2024 CMC Strategy Forum Japan
Tokyo Marriott Hotel, Japan
December 9-10, 2024

U.S. FOOD & DRUG ADMINISTRATION

Update on the initiatives at the Center for Biologics Evaluation and Research (CBER), U.S. FDA

Ingrid Markovic, Ph.D.
Senior Science Advisor for CMC
FDA/CBER

CBER ICH Quality Lead & Regulatory Chair for ICH Q6 EWG

CBER Products

- Gene therapies
- Human tissues and cellular products
- Xenotransplantation products
- Allergenics
- Live biotherapeutic products
- Vaccines (preventative and therapeutic)
- Whole blood, plasma, and blood products
- Devices related to biologics

Presentation Outline

- Lifecycle Management Tools – CP/PACMP
- Application of platform technology provision
- Efforts to facilitate CMC Readiness Pilot (CDRP) Program
- Exploring concurrent submission and product review with other regulatory authorities for Cell & Gene Therapies

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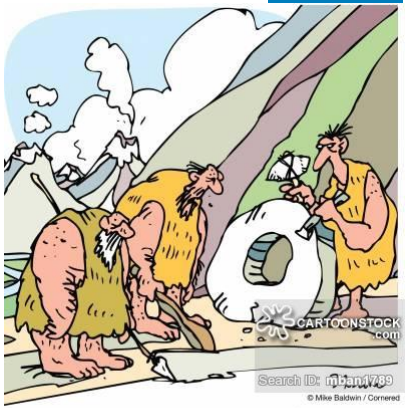
Lifecycle Management Tools
- CP/PACMP -
Past, Present & Future

Manufacturing Changes Are Inevitable

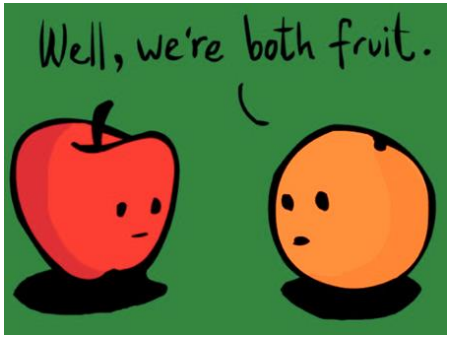
Some examples include:

- Scale-up/scale-out, new manufacturing site, new analytical assay
- Reacting to manufacturing problem or contamination
- Reagent or material is no longer available or in short supply
- Improve product quality based on new scientific or clinical information
- Process improvements (e.g., more efficient or streamlined process, better impurity profile, etc.)
- Cost effectiveness
- Cell bank has expired or been exhausted

Changes can occur at any point in the product lifecycle, but one needs to ensure that the change does not negatively impact product quality as it relates to S&E



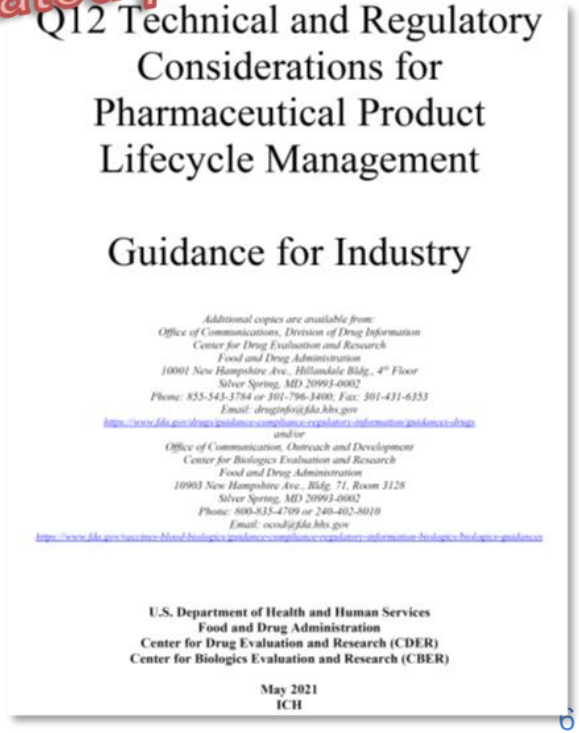
"What's with kids nowadays? Walking upright's not good enough for you?"



