontamination of equipment and surfaces
- Guidance provided to product developers of filters and blood tests
- No cases of transfusion-transmitted vCJD have occurred in the USA to date. Estimated risk has been reduced by more than 90%.
Synthetic Blood Substitutes: Promising Novel Therapy

- **Problem**: Supply limited, subject to contamination. Access difficult in remote areas, battlefield, mass casualty situations, disasters and terrorism.
- Synthetic blood substitutes may provide life support when blood unavailable and avoid transfusion risks
- Blood substitute (HBOC) product development has been stalled by unexpected toxicity, including cardiac and blood vessel injuries
- **Solutions**: CBER developed sophisticated assays (NMR) and models to test products in the lab and predict toxicity vs. safety and issued guidance to industry
Gene Therapy Challenge: Improve Safety of Gene Therapy Products for Patients with Pre-existing Diseases

- **Problem:** Patient with liver disease received gene therapy product and died unexpectedly of lung injury—all testing halted
- **Complication** had not been predicted by standard safety tests
- **Solution:** CBER develops new test in rats with liver disease

- **Outcome:** Predicting risk for lung damage before testing in humans = safer gene therapies. Smith *et al.* (2004). *Molecular Therapy* 9:932
Gene Therapy Safety Challenge: Reducing Cancer Risk

**Problem**: First highly successful gene therapy replaces deficient gene with normal gene
- 9 of 11 children with SCID ("bubble baby") cured, living normal lives *but*

- 3/11 then *develop leukemia* because the therapy genes are inserted into places that also turn on dangerous cancer genes

- How can we evaluate cancer risks of gene therapies in order to make them safer?
CBER Initiates Toxicity Study of Complex Biological Products With The National Toxicology Program (NTP)

- **Solution:**
  - CBER develops novel toxicology test to help design better gene therapies
  - NTP, an NIH-FDA program, to test the test
    - Tests to evaluate cancer risk before use in humans
    - Help identify new approaches to transfer needed genes without turning on cancer genes

- **Outcome:** Keep the promise of gene therapies while reducing risks
Cross-Cutting Challenge: Evaluate Safety of Medical Products in Clinical Use

- **Problem**: After FDA approval, safety problems become apparent during clinical use

- **Solutions**:
  - Detect and assess safety concerns more rapidly and efficiently by using innovative and new technologies to monitor/analyze safety data, including health care systems databases
    - Varicella, pneumococcal vaccines
    - Live, cold-adapted, intranasal influenza vaccine
    - Pilot studies for human tissues

- **Outcomes**:
  - Monitor risks while keeping safe products available to the patient
  - *Safer products, increased public confidence*
Thank you

- Biologics regulators face many challenges in public health, biodefense and the development of safe and effective new medicines for the 21st century
- New technologies need expert, innovative & interactive science led regulation
- Regulatory research can play a critical role in building bridges to help turn basic discoveries into real medicines – safer, better, faster