Center for Biologics Evaluation and Research

Current Activities
Future Directions

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To ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, blood and blood products, and cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions or injury.
CBER
The Vision

INNOVATIVE TECHNOLOGY
ADVANCING PUBLIC HEALTH

- Protect and improve public and individual health in the US and, where feasible, globally
- Facilitate development, approval and access to safe and effective products and promising new technologies
- Strengthen CBER as a preeminent regulatory organization for biologics
CBER Science
The Cutting Edge of Biologics

- The Challenge: Regulate complex biologics

- The Opportunity: Integrate new knowledge into facilitating development of safe and effective products
Challenges and Opportunity

Themes

- Assuring Product Sterility
- Enabling Product Characterization
- Improving Predictive Value of Nonclinical Tests
- Moving towards Personalized Medicine and Improving post-marketing surveillance/safety
- Addressing Globalization
Sterility
A Challenge Facing Biologics

- Most biologics cannot be terminally sterilized
- Many biologics cannot be subject to processing that inactivates or removes infectious agents
- Some products cannot be stored while waiting for sterility or mycoplasma testing
New Guidance
An Opportunity for Biologics

- **Draft Guidance for Industry**: Validation of growth-based rapid microbiological methods for sterility testing of cellular and gene therapy products
  - Recognition that certain cell-based products cannot be cryopreserved or terminally sterilized, but that *parenteral administration* requires assurance of sterility
  - Addresses need to develop, validate, and implement sterility methods that are more rapid than those described in 21 CFR 610.12
Mycoplasma testing
21 CFR 610.30 and Points to Consider

Advantages
- Limit of Detection (1 cfu/ml or less)
- Detection of viable mycoplasma contamination

Disadvantages
- Requires 2 agar/broth culture and indicator cell culture methods (for both cultivable & non-cultivable mycoplasmas, respectively)
- Use of different media and environmental incubation conditions
- Time-consuming (minimum 28 days)
Sensitive and rapid mycoplasma detection and identification by enrichment on MDCK cells

**ALTERNATIVE STRATEGY**

*Sensitivity of new method: ≤ 1 CFU/ml*

*Turnaround time: less than one week*  
*(instead of 28 days)*

V. Chizikhov, OVRR/CBER

*Public Workshop:* Rapid Methods for Detecting Mycoplasma Contamination in the Manufacture of Vaccines, Including Pandemic Influenza Vaccines, and Other Biological Products, Sept 08
Product Characterization
A Challenge Facing Biologics

- Complexity of genetic, cellular, and tissue-based products will require identification of predictive markers
  - fates & oncogenicity of products
  - cell differentiation, function, and regulation
  - cell responses to host environment

- Product characterization may require reference reagents, standardization of methods, etc.

www.gene.com
Opportunity
New Guidance Documents for Industry on Product Characterization

- **Process Validation: General Principles and Practices, November 2008** (draft)

- **Potency Tests for Cellular and Gene Therapy Products, October 2008** (draft)
New Science
New Opportunities

Breakthrough of the Year:
Induced Pluripotent Stem Cells
Opportunity
New Ways to Characterize Complex Products

Comprehensive mass-spectrometry-based proteome quantification of haploid versus diploid yeast; *De Godoy, et al, Nature 455:1251*
Opportunity
Reference Materials for Improved Product Characterization of Cell and Gene Therapy Products

- Retrovirus reference material
  CBER; available from ATCC

- Adenovirus reference material
  Consortium; available from ATCC

- External RNA spike-in controls

- Quantitative flow cytometry
  CBER, NIST; available from NIST

Fluorescent standard solution
Fluorescent micro-bead standard
Opportunity
Improved Reagents for Product Characterization

Potency assay for anthrax vaccine and therapeutic antibody development
Cell-based assay to detect Anthrax toxin function

**Problem:** Different lots *lethal factor* (LF) resulted in differences in potency measurements

*Why?*
The **N-terminal amino acid** of LF significantly affects its activity in cell-based assays.

