Cell & Gene Therapy Discussion Group (CGT DG): Progress toward Delivering a Strategic Roadmap

CASSS CMC Strategy Forum Japan

Kathleen Francissen, Ph.D.

BIO

10 December 2024

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Overview

- Describe the Cell & Gene Therapy Discussion Group (ICH CGT DG)
- Provide rationale for CGT DG formation
- Outline the remit
- Describe progress toward deliverables in the Work Plan

Cell & Gene Therapy Discussion Group

- Topic adoption date: August, 2023
- Rapporteur: Dr. Kathleen Francissen, BIO
- Regulatory Chair: Dr. Melanie Eacho, FDA, United States
- CGT DG Kick-off Meeting: October, 2023

ICH Website

- Work Plan endorsement: December, 2023
- Rapporteur Supporter: Elaine Shults, BIO

Cell & Gene Therapy Discussion Group

- CGT DG Remit Paper
- CGT DG Work Plan
- CGT DG Roster

Remit Paper

Endorsed by the ICH Management Committee on 12 May 2023

ICH Remit Paper

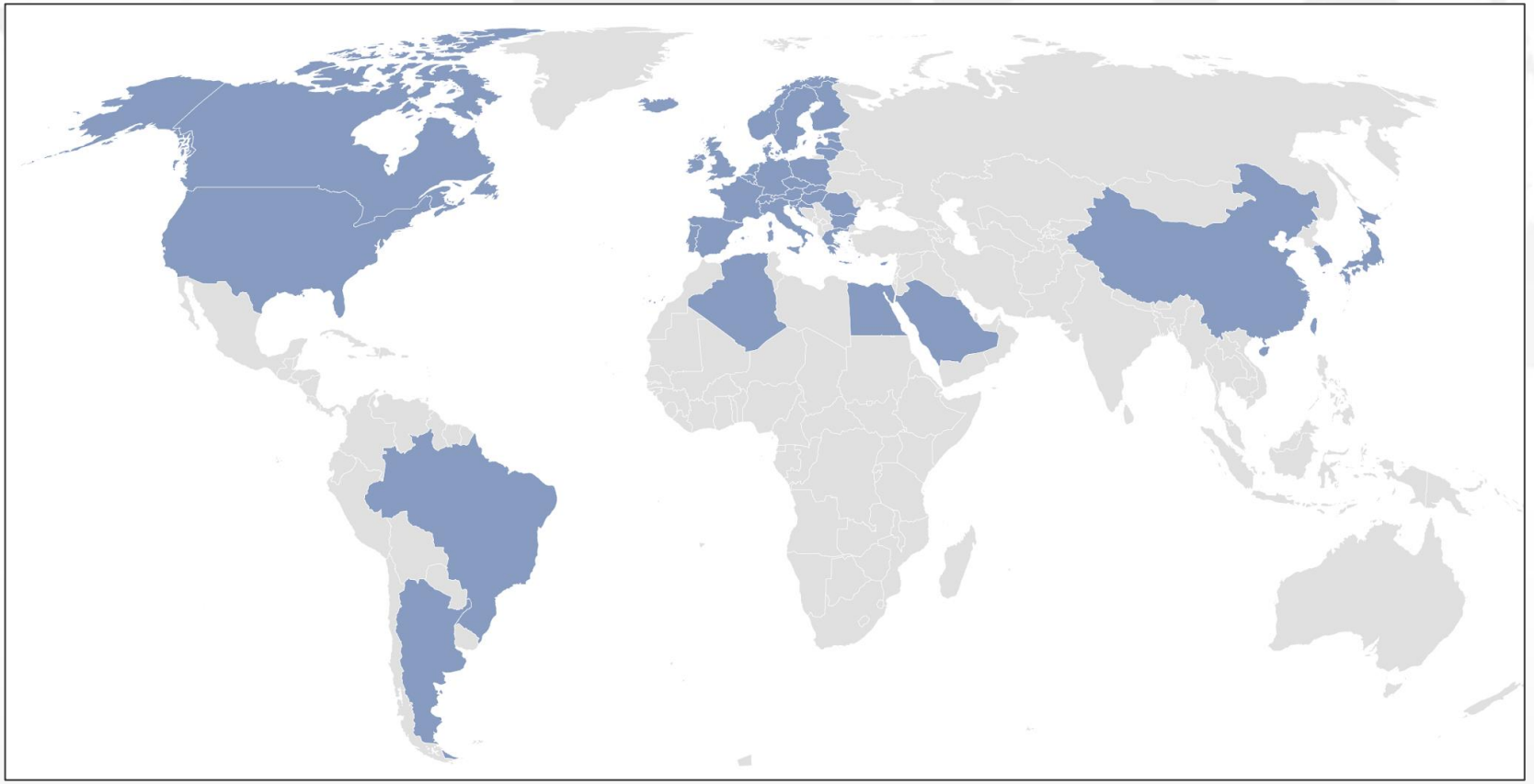
ICH Cell and Gene Therapies Discussion Group

General Description

The ICH Cell and Gene Therapies Discussion Group (CGTDG) will serve as a technical discussion forum for issues related to ICH harmonization efforts in the field of Cell and Gene Therapies (CGT) products. The CGTDG will develop a holistic CGT roadmap within the scope of modalities identified below, including prioritization of areas of most need for harmonization whereby technical consensus can be achieved with specific recommendations for new guideline development or revisions to existing ICH Guidelines.

