Update from the Center for Biologics Evaluation and Research (CBER): Advancing the Development of Complex Biologic Products

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Outline

• Products regulated
• Significance of complex biologics
• Product and process
• Relevance of scientific research
• Cutting edge products
• Facilitating development
CBER Regulated Products: Something Old and Something New

Diphtheria Antitoxin

CRISPR/Cas9 Genome Editing

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Products Regulated by CBER

- Blood Products
- Vaccines (preventative and therapeutic)
- Allergenics
- Live Biotherapeutic Products
- Devices Related to Biologics
- Human Tissues and Cellular Products
- Xenotransplantation Products
- Gene Therapies

[Image links to www.fda.gov]
The Significance of CBER’s Complex Biologics
CBER Regulated Products: Vaccines for Disease Prevention

>150 million doses of influenza vaccine given in 2016-2017

**VACCINES WORK**

These bubbles are sized according to the annual number of disease cases in the US during the 1900s versus 2010. We've come so far. It's a reminder that while disease rates are low, most diseases haven't disappeared. This is why we continue to vaccinate.

- **SMALLPOX**
  - THEN: 29,005
  - NOW: 0
- **DIPHTHERIA**
  - THEN: 21,053
  - NOW: 0
- **PERTUSSIS**
  - THEN: 200,752
  - NOW: 21,291
- **TETANUS**
  - THEN: 580
  - NOW: 8
- **POLIO**
  - THEN: 16,316
  - NOW: 0

### THEN
Annual US disease cases in the 1900s

- **MEASLES**
  - THEN: 530,217
  - NOW: 61
- **MUMPS**
  - THEN: 162,344
  - NOW: 2,528
- **RUBELLA**
  - THEN: 47,745
  - NOW: 6
- **MENINGITIS**
  - THEN: 152
  - NOW: 0
- **HAEMOPHILUS INFLUENZAE**
  - THEN: 20,000
  - NOW: 270

### NOW
US disease cases in 2010

- **MEASLES**
  - THEN: 61
- **PERTUSSIS**
  - THEN: 21,291
- **MUMPS**
  - THEN: 2,528
- **RUBELLA**
  - THEN: 6
- **MENINGITIS**
  - THEN: 0
- **TETANUS**
  - THEN: 8
- **POLIO**
  - THEN: 0
- **SMALLPOX**
  - THEN: 0

*Congenital rubella syndrome*

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Vaccines are Important for Combating Emerging Infectious Diseases

Global Examples of Emerging and Re-Emerging Infectious Diseases

Source: National Institute for Allergy and Infectious Diseases
CBER Regulated Products: Keeping the Blood Supply Safe

Need for continued vigilance against emerging threats
CBER Regulated Products: Advanced Therapies at the Leading Edge

*Ex vivo* or *In vivo* gene therapy to treat various conditions
CBER Regulated Products: Regenerative Medicine

• Involves cutting edge science in fields including
  – Cell therapies
  – Therapeutic tissue engineering products
  – Human cell and tissue products
  – Some combination products

• Field with great promise that goes directly to the FDA’s role in helping meet unmet medical need
Complex Biologics: 
Product and Process Intertwined
Complexity of Therapeutics

- One subunit of a protein: $10^2$ Atoms, L-tryptophan, Small Molecule Drug
- Protein composed of about 1100 subunits: $10^5$ Atoms, IgG antibody molecule, Protein Biologic
- Cell composed of about $3.6 \times 10^6$ proteins: $10^{14}$ Atoms, Mesenchymal stem cell, Cellular Biologic
Evolution of Hemophilia A Treatment

- **1930**: Blood Transfusion
- **1960**: Fresh Frozen Plasma
- **1990**: Factor VIII Purified from Plasma
- **2020**: Factor VIII Gene Therapy

www.fda.gov
Plasma Derivative Preparation

Factor VIII Purification from Plasma
Recombinant Factor VIII

Gene Therapy for Hemophilia A

<table>
<thead>
<tr>
<th>Vector</th>
<th>Capacity (kb)</th>
<th>Immune Response</th>
<th>Vector Genomes</th>
<th>Advantages</th>
<th>Problems</th>
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</thead>
<tbody>
<tr>
<td>Retrovirus</td>
<td>8</td>
<td>Low</td>
<td>Integrated</td>
<td>Stable expression in daughter cells</td>
<td>Works only in dividing cells; oncogenesis</td>
</tr>
<tr>
<td>Lentivirus</td>
<td>8</td>
<td>Low</td>
<td>Integrated</td>
<td>Stable expression in daughter cells</td>
<td>Integration may cause oncogenesis</td>
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<tr>
<td>Adenovirus</td>
<td>8</td>
<td>High</td>
<td>Episomal</td>
<td>Efficient transduction of most tissues</td>
<td>Capsid causes strong immune response</td>
</tr>
<tr>
<td>Helper-dependent adenovirus</td>
<td>30</td>
<td>High</td>
<td>Episomal</td>
<td>Efficient transduction of most tissues</td>
<td>Capsid causes strong immune response</td>
</tr>
<tr>
<td>Adeno-associated virus</td>
<td>≈5</td>
<td>Low</td>
<td>Episomal (&gt;90%) Integrated (&lt;10%)</td>
<td>Non-pathogenic</td>
<td>Small capacity; immune response</td>
</tr>
</tbody>
</table>

Complex Biologics: Relevance of Applied Scientific 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.