Tools: ICH Q12

Fully Implemented for CDER and CBER regulated products

- **Established Conditions (EC)**
  - Elements (e.g. parameters, attributes, controls, specifications, etc…) necessary to assure product quality that require a submission if changed
- **Post-approval Change Management Protocols (PACMP)**
  - Aligned with US FDA's comparability protocol (CP)
  - Predictability regarding timing of implementation of PA changes
  - Mechanism for changes across multiple products over the lifecycle of a product, applying the same principles
- **Product Lifecycle Management Document**
  - Central repository in the application for ECs and their reporting categories
- **Pharmaceutical Quality Systems (PQS)**
  - Effective PQS is necessary to support the use of Q12 tools
- **Relationship between Regulatory Assessment and Inspection**
  - Effective communication between assessors and inspectors to facilitate regulatory oversight of ICH Q12 implementation
- **Structured Approaches for Frequent CMC Post-Approval Changes**
  - Simplified approach to accomplish certain CMC changes for products where ECs were not identified



Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

Past Experience and Current Perspective on the Use of Comparability Protocols in Biologics: An Effective Tool to Manage Post-Approval Changes

Ingrid Markovic, Ph.D.

Special Advisor to the Associate Director for Review Management
Office of the Center Director
CBER
U.S. FDA

WCBP CMC Strategy Forum
November 9-10, 2015
Tokyo, Japan

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Experience with CP

- CPs for large molecules are generally:
  - Well designed
  - Well communicated
  - Risks are well evaluated
  - Backed up by prior knowledge
  - Successfully implemented

Experience with CPs (cont.)

Comparability Protocols Received from 2004 - 2014	
Attribute	**Percentage*/range**
Total CP per total CMC Supplements	~12.4%
Total trans-BLA per total CP	~58%
Trans-BLA members in trans-BLA applications	2 - 22
PAS resulting in CBE30	~39.3%
PAS resulting in CBE0	~50%

*Presented % may vary depending on the timing of CP receipt, revision, implementation, or discontinuation

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Types of CMC changes submitted as CPs

Comparability Protocols Received from 2004 - 2014	
CMC Changes (arranged in the order from most to least frequent)	**Percentage***
Facilities/equipment-specific: • Facility renovation/upgrade • Equipment qualification/upgrade • Introduction of new products into a licensed area • Site transfers (testing, filling, purification, etc.)	**~79%** (trans-BLA dominate for this category of changes)
Product/process-specific: • Process changes (e.g., scale-ups, purification, cell culture, etc.) • Working Seed/Working Cell Bank Qualification • Container/closure system • Analytical methods	**~21%**

*Presented % may vary depending on the timing of CP receipt, revision, implementation, or discontinuation

Experience with CPs/PACMPs (2004-2024)

	2004-2013	2014 - 2024	% Change
Number of CP/PACMP	422	498	18% ↑
Approval Rate	89.6% (378/422)	91%* (454/498)	1.4% ↑

*Projected approval rate considering that supplements received later in the year are under review

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Platform Technology Designation & Guidance

FDA Programs and Initiatives to facilitate development of new therapeutic products

Selected Quality-Related Provisions

- "PREVENT Pandemics Act" (Title II)
  - **Sec. 2503 – Platform Technologies**★
  - Sec. 2511 - Ensuring Registration of Foreign Drug and Device Manufacturers
  - Sec. 2512 Extending Expiration Dates for Certain Drugs
- "Food and Drug Omnibus Reform Act of 2022" (FDORA, Title III)
  - Sec. 3203 Emerging Technology Program
  - **Sec. 3213 Advanced Manufacturing Technologies Designation Program**
  - Sec. 3613 Improving Food and Drug Administration Inspections

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Section 2503. Platform Technologies (PT) Provision

