Outline

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

Diphtheria Antitoxin

CRISPR/Cas9 Genome Editing
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
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

**MEASLES**

**THEN** 530,217

**NOW** 61

**MUMPS**

**THEN** 162,344

**NOW** 2,528

**RUBELLA**

**THEN** 47,745

**NOW** 6

**HAEMOPHILUS INFLUENZAE**

**THEN** 20,000

**NOW** 270

**MEASLES**

530,217 Cases

**MUMPS**

162,344 Cases

**PERTUSSIS**

200,752 Cases

**RUBELLA**

47,745 Cases

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References:


Vaccines are Important for Combating Emerging Infectious Diseases

Global Examples of Emerging and Re-Emerging Infectious Diseases

- Cryptosporidiosis
- West Nile virus
- E. coli O104:H4
- Ebola hemorrhagic fever
- Drug-resistant malaria
- Diphtheria
- MERS-CoV
- Rift Valley fever
- Typhoid fever
- SFTSV bunyavirus
- E. coli O157:H7
- H7N9 influenza
- H5N1 influenza
- SARS
- Hendra virus
- Enterovirus 71
- Chikungunya fever
- Human monkeypox
- Plague
- Dengue
- Yellow fever
- Human African trypanosomiasis
- Cholera
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Human monkeypox
- Lassa fever
- Lyme disease
- vCJD
- Anthrax bioterrorism
- Hantavirus pulmonary syndrome
- 2009 H1N1 influenza
- Adenovirus 14
- MRSA
- H3N2v influenza
- Cyclosporiasis
- E. coli O157:H7
- Human monkeypox
- Listeriosis

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

Need for continued vigilance against emerging threats

Adapted from TRANSFUSION 2006;46:1624-1640
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

Protein composed of about 1100 subunits

Cell composed of about $3.6 \times 10^6$ proteins

$L$-tryptophan
Small Molecule Drug

IgG antibody molecule
Protein Biologic

Mesenchymal stem cell
Cellular Biologic

$10^2$ Atoms

$10^5$ Atoms

$10^{14}$ Atoms
Evolution of Hemophilia A Treatment

Blood Transfusion

1930

Fresh Frozen Plasma

1960

Factor VIII Purified from Plasma

1990

Recombinant Factor VIII

2020

Factor VIII Gene Therapy

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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>
</tr>
</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</td>
<td>Non-pathogenic</td>
<td>Small capacity; immune response</td>
</tr>
</tbody>
</table>

Complex Biologics: Products at the Cutting Edge of Science and Medicine
Chimeric Antigen Receptor-T Cells
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

- **Apheresis Product**
  - T cell activation and transduction with gene transfer vector
  - Expand in culture CD3/CD28 beads \+ IL-2 / IL-15

- **Gene modified T cell Infusion**

- **Dose formulation Product testing**

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

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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
CBER Breakthrough Therapy Designations Since Program Inception

Data as of Jun 30, 2017
CBER Breakthrough Therapy Requests by Product Type

- Vaccines/ Immunotherapies/ Allergenics: 25%
- Cell Therapies/Immunotherapies: 27%
- Gene Therapies: 38%
- Blood Factors: 27%
- Other: 1%

Data as of Jun 30, 2017
CBER BT Requests

Granted by Product Type

Data as of Jun 30, 2017
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

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Regenerative Medicine Advanced Therapy (RMAT) Provisions

- 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
  - Includes genetically-modified cellular therapies
- Products must be intended for serious or life-threatening diseases or conditions
RMAT Designation

• 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

• 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

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