CBER Regulatory Updates: Initiatives for Product Review and Licensure

CASSS
CMC Strategy Forum Japan
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Agenda

• Overview of CBER
• CBER Initiatives for Product Review and Licensure
• ICH Q12
• Innovative Technologies and Trends at CBER
Products Regulated by CBER

- Allergenic Products
- Antivenins
- Blood & Blood Products
- Hematologic Products
- Cellular Products
- Gene Therapies
- Live Biotherapeutics
- Fecal Microbiota Transplants

- Human Cells & Tissue products
- Bacteriophage Therapies
- Vaccines (preventative and therapeutic)
- Xenotransplantation products
- Devices (IVD, Cell Therapy)
- Combination Products
CBER Initiative – Priority Review

• *Eligibility*: 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)

Prescription Drug User Fee Act of 1992
CBER Initiative – Accelerated Approval

- **Eligibility:** Allows for the use of a surrogate endpoint or intermediate clinical endpoint as the basis of approval of drugs for serious conditions that fill an unmet medical need.

- **Requirement to conduct Phase 4 confirmatory trials**

Sec 506(a) FD&C Act, added FDASIA 2012
CBER Initiative – Fast Track

- **Eligibility:** Provides an unmet medical need where none exists or provides therapy that is potentially better than the available therapy
- Allows for more frequent communications with FDA; incorporates end of Phase 1 meeting
- May allow for a “rolling” review of the BLA
- May allow for Priority Review and Accelerated Approval

Sec 506(a) FD&C Act, added FDASIA 2012
CBER Initiative – Breakthrough Therapy

- **Eligibility**: 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
- To provide timely advice and interactive communications to expedite the development and review of the application
- Eligible for all Fast Track designation features

Sec 506(a) FD&C Act, added FDASIA 2012
CBER Initiative - 21st Century Cures

- Patient-focused drug development
- Medical Device Innovations
- Improving Scientific Expertise and Outreach at FDA

- Regenerative Medicine Advanced Therapy (RMAT) Designation Program
RMAT Designation Eligibility

- It is a **cell therapy**, **therapeutic tissue engineering product**, **human cell and tissue product**, or any **combination product** using such therapies or products*; Includes**:
  - Genetically modified cells
  - Gene therapies that lead to a durable modification of cells or tissues
- The drug is intended to treat, modify, reverse, or cure a **serious or life-threatening disease or condition**;
- Preliminary clinical evidence indicates that the drug has the potential to address **unmet medical needs** for such disease or condition

*except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations

** See CBER November 2017 draft guidance: “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions”
RMAT Designation Benefits

• Provides for interactions with FDA to expedite development and review of regenerative medicine advanced therapies
  – Same benefits available to Breakthrough Therapies
  – Including early discussions of any potential surrogate or intermediate endpoints to support Accelerated Approval
CBER RMAT Designation Requests Received by Fiscal Year

Annually: September 30 – October 1

Data as of September 30, 2019


www.fda.gov
CBER Advanced Technologies Team (CATT) Program

• Advanced manufacturing may bring new tools to address:
  – Flexibility
  – Availability
  – Scalability
  – Cost

• Innovative technologies, such as:
  – 3D bioprinting
  – Continuous manufacturing
  – Cell culture systems supporting large scale or rapid production
  – Monitoring/measurement technologies

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt
INTERACT Meetings

• Created for potential sponsors to engage with CBER staff and obtain advice on a specific topic or issue that is critical to early product development

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products
Earlier Engagement with CBER via CATT

**Informal regulatory advice**

- **CATT Interaction**
  - CMC
  - Innovative approaches to product development

- **INTERACT Meeting:**
  - Specific product and indication for first-in-human use
  - CMC
  - Pharm/tox
  - Clinical

**Formal regulatory advice**

- **Phase 1**
  - Pre-IND Meeting:
    - Manufacturing
    - Lot Release
    - Animal safety & immunogenicity
    - Phase 1 protocol

- **EOP 2 meeting:**
  - Phase 3 protocol(s)
  - Phase 1 & Phase 2 data
  - Animal efficacy protocols & data (if “Animal Rule” used)
  - Update on manufacturing & lot release

- **Phase 2**

- **Phase 3**

- **Application (BLA)**

**IND = Investigational New Drug**
**BLA = Biologics License Application**
**NDA = New Drug Application**
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), Group 15 (vaccines) and a Gene Therapies Working Party
• VAC2VAC
• Other scientific and regulatory engagements as appropriate
CBER ICH Q12 Update

• ICH Q12 reached Step 4 in November 2019
• The ICH Expert Working Group is preparing the materials for training
  – Mock examples and case studies are needed
  – Target is 1 year for completion
• It is also important to understand ICH Q8 to Q11
• January 2020: CBER will provide training for CMC reviewers and inspectors
• For some of the complex products regulated by CBER, it may be challenging
to utilize the tools described in Q12, because the knowledge about products
and process may be very limited
• Specific recommendations should be discussed for those products with the
emphasis on the effective knowledge management
Innovative Technologies and Trends at CBER

- Considerations for
  - Cell & Gene Therapy Products
  - Live Biotherapeutic Products (LBPs)
  - Bacteriophage Therapy
  - Fecal Microbiota Transplantation (FMT)
  - Reduction in Animal-based Testing for Vaccines
The double-edge nature of cell & gene therapies

**Advantages:**
- Multiple potential mechanisms of action
- Can be highly patient-specific
- Scalable through cell expansion
- Single treatment can give durable clinical response, even cure disease
- Same cells might treat many diseases

