Center for Biologics Evaluation and Research

Overview of Regulatory Science

Peter Marks, M.D., Ph.D.
Deputy Center Director
Center for Biologics Evaluation and Research
December 8, 2015
Center for Biologics Evaluation and Research (CBER)

• Established in 1902 by the Biologics Control Act following two incidents in which contaminated products led to the deaths of 22 children

• Initially part of National Institutes of Health, and moved to FDA as the Bureau of Biologics in 1972

• Approximately 1055 full time employees distributed in review offices and laboratories
CBER: Innovative Technology
Advancing Public Health

• Facilitate development, approval, and access to safe and effective products and promising new technologies
• Protect and improve public and individual health in the US and globally
• Strengthen CBER as a pre-eminent regulatory organization for biologics globally
CBER: Our Products

- Allergenics
- Blood Products
- Devices (specific subsets)
- Gene Therapy
- Human Tissues and Cellular Products
- Live Biotherapeutic Products
- Vaccines (preventive and therapeutic)
- Xenotransplantation Products
Regulatory Pathways Used at CBER

- Investigational New Drug Applications (INDs)
- Biologics License Applications (BLAs)
- New Drug Applications (NDAs)
- Abbreviated New Drug Applications (aNDAs)
- 510(k) Clearances (Devices)
- Investigational Device Exceptions (IDEs)
- Pre Market Authorizations (PMAs)
- Human and Cell Tissue Products (HCT/P’s)
Examples of Regulatory Challenges

- Delivery of therapies by live viral vectors that can be shed into the environment
  - Oncolytic viruses
- Investigation of live biotherapeutics for disease prevention, mitigation, treatment, cure
  - Fecal microbiota transplants for recurrent or refractory *C. difficile* infection
- Delivery of genetically modified cells or organisms
  - Chimeric antigen receptor T (CAR-T) cells for relapsed acute lymphoid leukemia
CBER Organization

Offices involved in research with regulatory relevance

Office of the Director

- Office of Vaccines Research and Review
- Office of Blood Research and Review
- Office of Cellular, Tissue and Gene Therapies
- Office of Biostatistics and Epidemiology
- Office of Compliance and Biologics Quality
- Office of Communication, Outreach and Development
- Office of Management
Office of Vaccines Research

- Recently there has been a resurgence in whooping cough caused by \textit{B. pertussis}

- CBER scientists developed a non-human primate model for this disease that could facilitate further vaccine development
  
Baboon Model Suggests Mechanism of Vaccine Failure

• Acellular pertussis vaccine (current) compared to whole cell pertussis vaccine (older generation)

• Both vaccines induced robust antibody responses, but T cell responses were significantly different

Acellular vaccine protected against disease related to pertussis, but failed to prevent infection and transmission
Office of Blood Research

- Use of immune globulin products associated with a number of thrombotic serious adverse events that were reported to FDA
  - Included myocardial infarction, stroke, and venous thromboembolism
- Causes of adverse events were uncertain
- During a cluster of cases associated with specific lots of immune globulins researchers examined factor XIa levels, a potential risk factor
Identifying and Addressing Potential Cause of Thrombotic Events

Similar results were obtained when FXIa was spiked into five different IGIV products.

- Product withdrawal
- Investigation extended to all immune globulin products
- Assay transfers: on-site training and consultations with industry and regulators
  - 1st international reference reagent for Activated Blood Coagulation Factor XI (FXIa), Human, NIBSC 11/236
Office of Biostatistics and Epidemiology Research

• Involved with several collaborations to investigate important public health issues related to product safety using large healthcare databases
  – HealthCore, Medicare, Sentinel, others

• Rigorous methodology developed including protocol development and execution to facilitate signal identification and confirmation
Identification of a Safety Signal Leading to Regulatory Action

• Use of Mini-Sentinel Post-licensure Rapid Immunization Safety Monitoring program to examine the risk of intussusception following the administration of rotavirus vaccine
  – More than 1.3 million doses evaluated
  – The pentavalent rotavirus vaccine was associated with an excess of 1.5 cases of intussusception/100,000 recipients of the first dose
  – Led to safety labeling change for rotavirus vaccines noting potential for intussusception
Office of Cellular, Tissue and Gene Therapies – Current Challenges

• Gene modified T cells harness T cell immunity (cytotoxic functions, cytokine secretion, etc.) to attack tumor cells

• Conventional \textit{ex vivo} expanded T cells targeting tumor antigens show some efficacy, but poor persistence

• Use gene transfer to improve functional properties of transduced T cells (properties encoded by transgene)
  – Control of T cell specificity (recognition of defined tumor antigens)
  – Remove need for HLA specificity
  – Enhanced engraftment and proliferation
  – More potent effector function
Basic Overview of Therapy

Apheresis Product

T cell activation and transduction with gene transfer vector

Expand in culture CD3/CD28 beads ± IL-2 / IL-15

Dose formulation Product testing

Gene modified T cell Infusion

Patient may receive pre-conditioning chemotherapy prior to infusion

Sometimes cytokine support (IL-2) post infusion

Cancer patient
Rapid Evolution of Field

- Allogeneic Chimeric Antigen Receptor (CAR) T cells
  - Potential for Graft versus Host Disease (GvHD) and rejection

- Limitation of “on target, off tumor” toxicity
  - Co-express inhibitory CAR that binds antigen expressed on non-tumor cells but not on tumor cells

- Improved suicide genes/deletion methods
  - Inducible caspases, antibody deletion targets

- Non-viral transduction methods
  - mRNA electroporation?

- Move from fresh to cryopreserved cells
  - More time for release/characterization testing
Production Challenges

• Product consistency
  – Lot to lot variation in transduction efficiency

• Product tracking and labeling
  – Critical to ensure correct product administered

• Testing for potency
  – What assays are most appropriate?

• Testing for replication-competent vector
  – Different methodologies have different sensitivity

• Personalized products; time window for release testing may be limited
Clinical Challenges

• Pre- and post-infusion issues
  – Conditioning to make “immunologic space”
  – Post-infusion management (cytokines, others)

• Dosing Issues
  – Choosing the correct cell dose to use

• Potential Toxicities
  – On and off target
  – Off target may be greatest risk with cytokine release syndrome possible
Additional Challenges

• Access to key reagents/intellectual property issues
  – Need Good Manufacturing Practice grade reagents
  – Certain reagents often only available from single supplier

• Current generation of products requires manufacturing capacity for patient-specific products
  – Labor intensive

• Comparability studies needed if manufacturing methods or sites changed between early and late stage studies

• Product characterization needs to be demonstrated
Regulatory Science Program

• Fills a unique niche to facilitate product development and meet our regulatory mission
  – Cadre of scientific experts who also understand the regulatory process
  – Allows facile responses to public health/regulatory emergencies
  – Allows proactive research to address regulatory science gaps