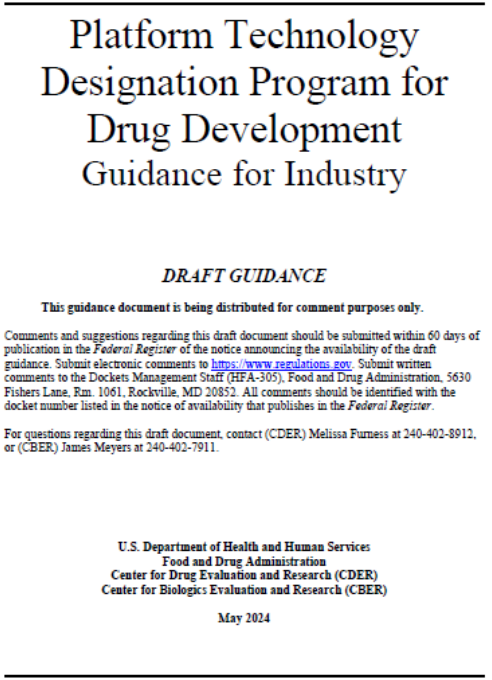
Section 3213. Advanced Manufacturing Technology (AMT) Provision

Section 2503. Platform Technologies

- A platform technology is a well understood and reproducible technology, which may include a nucleic acid sequence, molecular structure, mechanism of action, delivery method, vector, or a combination of any such technologies that FDA determines to be appropriate
  1) …it is incorporated in, or used by, an approved drug
  2) …can be … incorporated into, or utilized by, more than one drug sharing common structural elements
  3) …reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process.

Platform Technology Designation Program for Drug Development Draft Guidance

- Key considerations
  - Eligibility
  - Potential benefits
  - Recommended content of request
  - Meetings to discuss request
  - Lifecycle
- Revocation
- Post-approval changes
- General considerations



Platform Technology Designation Program for Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Melissa Furness at 240-402-8912, or (CBER) James Meyers at 240-402-7911.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2024

https://www.fda.gov/media/178938/download

Benefits of the PTD Program

Key benefit	• Opportunities to leverage information from the designated PT in subsequent application(s) • The application should be from the same sponsor that was granted PTD, or from a sponsor that has been granted a full right of reference
Additional benefits	• Early interactions and/or additional interactions and/or meetings with possibility to prioritize such interactions (resource-permitting)

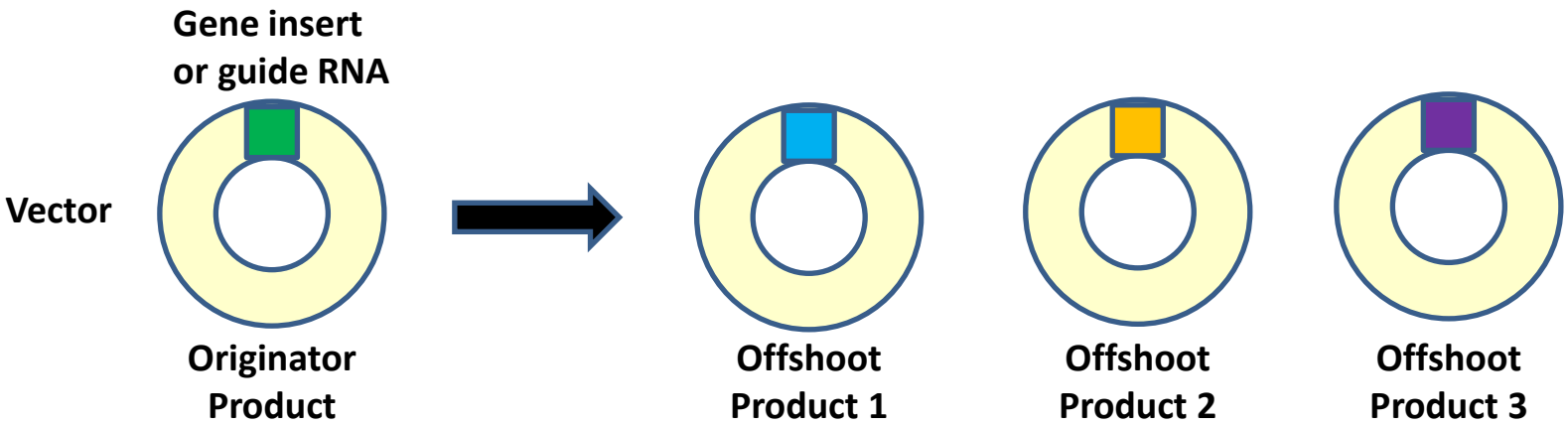
Selected examples of PTs

Examples of PTs	• LNP platform for mRNA vaccine or gene therapy product • Vector • Monoclonal antibody platform • LNP platform encapsulating oligonucleotides
Examples of data that may be leveraged	• Batch data, stability data • Previous inspectional findings • Certain nonclinical safety data