- **Recombinant forms of LF** should be designed with this characteristic in mind.
- **Care should be taken** to ensure that proteolytic nicking of the N-terminal residue does not occur during purification.

*D. Burns, OVRR, CBER*
Challenge
Developing Predictive Nonclinical Tests

- Identification of *in vitro* or *in vivo* correlates of bioactivity, safety, toxicity
  
  - Lack of appropriate nonclinical models
  
  - Undefined biomarkers in some clinical indications
  
  - "Animal Rule" for bio-defense-related products
Opportunity
CBER Concept Paper

Animal Models – Essential Elements to Address Efficacy Under the Animal Rule
(Sept. 2008)

- Additional data elements to consider
  - Characteristics of agent
  - Host susceptibility and response to etiologic agent
  - Pathophysiologic comparability
  - Trigger and characterization of intervention
  - Design considerations for efficacy studies
  - Safety information
Opportunity
Develop *in vitro* Assay for Adjuvant Safety Assessment

- **Issue:** Improving prediction of adverse events from novel adjuvants.
  - **Most common:** pain, tenderness, erythema, and granuloma at the injection site
  - **Rare:** systemic (e.g., chills, fever, myalgia, headaches)

- **Approach:** Studies in animals have shown that fever is associated with an increase in the levels of pro-inflammatory cytokines.
  - Human promonocytic MM6 cell line with known spectrum of TLRs was used to determine the levels of pro-inflammatory cytokines released in presence of adjuvants.
Induction of IL-6 & TNFα in MM6 cells cultured with adjuvants

- IL-6 (pg/ml) levels:
  - 5903.5 (pg/ml)

- TNFα (pg/ml) levels:
  - 1474.8 (pg/ml)

Adjuvants (μl/ml):
- QS21
- MF59
- AlOH
Development of *in vitro* Assay for Adjuvant Safety Assessment

- **CBER Research Finding:** Good correlation between *in vitro* results with *in vivo* safety records for several adjuvants and delivery systems.

- **Implications:** May provide more rapid, inexpensive screen of toxicity for novel adjuvants. Other detector cell lines are under development to evaluate potential neurotoxicity and hepatotoxicity.

- **Public Workshop** on Adjuvants, December, 2008
Opportunity

Improve Predictive Value of Preclinical Testing of Hemoglobin-Based Oxygen Carriers

**Issue:** Hb-based oxygen carrying solutions might save lives of trauma victims where blood is not available, but to date, products have shown unexplained toxicities.

**Approach:**

- Identify the link between the “oxidative chemistry” of a given hemoglobin and its toxicity.
- Develop suitable animal model (rat and guinea pig) systems to study blood substitute toxicity.

Pittsburgh Supercomputing Center
http://www.psc.edu/
Improved Predictive Animal Models

Ascorbate (vitamin C) limits HBOC oxidative reactions

Rat
- Ascorbate-producing

Guinea pig
- Non-producer of ascorbate
  (similar to humans)

Heme Oxygenase

Buehler PW et al, JPET (2007)

D'Agnillo, OBRR/CBER
Identification of Improved Nonclinical Model

Outcomes

- Nonclinical testing is becoming more predictive of clinical performance
- Facilitate design of safer Hb-based blood substitutes
- CBER is able to develop guidance on product development and nonclinical testing
Challenge
Personalized Medicine

- Biomarker Discovery
  - Improve outcome
  - Reduce risk

- Improve Post-Marketing Surveillance
  - safety surveillance
Opportunities

- **Voluntary Genomics Data Submission**
  - [http://www.fda.gov/cder/genomics/VGDS.htm](http://www.fda.gov/cder/genomics/VGDS.htm)
  - Sharing technology, data, and insights with industry
  - Joint learning venture

- **Guidance for Industry:** Post-marketing adverse event reporting for medical products and dietary supplements during an influenza pandemic
  - Preparing for an outbreak

