CBER Regulatory Updates: Initiatives for Product Review and Licensure

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Products CBER Regulates

- Allergenics
- Antivenins
- Blood Products
- Cellular Products
- Fecal Microbiota Transplants
- Gene Therapy Products
- Hematologic
- Human Tissues
- Phage Therapies
- Vaccines (preventative and therapeutic)
- Xenotransplantation products
- Devices (IVD, Cell Therapy)
- Combination Products
CBER Organization
CBER initiatives – 21st Century Cures

• 21st Century Cures
  • Patient-focused drug development
  • Medical Device Innovations
  • Improving Scientific Expertise and Outreach at FDA
  • (Section 3016) - FDA may award grants to institutions of higher education and non-profit organizations for advanced manufacturing
    • Closed and automated manufacturing technologies
    • Modular platforms for manufacturing and testing
    • Integrated data management
    • Process modeling and simulation
  • Regenerative Medicine Advanced Therapy (RMAT) Designation Program
CBER initiatives – Standards

• Standards development
  • Facilitate development and use of appropriate standards in product development and manufacturing
  • Collaboration with NIST – workshop held in April on standards development for assays used to determine off-target genome editing
  • Assessing the feasibility and prioritization of RMAT standards.
    • Engagement with outside experts to outline a strategic plan, including identifying gaps, and developing criteria for standards development.
CBER Initiatives - International Activities

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC/LSIF RHSC)
- World Health Organization
- Pan American Health Organization
- Coalition for Epidemic Preparedness Innovations (CEPI)
- EDQM – Group 8 (blood products) and Group 15 (vaccines)
- VAC2VAC
- Other scientific and regulatory engagements as appropriate
CBER Initiatives - CMC Activities Related to Product Licensure

• Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (Draft Guidance for Industry posted in December, 2017)
  — Review of public comments underway
• ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Draft Guideline posted in November, 2017)
• Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (Draft Guidance for Industry posted in May, 2018)
CBER Initiatives - Guidance Documents (1)

- **Guidance Documents Issued since the July 2017 Guidance Agenda Update:**
  - Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Draft Guidance for Industry (issued November 2017)
  - Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry (issued November 2017)
  - Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff (issued November 2017; updated December 2017)

CBER Initiatives - Guidance Documents (2)

• Tissues and Advanced Therapies: *Guidance Documents CBER is Planning to Issue in 2018:*
  • Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus during Product Manufacture and Patient Follow-up; Draft Guidance for Industry
  • Observing Subjects Who Received Human Gene Therapy Products for Delayed Adverse Events; Draft Guidance for Industry
  • Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Draft Guidance for Industry
  • Gene Therapy for the Treatment of Hemophilia; Draft Guidance for Industry

CBER Initiatives - Guidance Documents (3)

- Blood and Blood Components: **Guidance Documents CBER is Planning to Issue in 2018:**
  - Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion; Draft Guidance for Industry (Revised Draft)
  - Labeling of Red Blood Cell Units with Historical Antigen Typing Results; Guidance for Industry
  - Further Testing of Donations that are Reactive on a Screening Test for Antibodies to Hepatitis C Virus; Draft Guidance for Industry
  - Recommendations for Testing Donations, Donor Screening, Deferral and Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Babesiosis: Draft Guidance for Industry
  - Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components; Draft Guidance for Industry

CBER Initiative - Expediting Product Development and Review

• Fast track
• Breakthrough Therapy Designation
• Regenerative Medicine Advanced Therapy Designation
• Priority review

These programs are intended to be utilized for all products that meet the criteria and are intended to prevent or treat serious conditions
Fast Track

• Allows for more frequent communications with the FDA
  • Incorporates an end of Phase I meeting

• May allow for a “rolling” review of the BLA

• May allow for priority review

• May allow for an accelerated approval of the product

Sec 506(b) FD&C Act, FDAMA of 1997, amended FDASIA 2012
Breakthrough Therapy Designation

• Treatment of serious or life threatening disease or condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies

• Benefit is increased interaction with FDA to expedite the development and review of the application

Sec 506(a) FD&C Act, added FDASIA 2012
CBER Has Granted 40 Breakthrough Therapy Designations Since Program Inception

- 27 of the 40 products have Orphan Product designation
- 15 of the 40 products have Fast Track designation

Data as of September 28, 2018
CBER Has Granted 27 Regenerative Medicine Advanced Therapy Designations Since Program Inception

- 59 of the 77 are Cell Therapy products
- 17 of the 27 RMAT Granted products have Orphan Product designation
- 10 of the 27 RMAT Granted products have Fast Track designation

Data as of September 28, 2018
CBER Breakthrough Therapy Requests by Product Type

Data as of September 28, 2018
CBER BT Requests Granted by Product Type

Data as of September 28, 2018
Priority Review

• Products regulated by CBER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a serious, life-threatening disease

• 6 months review of the entire BLA (instead of 10 months)

• A fast track product would ordinarily meet the criteria for a priority review (but not always)

Prescription Drug User Fee Act of 1992
Examples of expedited reviews - vaccines

- **Fast Track and priority** – Prevnar 13 for unmet need of prevention of IPD caused by serotypes 1,3,5,6A,7F,19A which were not in Prevnar 7

- **Fast Track and priority** – Vaxchora cholera vaccine – first vaccine approved in US based exclusively on efficacy data from human challenge studies

- **Fast Track and priority** – Gardasil

- **Fast Track but no priority review** – Gardasil 9, Cervarix

- **Breakthrough, priority review, and accelerated approval** – Trumenba and Bexsero Meningococcal Group B vaccines

- **Accelerated approval** – Three new seasonal influenza vaccines.
Vaccine Development - Overview

Process Development
- Source characterization
- Raw material qualification
- Cell Bank Characterization
- DS/DP characterization
- Assay Development
- Formulation Development
- Process controls

Process Optimization
- In-process controls
- DS/DP Characterization
- Formulation Optimization
- Assay Qualification
- Specification development
- Stability

BLA Supplement:
- Manufacturing Changes
- Formulation Changes

Incremental approach CMC/cGMP

IND STAGE

R&D Pre-clin Phase 1 Phase 2 Phase 3 BLA Phase 4

Proof of Concept Pre-clinical safety

Manufacturing Process Validation
Assay Validation
Final Product Specification
Final Formulation
Stability
Vaccine Development Pathway Expedited Clinical Development

Process Development
- Source characterization
- Raw material qualification
- Cell Bank Characterization
- DS/DP characterization
- Assay Development
- Formulation Development
- Process controls

Process Optimization
- In-process controls
- DS/DP Characterization
- Formulation Optimization
- Assay Qualification
- Specification development
- Stability

Incremental approach CMC/cGMP

Pre-clin Phase 1 Phase 2 Phase 3

Manufacturing Process Validation
Assay Validation
Final Product Specification
Final Formulation
Stability
CBER Initiatives – Cell and Gene Therapy

• Tremendous expansion of product development
• Facilitation of additional Interactions with FDA to support these critical products
  • RMAT (Regenerative Medicines Advanced Therapy)
  • INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER products)
Rapid Growth in GT IND Applications
CAR T cell Targets

111 active CAR T cell investigations in OTAT as of 6/30/18

CD19:
- Expressed on B-cells
- Targets hematologic cancers

BCMA:
- B-cell maturation Antigen
- Expressed on malignant plasma cells
Summary

• CBER continues to partner with developers, academics, industry, regulators, patients and other stakeholders, both domestically and internationally, to understand and solve clinical, preclinical, product, manufacturing and other challenges

• CBER has implemented and is using review modalities that enhance the expedited review of critical products intended to treat or prevent serious disease