- Remit paper describes scope and timelines
- Final deliverable by October, 2025

ICH CGT DG Members



25 member organizations representing 45 countries

ICH CGT DG Members

Regulatory/Administrative Authorities

- EU commission, Europe
- FDA, USA
- MHLW/PMDA, Japan
- ANVISA, Brazil
- EDA, Egypt
- HSA, Singapore
- MFDS, Republic of Korea
- MHRA, UK
- NMPA, China
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- Health Canada, Canada
- Swissmedic, Switzerland
- ANMAT, Argentina
- ANPP, Algeria

Industry Associations

- EFPIA
- JPMA
- PhRMA
- BIO
- IFPMA
- IGBA

Other/International Associations

- EDQM
- USP
- IPRP
- WHO

Cell & Gene Therapy *Discussion* Group

- Technical discussion forum
- Ultimate deliverable: Strategic Roadmap

Rationale for forming CGT DG

- Numerous studies: estimate ~1400 active ATMP clinical trials worldwide.*

- Largest numbers are:
  - CAR T-cell products and
  - Adeno-associated viral (AAV) vector-based gene therapy products

- Estimate ~5,800 patients dosed with AAV-based GT and ~38,000 with CAR T-cell products (including clinical + commercial setting).

- This figure refers to Advanced Therapy Medicinal Products (ATMPs) as defined by WHO. Therefore, it does not include prophylactic vaccines against infectious disease or synthetic oligonucleotide products. Excludes preclinical programs. Includes active/open trials only. Verified number of trials (vs clinical trial sites).Estimates as of March 2024
- ** These numbers were estimated using Trial Trove and ClinicalTrials.gov as the main source of information, in addition to review documents from FDA and EMA, as well as company press releases and SEC filings, in Feb 2022.

Global Development

- Increasingly global development and commercialization.

~111 CGT products approved worldwide*

* This estimate refers to Advanced Therapy Medicinal Products (ATMPs) as defined by WHO, which are approved in at least one country worldwide.

Rationale for forming CGT DG

- Application of current ICH guidelines for traditional biologics does not fully address the unique characteristics of ATMPs and may even cause additional challenges.

- Nonclinical, clinical, and manufacturing development of ATMPs can be uniquely complex *and interdependent*.

- Important to advance and converge on a science-based regulatory framework across all regions to make clear the development and lifecycle management requirements.

ICH MC Endorsed Formation of CGT DG

- Overall aim: Develop a strategic framework to address future harmonization needs for ATMPs.

- Roadmap: Prioritized areas of most need for harmonization where technical consensus can be achieved with specific recommendations for new guideline development or revisions to existing ICH Guidelines.

- ICH CGT DG to work in close coordination with IPRP and WHO to ensure a holistic approach to harmonization efforts and minimize duplicative efforts.

CGT DG to Advise Existing ICH EWGs

- CGT DG is not tasked with the development or revisions of specific ICH Guidelines but may act as an advisor group to existing ICH Expert Working Group (EWG) undergoing new or revised guideline development where CGT products are in scope.

- Completed: Review ATMP Annex for ICH Q1/Q5c Stability Revision EWG (January, 2024).

- CGT DG agreed to use the term Advanced Therapy Medicinal Product (ATMP).
  - WHO Annex 3 (adopted March 2023): *Considerations in developing a regulatory framework for human cells and tissues and advanced therapy medicinal products*
- Advise ICH Q6 Specifications Revision EWG

Scope of CGT DG

- Initial focus on CGT modalities of relatively high maturity.

- Classes of products with global marketing authorization or prominent in global clinical development programs.