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
Example 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 Xla levels, a potential risk factor
Identifying and Addressing a Cause of Thrombotic Events

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

Example of Cell, Tissue and Gene Therapy Research

• How best to characterize cellular therapies is still evolving
  – Particularly the case for stem cells taken from an individual
• The parameters that define how cells that are administered to an individual will ultimately perform in terms of safety and efficacy are not yet well-defined
• A multidisciplinary approach of applied science using molecular genetics and cell biology may help elucidate such parameters
Ability of Cells to Differentiate Depends on Cell Line and Passage

Automated microscopy-based quantification

Example of Biostatistics and Epidemiology Research

• Use of real world evidence at FDA for evaluation of product safety has been ongoing for a number of years using large healthcare databases
  – Sentinel, Medicare, Healthcore, others

• Rigorous methodology developed including protocol development and execution to facilitate signal identification and confirmation

• Investigation of the ability of real world evidence to evaluate effectiveness is in progress
Comparison of High-Dose and Standard-Dose Influenza Vaccine

- Used Medicare Database to evaluate efficacy of high-dose (929,730 recipients) versus standard-dose vaccine (1,615,545 recipients)
- High-dose vaccine was 22% (95% CI 15-29) more effective than the standard-dose vaccine for prevention of probable influenza infections and 22% (95% CI 16-27%) more effective for prevention of influenza hospital admissions
- In agreement with a randomized clinical trial conducted in 31,989 individuals which showed relative efficacy of 24.2% (95% CI 9.7-36.5)

Regulatory Science at FDA

• Fills an important niche to meet our regulatory mission and facilitate product development through availability of scientific experts who
  – Understand the regulatory process
  – Proactively address regulatory science gaps
  – Respond to public health emergencies
Complex Biologics: Products at the Cutting Edge of Science and Medicine
Chimeric Antigen Receptor-T Cells

- Chimeric antigen receptor-T cells (CAR-T cells) represent a cell-based gene therapy with potential applications to multiple diseases
  - Hematologic malignancies
  - Solid tumors
  - Infectious disease
  - Autoimmune disease
- Possibility to provide therapeutic benefit with an extended duration of effect
Chimeric Antigen Receptor-T Cells

- Conventional *ex vivo* expanded T cells targeting tumor antigens show some efficacy, but poor persistence
- Genetically modified T cells harness immunity (cytotoxic functions, cytokine secretion, etc.) to attack tumor or other immune effector cells
- Gene transfer improves functional properties of transduced T cells (e.g., antigen recognition, effector function)
Basic Overview of CAR-T Therapy

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

Apheresis Product

Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post infusion

Patient
Genetic Modification: Introduction of Chimeric Antigen Receptor

- Using molecular genetics, novel protein receptors can be created that combine features of different proteins into one
- This allows one to both target and activate T cells to eliminate a cancerous or undesirable cell type
Potential Advantages to Use of Genetically-Modified Cellular Therapies

• Appropriate methods can be used to address the issue of location of genomic integration
  – Use of genome editing possible (CRISPR/Cas9*)

• Ability to select appropriately transduced cells for administration to recipients
  – Use of next generation sequencing

• It is possible to turn off the effect of the cells, if necessary, through use of certain approaches
  – Use of suicide genes

*Clustered regularly interspaced short palindromic repeats/Cas9 enzyme gene editing system
Potential Challenges to Use of Genetically-Modified Cellular Therapies

- Process must be developed to consistently manufacture and characterize cells
- Logistics facilitating production and delivery of cells must be carefully orchestrated
- Administration of therapies may be associated with various short and longer term side effects
  - Acute inflammatory process
    - Cytokine release syndrome
  - Immune function
Complex Biologics: Facilitating Development
Expedited Pathways

• Fast Track Designation
• Breakthrough Designation (2012 – FDASIA)
• Accelerated Approval
• Priority Review
2016 – 21st Century Cures Act

• Patient-focused drug development
• Advancing New Drug Therapies
• Modern Trial Design and Evidence Development
• Patient Access to Therapies and Information
• Antimicrobial Innovation and Stewardship
• Medical Device Innovations
• Improving Scientific Expertise and Outreach at FDA
• Regenerative Medicine Provisions
Regenerative Medicine
Advanced Therapy (RMAT) Provisions

• Section 3033
  – Accelerated Approval for Regenerative Advanced Therapies

• Section 3034
  – Guidance Regarding Devices Used in the Recovery, Isolation, or Delivery of Regenerative Advanced Therapies

• Section 3035
  – Report on Regenerative Advanced Therapies

• Section 3036
  – Standards for Regenerative Medicine and Regenerative Advanced Therapies
RMAT Designation (Section 3033)

• A designation has been created to expedite the development and review of regenerative advanced therapies
• Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
  – May include genetically modified cells
• Products must be intended for serious or life-threatening diseases or conditions
RMAT Designation (Section 3033)

- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designation requests to FDA from sponsors must receive a response within 60 days
- Designated products are eligible as appropriate for priority review and accelerated approval
RMAT Designation (Section 3033)

- Post-approval requirements for accelerated approval can be fulfilled as appropriate through submission of:
  - Clinical evidence, clinical studies, patient registries or other sources of real world evidence such as electronic health records
  - The collection of larger confirmatory datasets as agreed upon
  - Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy

www.fda.gov
Process for Regenerative Medicine
Advanced Therapy Designation

• Sponsor can request with a new investigational new drug submission or as an amendment to an existing one

• Request for designation should describe
  – How definition of regenerative medicine therapy is met
  – How criterion to address a serious or life-threatening disease or condition is met, and
  – Preliminary clinical evidence indicating that the drug has the potential to address an unmet medical need

Website with information about process:
http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm
Progress on RMAT Designation

• Already receiving RMAT designation requests
• Though FDA generally cannot comment on unapproved applications, able to note that one company has issued a press release noting that they have received RMAT designation
• We look forward to continuing to work with sponsors of these products and other stakeholders to help make these exciting new therapies available to those in need.