Center for Biologics Evaluation and Research

Overview of Regulatory Science

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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

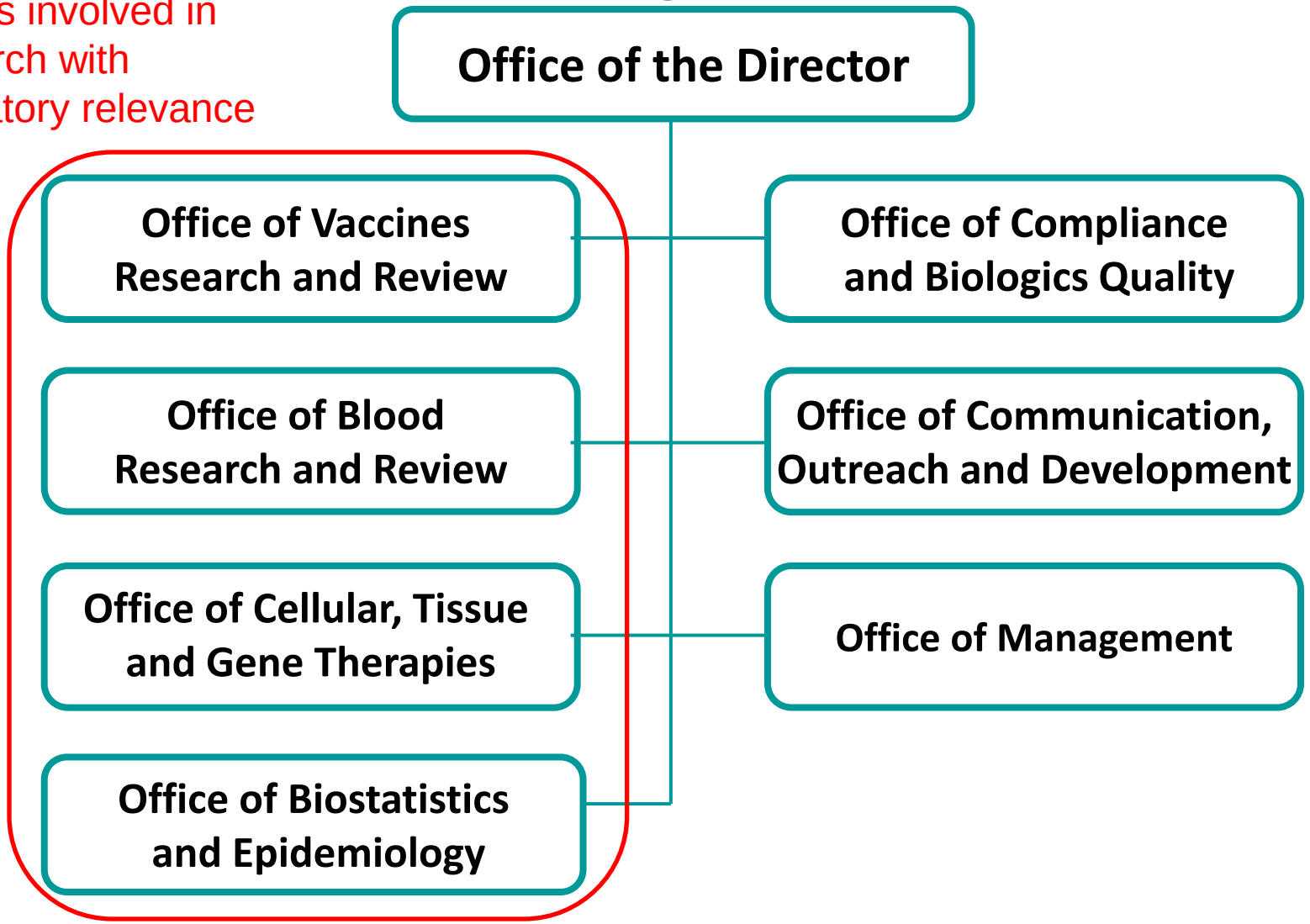
- Investigational New Drug Applications (INDs)
- Biologics License Applications (BLAs)
- New Drug Applications (NDAs)
- Abbreviated New Drug Applications (aNDAs)
- 510(k) Clearances (Devices)
- Investigational Device Exceptions (IDEs)
- Pre Market Authorizations (PMAs)
- Human and Cell Tissue Products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

Examples of Regulatory Challenges

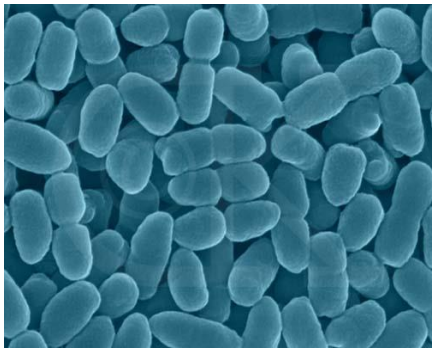
- Delivery of therapies by live viral vectors that can be shed into the environment
  - Oncolytic viruses
- Investigation of live biotherapeutics for disease prevention, mitigation, treatment, cure
  - Fecal microbiota transplants for recurrent or refractory *C. difficile* infection
- Delivery of genetically 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 Vaccines Research