**Challenges:**
- CQA and specifications difficult to establish
- Cells very sensitive to growth conditions
- Limited stability
- Limitations on testing
- Can have high lot-to-lot variability
- Logistics
- Characterization often limited
Different strategies to increase manufacturing scale

Scale up

Scale out
(replicate)
Scale-up Considerations

• Increase in yield:
  – Increased by culturing for longer- length in time in culture and the number of passages can in some cases profoundly impact product properties
  – Incubate with growth factors/cytokines/reagents to stimulate proliferation – can affect differentiation or activation state

• Cells can also be sensitive to cell density and ratio of cell types

• Adherent cultures and suspension cultures may need different strategies

• Not all processes scale well:
  – Working with huge numbers of flasks can be problematic
  – Time sensitive steps (such as enzymatic treatment)
Scale-out by Replicating a Process

- Typically involves modular facilities (in various configurations)
- Increase in scale accomplished by adding additional modules – sometimes modules are housed inside a much larger space for future expansion
- Additional modules could be at same facility or additional facility of same design
- Can dedicate modules to specific products
- Usually balances dedicated equipment & workspace to each lot with shared resources for all lots
- Can be accomplished using manual processes or automation
Considerations for Replicating a Process

- How will you maintain appropriate product segregation and product tracking? Shared equipment and resources?
- Line clearance: will module/workstation be assigned start to finish for a product lot, or used for multiple lots at different stages?
- How will you appropriately monitor each process? - logistics
- What happens when there is a disruption to the manufacturing schedule?
- Simultaneous processing of multiple lots can increase risk- if you are making 20 lots at once and something goes wrong, you potentially impact 20 lots instead of one. Material qualification and risk mitigation are important
- Process validation- factor in multiple workstations as part of a PV study, and compare variation between
- Sometimes capacity validation studies are conducted to show that the logistics work
Donor Testing and Screening for Allogeneic Human Cellular Immunotherapies

• Testing and screening for communicable disease agents is required when source material is collected from allogeneic human donors (21 CFR 1271)

• It is important to follow both FDA regulations and guidance on expectations for donor screening and testing - which are very specific

• Donor eligibility screening and testing requirements often differ by country. For example, other countries may not be using:
  • FDA licensed test kits
  • CLIA certified lab
  • Performing all the nucleic acid and antibody-based testing required

• If using source material from non-US donors, we recommend you consult with FDA very early in product development for advice
Gene Therapy Guidance Documents


• All of the Cell and Gene Therapy Guidance Documents can be found here:

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
Trends in OVRR

vaccine virus
wild type virus
Live Biotherapeutic Products (LBPs)

- Widely available commercially without good investigative support for their use
- Early phase requirements were interfering with good studies initiated and executed
- Guidance document issued Feb 2012; Updated June 2016
  - Relaxed CMC requirements for early phase clinical trials


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Bacteriophage Therapy

- Viruses that can attack, integrate into, and kill bacteria
- Widely available but technologically challenging to manufacture
- Treatment can be tailored to a specific patient and infection or with pre-selected cocktails
- Phage Cocktails: Potential opportunity to treat drug resistant bacterial infections
  - To increase spectrum of treatment (e.g., against different strains of a given organism)
  - To avoid resistance (TB and HIV drug resistance paradigm - use of multiple anti-infectives prevents single resistance from arising)
Fecal Microbiota Transplantation (FMT)

How do we ensure safety?

Extrinsic safety
- Screening of donors
  - How frequently should donors be tested?
  - Should off-site donations be allowed?
- Testing of stool
  - What organisms should we test for?
  - How good are our tests?

Intrinsic safety
- What are the long-term health effects of changes to the gut microbiome?
  - Metabolic syndrome/diabetes?
  - Weight loss / weight gain?
  - Inflammatory disease?
  - Behavioral changes?

How do we characterize the product to ensure consistency of effectiveness?

- Are there specific organisms/consortia that mediate effectiveness?
- Are there specific functions provided by these organisms that mediate effectiveness?
- What is a good potency assay?
Reduction of Animal-Based Testing for Vaccines

Reduction of animal testing

• Removal of the requirement for the General Safety Test (GST)

Refinement of animal testing

• Mumps vaccine
  – Monkey neurovirulence vs. rat neurovirulence

Replacement (substitutions) of animal testing

• Adventitious agents testing
  – Multiple animal assays vs. high throughput sequencing (HTS)

• DTaP vaccine
  – Lethal histamine sensitization assay in mice vs. *in vitro* CHO cell-based assay

• Inactivated poliovirus vaccine
  – Rat immunogenicity vs. antigen ELISA

• HepB virus, HPV and other vaccines
  – Immunogenicity in mice vs. ELISA

• Inactivated rabies virus vaccine
  – Lethal challenge in mice vs. antigen ELISA
Additional New Technologies Under Consideration

• Next Generation Sequencing  
  – Arifa Khan @ 9 AM on Dec 12
• New Vaccine Platforms
• Enhanced Product Characterization
• Advanced Manufacturing  
  – Continuous Manufacturing
  – Process and Assay Automation
  – Modular Facilities for Replicated Processes (scale-out)
• Emerging Diseases and Licensure Pathways

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Summary

• CBER has implemented initiatives to enhance the review of critical products intended to treat or prevent serious disease, innovative product technologies, and new approaches to product manufacture.

• 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 receives a wide variety of products to review, but for every product, science drives the regulatory decision-making.

• Contact the appropriate product office for questions!
  – Not sure? CBERProductJurisdiction@fda.hhs.gov
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