Global CMC Convergence: an FDA Perspective

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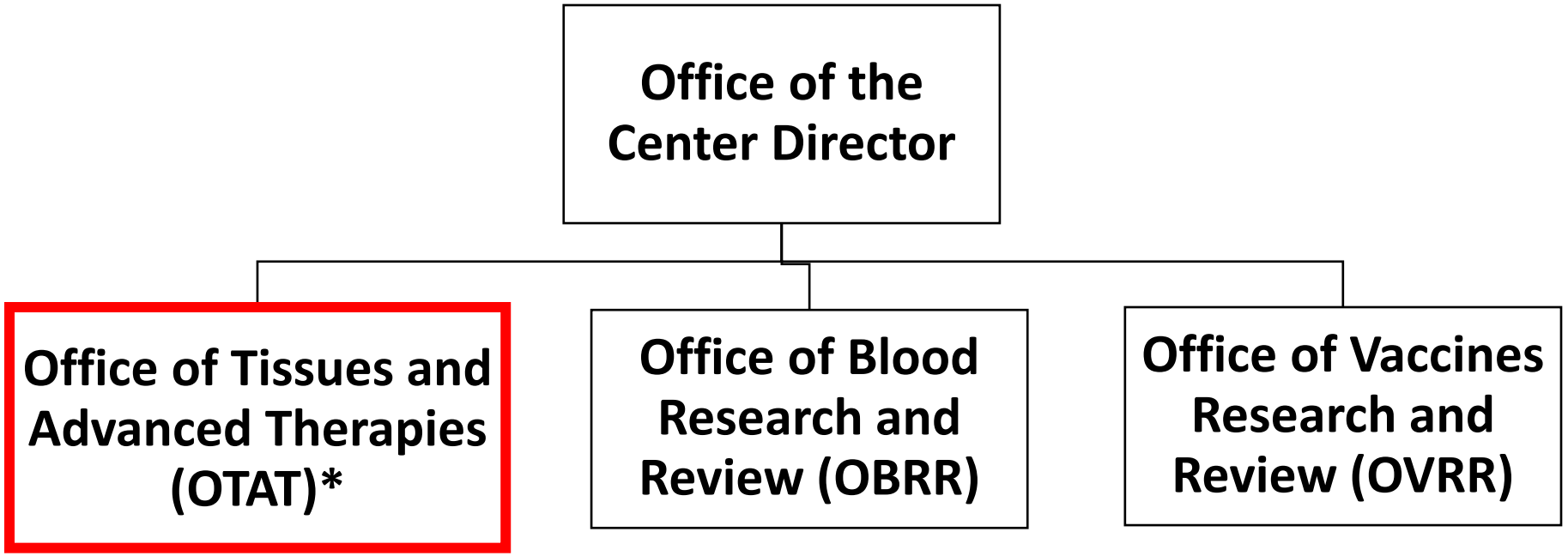
Center for Biologics Evaluation and Research (CBER) - Product Review Offices



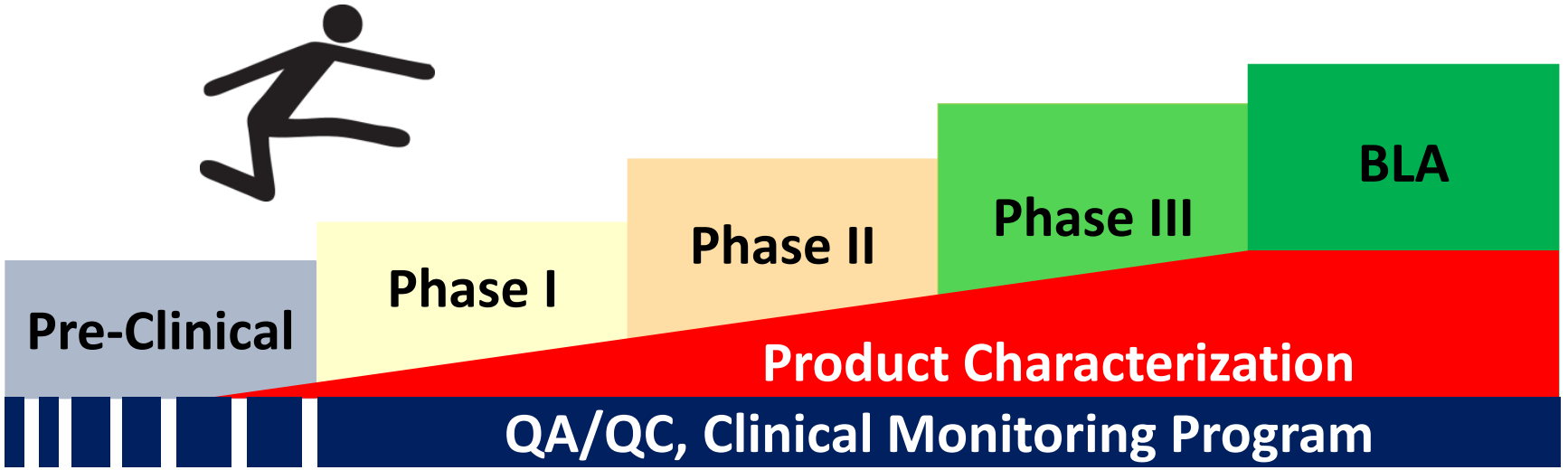
*Formerly the Office of Cellular, Tissue, and Gene Therapies (OCTGT)

Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

Objective of FDA Review (21 CFR 312.22)

- **Lifecycle approach to product development**
- … in all phases of the investigation to assure the safety and rights of subjects
- ….and in phase 2 and 3 studies, to help assure that the quality of the scientific evaluation of drug product is adequate to permit an evaluation of the drug's effectiveness and safety



CBER Guidance for Industry

- Finalized 2020
- GT CMC for IND
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up
- Long Term Follow-up After Administration of Human Gene Therapy Products
- Human Gene Therapy for Hemophilia
- Human GT for Rare Diseases,
- Human GT for Retinal Disorders

- Draft 2020/2021
- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (draft January 2020)
- Human Gene Therapy for Neurodegenerative Diseases (draft January 2021);
- Plan to release in 2021*
- Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing;
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies;
- Studying Multiple Versions of a Cellular or Gene Therapy Product in a Clinical Trial
- CMC Changes to an Approved Application: Certain Biological Products

*https://www.fda.gov/media/120341/download

Regulatory review at FDA is highly product dependent…

- Scale– one “lot” for some products could treat thousands of patients, whereas patient-specific products treat just one
- Manufacturing procedures, technologies, and methods can differ widely
- Comprehensive testing is challenging for products with little test material or very short shelf lives
- Risk of product depends greatly on source material and how the product is made
- High inherent variability of some product types makes demonstrating manufacturing comparability and consistency challenging

Comparison of Expedited Programs Criteria

Fast Track (FT)	Breakthrough Therapy (BT) [1]	RMAT [2]	Accelerated Approval	Priority Review
-**Serious condition** AND -Nonclinical or clinical data demonstrate the *potential* to address unmet medical need Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-**Serious condition** AND -Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-**Serious condition** AND -It is a regenerative medicine therapy - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	-**Serious condition** AND - Meaningful advantage over available therapies - Demonstrates an **effect on** either: a **surrogate endpoint or an intermediate clinical endpoint**	-**Serious condition** AND -Demonstrates potential to be a significant **improvement in safety or effectiveness**

[1] FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
[2] FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February, 2019

Comparison of Expedited Programs Features

Fast Track (FT)	Breakthrough Therapy (BT) [1]	RMAT [2]	Accelerated Approval	Priority Review
Frequent meetings **Eligibility** for *: ✓ Priority Review ✓ Rolling Review *if relevant criteria are met	**All FT Features, including:** Actions to expedite development and review; Rolling review **+** **Intensive** guidance on an efficient drug development program **Organizational** commitment involving senior managers	**All FT and BT Features,** **including** early interactions to discuss any potential surrogate or intermediate endpoints **+** **Statute** addresses potential ways to support accelerated approval	**Approval** based on surrogate or intermediate clinical endpoints **Save valuable time** in the drug approval process **Reduce waiting period for patients to obtain clinically meaningful benefit.**	**Shortened Review** Clock FDA will take action on an application within 6 months (compared to 10 months under traditional review)

[1] FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
[2] FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February, 2019