Not amenable to PT designation

- Approaches to viral clearance for certain unit operations
- Established unit operations
- Established formulation technologies
- NIR for in-process material attributes
- Analytical methods leveraging prior knowledge
- Common device delivery technologies

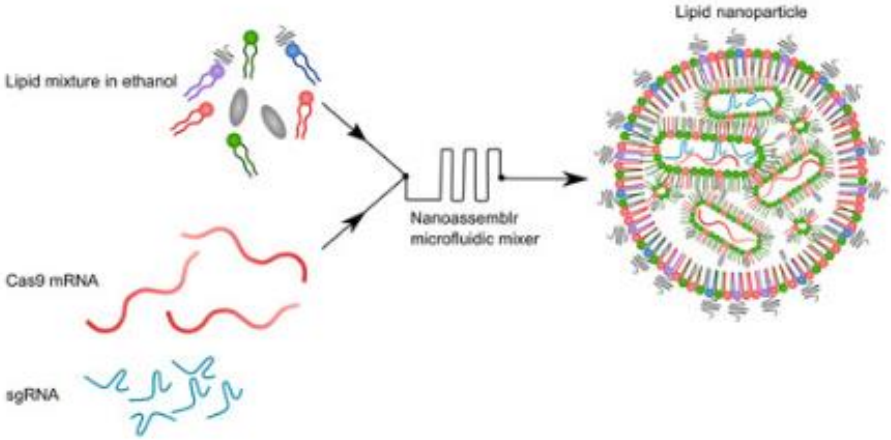
Platform Technologies



Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Promise of the mRNA Platform



From: Rosenblum et al., Sci. Adv. 2020; 6:eabc9450.

Broader consideration regarding PT

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 September 2024

Quality Innovation Group (QIG)

Listen and Learn Focus Group (LLFG) meeting on

Platforms Technologies

Agenda

19th - 20th November 2024

Virtual meeting

Chair: Marcel Hoefnagel

Day 1

Chair: Marcel Hoefnagel

Timing		Contributors:
09:30 – 09:45	**Opening of the LLFG** Welcome to participants. Introduction to QIG, meeting scope and objectives of the 4th QIG LLFG.	Marcel Hoefnagel (QIG Chair, MEB)
09:45 – 10:15	1: Regulatory Presentation (Title to be confirmed)	René Thürmer (QIG Member, BfArM)
	Session 1	
10:15 – 10:25	2. Platforms technologies are critical to accelerating vaccine development	Cathy Hoath - CEPI
10:25 – 10:55	3: mRNA-LNP platform technology to support specification setting and determination of product shelf life	Brian Doyle - Moderna
10:55 – 11:10	Q&A	

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- EMA hosted public w-shop with Industry, other health authorities (FDA, PMDA, etc.) and Academia to discuss anticipated benefits and ways of thinking about it
- Robust discussion with early promising steps towards broader dialogue on PT with other health authorities

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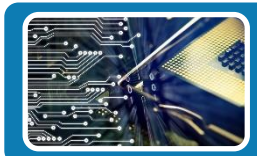
PDUFA VII CMC Programs Facilitating CMC Development

PDUFA VII: CMC Commitments

CMC Development & Readiness Pilot (CDRP) Program



Advancing utilization and implementation of innovative manufacturing

Considering alternative tools to assess manufacturing facilities

Enhancing Communication Between FDA and Sponsors During Application Review (i.e., 4-Part Harmony)

Enhancing Inspection Communication for Applications

CMC Development and Readiness Pilot (CDRP) Program

Aligning Clinical Development with CMC Development

CDRP Program Origin: Why is it needed?