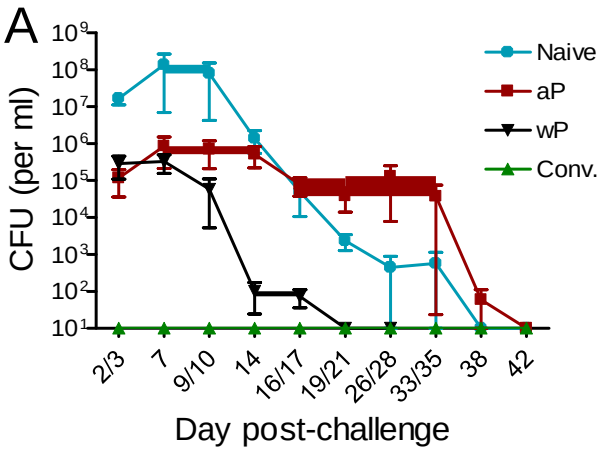
- Recently there has been a resurgence in whooping cough caused by *B. pertussis*

- CBER scientists developed a non-human primate model for this disease that could facilitate further vaccine development
  - Warfel JM et al. Infect Immun. 2012; 80: 1530–1536

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

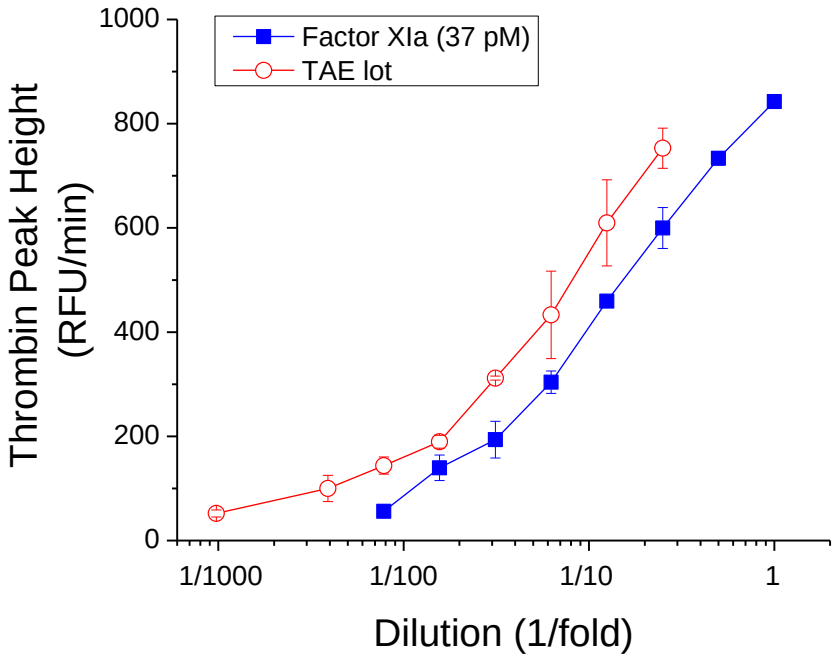


Office of Blood Research

- 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

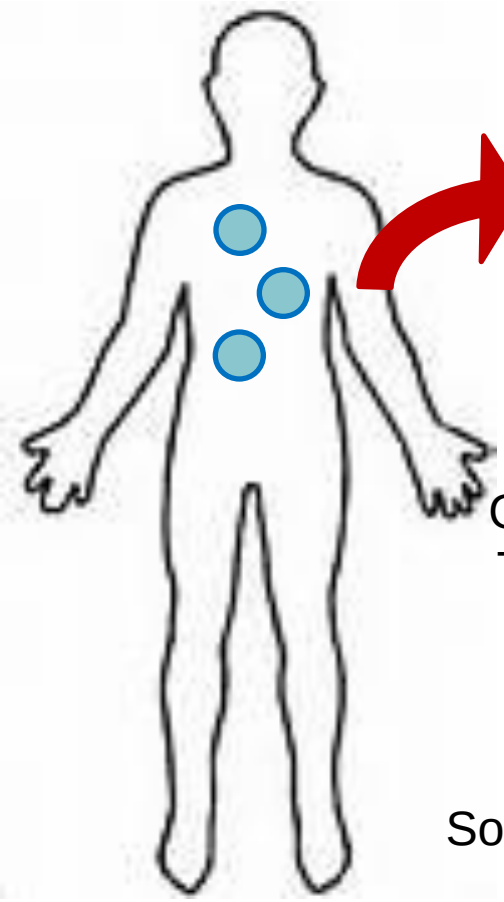
Identification of a Safety Signal Leading to Regulatory Action

- 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 *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

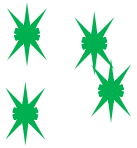
Basic Overview of Therapy



Cancer patient

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

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