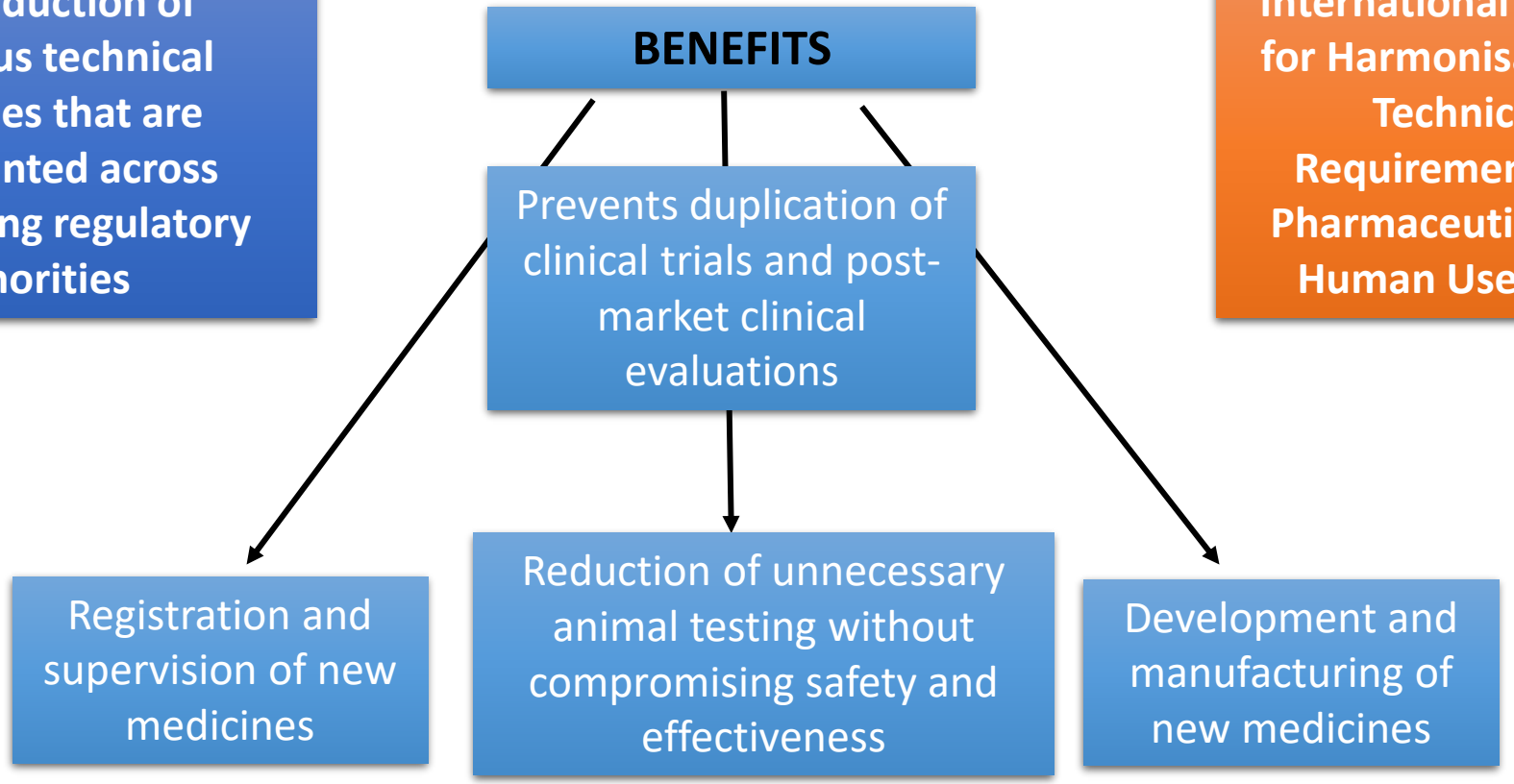
Navigating the FDA Framework During Global Development

- Align regulatory and scientific development through productive interactions
- Leverage accumulated data

Regulatory Harmonization

The production of consensus technical guidelines that are implemented across participating regulatory authorities

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)



Regulatory Convergence

Convergence of regulatory perspectives that informs the independent development of national guidelines and regulations

Does not necessarily represent the harmonization of laws and regulations, which is not a prerequisite for allowing the alignment of technical requirements and greater regulatory cooperation

Example:

International Pharmaceutical Regulators Programme (IPRP) Gene Therapy Working Group

- Regulators only
- Forum for information sharing where less experienced regulators can learn from more experienced regulators

Forums for Collaboration

- Discussion “Clusters”
- International Pharmaceutical Regulators Programme (IPRP)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Asia Pacific Economic Cooperation (APEC)- Regulatory Harmonization Steering Committee (RHSC)
- Ad Hoc Interactions