Industry expressed concerns that CMC has become a bottleneck for the premarket review of expedited products

FDA observed gaps in the CMC information in expedited applications, which may suggest that CMC development is not progressing at the same pace as clinical development

Sponsors with expedited programs would benefit from a proactive focus on CMC activities early on. This, coupled with additional guidance from the FDA would help ensure that CMC can keep pace with clinical dev. mitigating delays and better aligning overall product development

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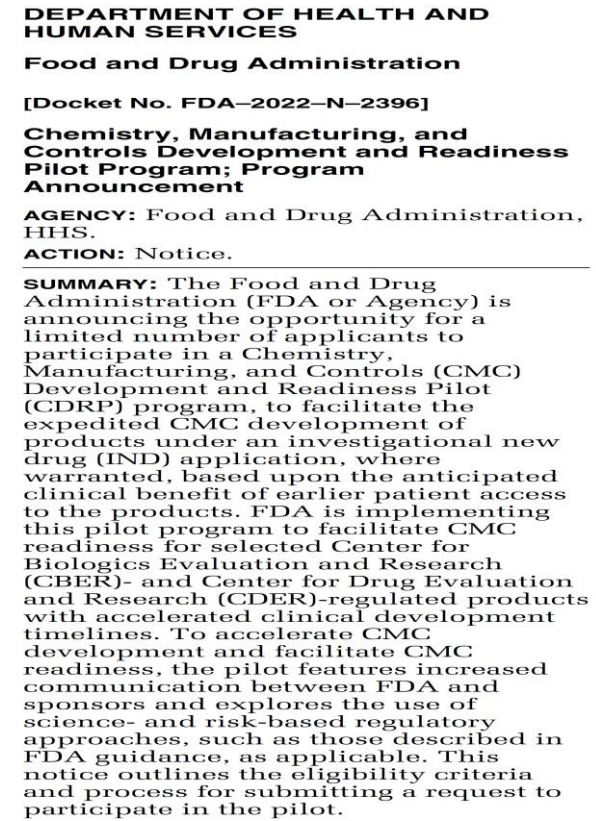
CMC Development and Readiness Pilot Program (CDRP)

- CDRP Start Date : April 1, 2023
- Duration: 2023-2027 (PDUFA VII Period)
- Intended for Sponsors developing products under highly accelerated clinical development timelines
- Excellent opportunity for an additional help provided by the FDA to obtain CMC-focused advice



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–2396]

Chemistry, Manufacturing, and Controls Development and Readiness Pilot Program; Program Announcement

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the opportunity for a limited number of applicants to participate in a Chemistry, Manufacturing, and Controls (CMC) Development and Readiness Pilot (CDRP) program, to facilitate the expedited CMC development of products under an investigational new drug (IND) application, where warranted, based upon the anticipated clinical benefit of earlier patient access to the products. FDA is implementing this pilot program to facilitate CMC readiness for selected Center for Biologics Evaluation and Research (CBER)- and Center for Drug Evaluation and Research (CDER)-regulated products with accelerated clinical development timelines. To accelerate CMC development and facilitate CMC readiness, the pilot features increased communication between FDA and sponsors and explores the use of science- and risk-based regulatory approaches, such as those described in FDA guidance, as applicable. This notice outlines the eligibility criteria and process for submitting a request to participate in the pilot.

CDRP Website, CDRP Webinar, FRN YR3

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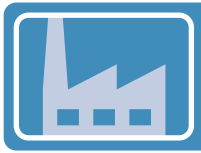
CDRP Program: Anticipated benefits

 Patient access	• Provide patients with earlier access to transformative therapies
 Time to market	• Speed time to market to realize commercial benefits sooner
 Data supporting approval mitigating knowledge gaps	• Identify CMC areas requiring attention to de-risk future manufacturing, and identify opportunities for improvement and optimization
 Application process	• More complete CMC application package reducing burden on the FDA & Applicant - 1st cycle approvals, fewer major amendments, fewer IRs, facility readiness
 Meet market demand once approved	• Ensure robust supply to patients once product is on the market