- **Clinical biomarker discovery** – predictive of cancer development (CBER/OCTGT - Marti)
Opportunity
Collaborations Increase Vaccine Safety Monitoring

- CDC and Vaccine Safety Datalink
- PAHO/ CDC/ FDA post-marketing surveillance of rotavirus vaccines in Latin America
- Pilot project with CMS to evaluate safety of influenza and pneumococcal vaccines as part of pandemic preparedness
- MOU with Veterans Health Administration to share information on FDA-regulated products, including vaccines
- Collaboration with Department of Defense Medical Surveillance System and Vaccine Health Centers
Improving Post-marketing Surveillance

- **Issue:** Need to improve ability to detect low frequency adverse events in populations receiving approved biologics.

- **CBER Research Finding:** Analysis of CMS database, 40 million >65 yo, allowed rapid analysis of GBS and seasonal flu vaccine (2006).

- **Implications:** Pilot study demonstrates power of approach; could be applied to other areas.
CMS – RAPID ANALYSIS OF GBS AND SEASONAL FLU VACCINE (2006)
Globalization

Confronting a World of Emerging Challenges

HTTP://Biodefense.niaid.nih.gov
Opportunity
CBER & PATH
Partners in the Fight Against Malaria

PATH: Program for Appropriate Technology in Health
- Created in 1999 with funding from Gates Foundation

CBER/PATH collaboration (Sanjai Kumar, OBRR)
- Develop laboratory tests to predict the level of safety and activity of experimental malaria vaccines before they are used in human clinical trials.
Opportunity
CBER & MVP
Partners to Fight Epidemic Meningitis

Meningitis Vaccine Project
- 2001 Gates Foundation fund PATH & WHO to develop vaccines for Africa

CBER/ MVP collaboration
- Developed improved polysaccharide conjugate technology to dramatically increase yields and lower the cost per dose

CREDIT: MONIQUE BERLIER/MVP-PATH
in SCIENCE: 6/27/08
Opportunities
Global Assistance, Cooperation, Leadership

- **PAHO/WHO Collaborating Center for Biological Standardization**
  - Vaccines, blood products & related biologicals

- **FDA/WHO/Health Canada Pandemic Regulators**
  - Emerging threat preparedness

- **WHO Global Collaboration for Blood Safety**
  - Safety and availability

- **European Medicines Agency (EMEA)**
  - Regulatory dialogue with peer counterparts (e.g., EMEA)

- **International Conference on Harmonisation (ICH)**
  - Expedite economical approvals in US, Europe, & Japan

- **Pharmaceutical Inspection Cooperation Scheme (PIC/S)**
  - International inspection and oversight authority
Opportunity
Computational modeling to prepare for pandemic influenza

- **Computer simulation**
  - Aggregate US blood supply, daily donations, daily demand
  - Centers for Medicare and Medicaid Services (CMS) database (>65 yo), transfusions
  - Impact of pandemic influenza
    - 50% decrease in blood donations over 3 months
    - Simulation shows blood supply is protected with controlled use
90-day donations cut in half

Reduced donations start on January 6th
Because of small difference between inflow and out, after three years, the system is still not back to normal

Blood use restrictions started 45 days into outbreak, but continued for six months.
Note reappearance of expired blood

CBER Collaborates and Cooperates with Stakeholders

CBER responds to the complexity of biologics by working closely with industry, outside experts, and other government agencies

- Industry workshops
- Advisory committee assistance in defining issues, product development pathways, study designs
- Collaborative Research, e.g.,
  - Critical Path
  - National Toxicology Program
  - IAGs with NIH, CDC, others
- Standards Development Organizations
  - In 2008, 100 CBER staff participated in 89 standards activities with ~30 organizations
Challenges and Opportunities

Goal:
Improve public health through new regulatory pathways that facilitate development of safe and effective biologics

Proactive Strategies:

Identify the Challenge!

Harness new scientific technology and knowledge!

Create Partnerships!