IPRP
International Pharmaceutical Regulators Programme

FDA

IPRP Working Groups

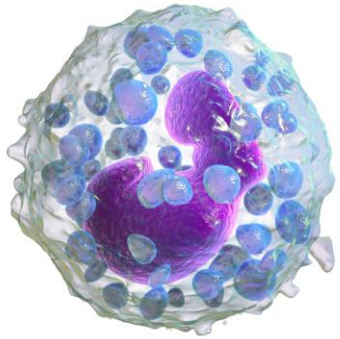
- Bioequivalence for Generics
- Biosimilars
- Cell Therapy (CTWG)
- Gene Therapy (GTWG)
- Identification of Medicinal Products
- Information Sharing for Generics
- Nanomedicines
- Quality for Generics
- Pharmacovigilance

IPRP Cell Therapy Working Group and Gene Therapy Working Group

- **Regulators only, no industry involvement**
- **Discussions are not confidential**
- Cell Therapy Working Group (CTWG)

  Scope: Cell and tissue based products (without gene modification), tissue engineered products, xenotransplantation products
- Gene Therapy Working Group (GTWG)

  Scope: Viral vectors, plasmids/mRNA, some oncolytic vectors, genetically modified bacterial-based products, ex vivo genetically modified cells, genome editing technologies



Objectives of CTWG & GTWG

1. Open discussion and sharing of best practices for the regulation of cell and gene therapy products;
2. Focused discussion on topics that are potentially suitable for regulatory convergence, and production of reflection documents;
3. Support harmonization initiatives such as APEC and Pan American Network for Drug Regulatory Harmonization
4. Refer topics to appropriate organizations such as ICH, PIC/S, WHO.

Current CTWG & GTWG Projects

Cooperation between the working groups for cross-cutting topics

1. Regulatory Framework
   - Provide a reference to stakeholders for the regulatory expectations across regions
   - Allows identification of areas for possible regulatory convergence
2. Raw materials project
   - Evaluate expectations for raw material qualification

https://admin.iprp.global/sites/default/files/2020-12/IPRP_CTWG_Workplan_2020_1026.pdf
https://admin.iprp.global/sites/default/files/2020-12/IPRP_GTWG_Workplan_2020_1026.pdf

CTWG Work Products

2013 Meeting Report: “International Regulatory Perspectives: Degree of Regulatory Oversight for Eight Categories of Cell Therapy Products” (New Zealand)

- Characteristics of the Product
  - Degree of manipulation
  - Proposed use- homologous vs non-homologous
  - Cell source- autologous vs allogeneic
- Levels of Oversight
  - No oversight
  - Limited oversight
  - Pre-review and authorization

Reflection Paper: “General Principles to Address the Nature and Duration of Follow-Up for Subjects of Clinical Trials Using Cell Therapy Products”, October 2018

- Monitoring for safety on a product-by-product basis and indication
- Factors that influence the Nature and Duration of Follow-up
  - Characteristics of the Cell Product and its Manufacturing Process
  - Characteristics of the study population
  - Posology
  - Procedures or concomitant therapies
  - Previous experience with existing therapies

GTWG Work Products

Meeting Title: Assessment of Biodistribution Data in the Development of Gene Therapy Products Meeting Date:16-17 May 2015 Meeting Location: New Orleans, Louisiana, U.S.A

- Reflection Paper: “Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products”, April, 2018
- Meeting Report: “IPRP Reflection Paper on Biodistribution”. *Molecular Therapy Methods and Clinical Development*, volume 11, December, 2018.
- **ICH: S12: Nonclinical Biodistribution Considerations for Gene Therapy Products**

S12: Nonclinical Biodistribution Considerations for Gene Therapy Products

- The topic was endorsed by the ICH Assembly in June 2019
- Concept Paper and Business Plan were endorsed in Singapore in November 2019

ICH 5-Step Harmonization Process

https://www.ich.org/page/formal-ich-procedure

IPRP Link to ICH

- IPRP Management Committee meets on the borders of the biannual ICH meetings
- Activities in ICH include regulators and industry
- IPRP Regulators may propose topics to ICH that are appropriate for harmonization.
  - For example, the Reflection Paper on the biodistribution of gene therapy products “Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products” (2018) is now a topic for harmonization in ICH

How do these efforts support regulatory harmonization?

- Allow for common understanding of state of regulations across regions
  - Regulations cannot be harmonized across regions
  - Mutual understanding of regulatory schemes can support harmonized regulatory approaches
  - Unharmonized Terminology- knowledge of terms used across regions can assist in understanding regulatory requirements among regions
  - Communication during review of regulatory applications across regions where confidentiality agreements are in place.

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