Key improvements to the pilot to address perceived burden of the application process

In May 2024, FDA partnered with BIO and PhRMA to co-host a webinar to showcase and reinforce the benefits of the pilot (much like STAR pilot)

Had a pre-webinar survey to collect industry's feedback to help inform our next steps

Based on the feedback received, we reassessed pilot criteria and made considerable improvements posted in FRN3

- **Selection and Eligibility Criteria Revisions**:
  - Revised to enable broader participation, including sponsors further along in the development and those with wide range of experiences
- **CMC Development Plan Requirements**:
  - The requirements for the CMC Development Plan have been made less burdensome clarifying that knowledge gaps are acceptable at this stage.
- **FDA Response Timeline and Review Process:**
  - The FDA's response timeline for participation requests has been shortened from 180 days to 90 days.
  - The review process has shifted from a quarterly review to a continuous review approach.

Global Regulatory Convergence Initiatives for CGTs

Global Regulatory Convergence

- Robust commercial viability requires at least about 100 gene therapy treatments per year
- Any one country may not have enough patients to make many products commercially viable
- However, marketing across high income countries could result in commercial viability
- Relying on a provided regulatory framework and on harmonized regulatory decisions equivalent to “pre-qualification” could help facilitate access

Practical Next Steps

- More active harmonization of regulatory approach in high income countries
  - CoGenT Regulatory Pilot
- Provide education and regulatory information for low- and middle-income countries
  - International Conference of Drug Regulatory Authorities (ICDRA) supported by WHO Cell and Gene Therapy Initiative

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Potential areas for convergence
  - Manufacturing information
  - Clinical outcomes
  - Preclinical study requirements
  - Environmental assessments
- Resolving differences can facilitate simultaneous regulatory submissions globally

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Initial participation by US FDA and European Medicines Agency
- Expansion possible to 8 to 10 additional high-income country regulators
  - Partners may participate in internal and external regulatory meetings
  - Specific regulatory reviews are shared and discussed with partners
  - All activities under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

WHO Workshop, Muscat, Oman 2024

Request for WHO to facilitate:

- **Emphasis on** global regulatory convergence (especially on terminology) and **regulatory reliance on the decisions of advanced NRAs/WHO**
- Regulatory capacity building
- Development of international, regional, local guidelines on regulation of cell, tissue, and gene therapies
- Development of risk-based approach(es) for regulation of CGTPs, classification, terminology
- Technical assistance for review of CGTP applications
- Development of WHO international standards for CGTPs

Executive Summary of WHO Implementation Workshop on 'WHO Considerations in Developing a Regulatory Framework for Human Cells and Tissues and for Advanced Therapy Medicinal Products'

14-16 May 2024
Muscat, Oman

The implementation workshop on WHO considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products was held in Muscat, Oman from 14-16 May 2024 and was attended by 68 participants from 31 countries across 6 WHO regions, including regulators, members of the Expert Advisory Panel on Biological Standardization, manufacturers and WHO staff from HQ, EMRO, AFRO, and Oman country office.

Fig 1. Participants from 31 countries across six WHO regions.

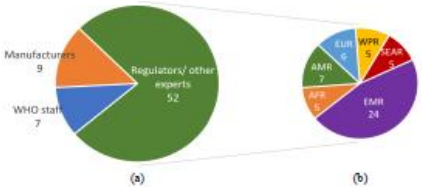


Fig 2. (a) The number of participating regulators/experts, manufacturers and WHO staff (total 68). (b) Breakdown by region of participating regulators/other experts.

Summary

- CBER is committed to advancing the science and regulatory evaluation of complex biological products
- Through various initiatives underway, the center aims to assist developers and manufacturers of biological products in improving the efficiency of their development processes, ultimately providing patients with earlier access
- Global regulatory convergence could help facilitate commercial availability and pave the way for the use of gene therapies world-wide

Acknowledgements!

- CBER Leadership:
  - Dr. Peter Marks
  - Dr. Celia Witten
  - Julie Tierney
- And the rest of incredibly committed and dedicated CBER staff

Thank you!