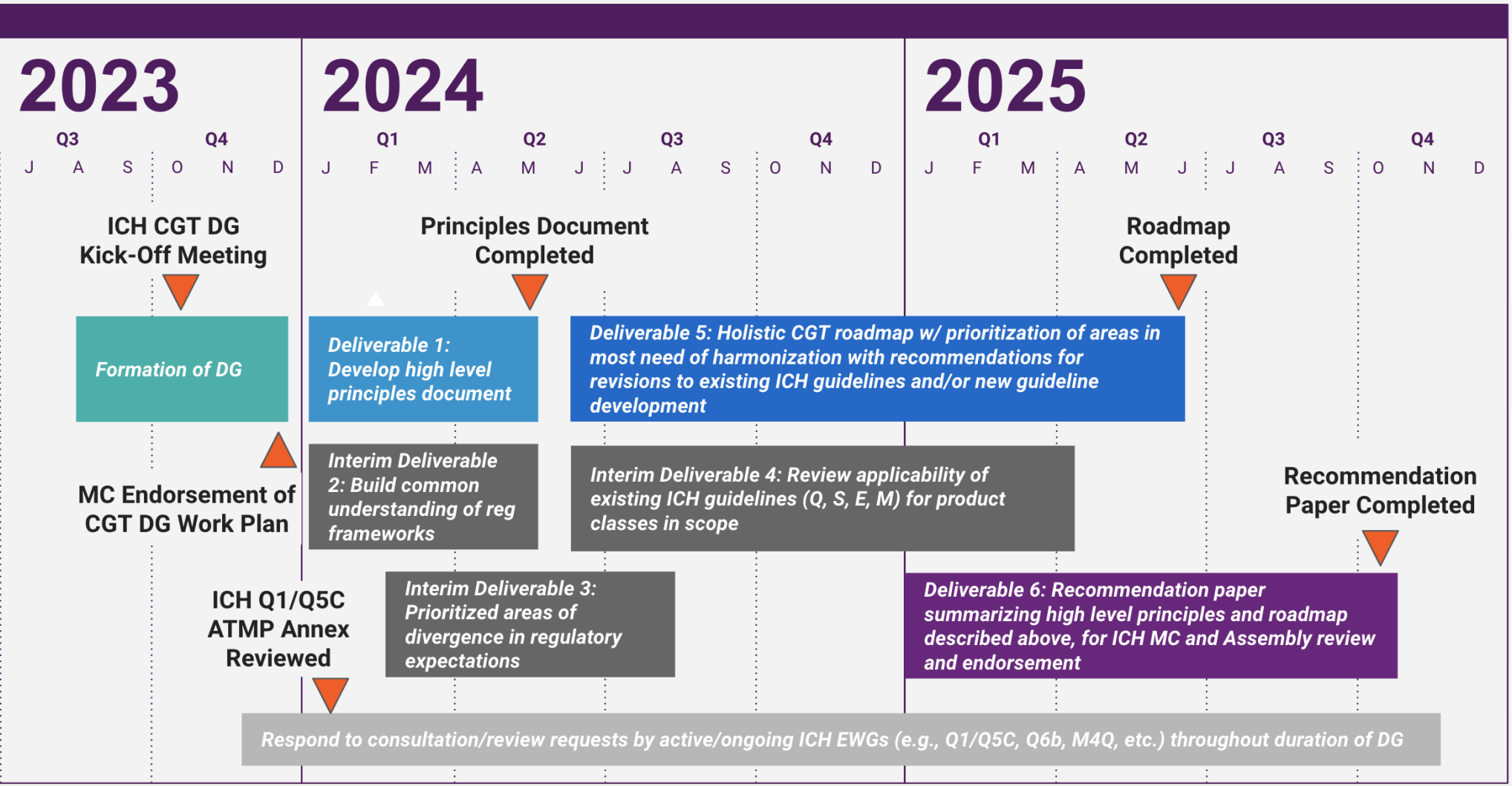
  - *In vivo* viral vector-based gene therapy products (e.g. AAV vector-based gene therapies)

  - *Ex vivo* genetically modified cells (e.g. CAR T-cell products), both autologous and allogeneic

Work Plan: Expected Future Key Milestones

Expected Completion date	Deliverable
Apr 2025	(“Interim Deliverable 4”) Review existing ICH guidelines (Q, S, E, M) in terms of their applicability to CGT product classes in scope and identify areas where harmonisation already exists and areas for improvement in harmonisation
Jun 2025	(“Deliverable 5”) Holistic CGT roadmap w/ prioritization of areas in most need of harmonization with recommendations for revisions to existing ICH guidelines and/or possibly new guideline development
Oct 2025	(“Deliverable 6”) Recommendation paper summarizing high level principles and roadmap described above, for ICH MC and Assembly review and endorsement

Work Plan Milestones Timeline



Deliverables Progressing in Parallel

- Work Plan reflects milestones outlined in remit paper.

- Deliverables:
  1. High level principles document
  2. Global regulatory framework for ATMPs
  3. Areas of divergence and harmonization in regulatory expectations
  4. Stepwise review of existing ICH guidelines for applicability to ATMPs
  5. Holistic ATMP roadmap with staggered approach
  6. Recommendation paper

High Level Principles for ATMPs

- What makes ATMPs different from other medicinal products
- Completed initial full draft in October 2024
- Focus on more mature CGT product classes
  - Concepts may also be applicable to ATMPs more broadly

- Special circumstances during development and/or life cycle management

Global ATMP Regulatory Framework

- ❖ CGT DG built common understanding of existing regulatory frameworks across regions .

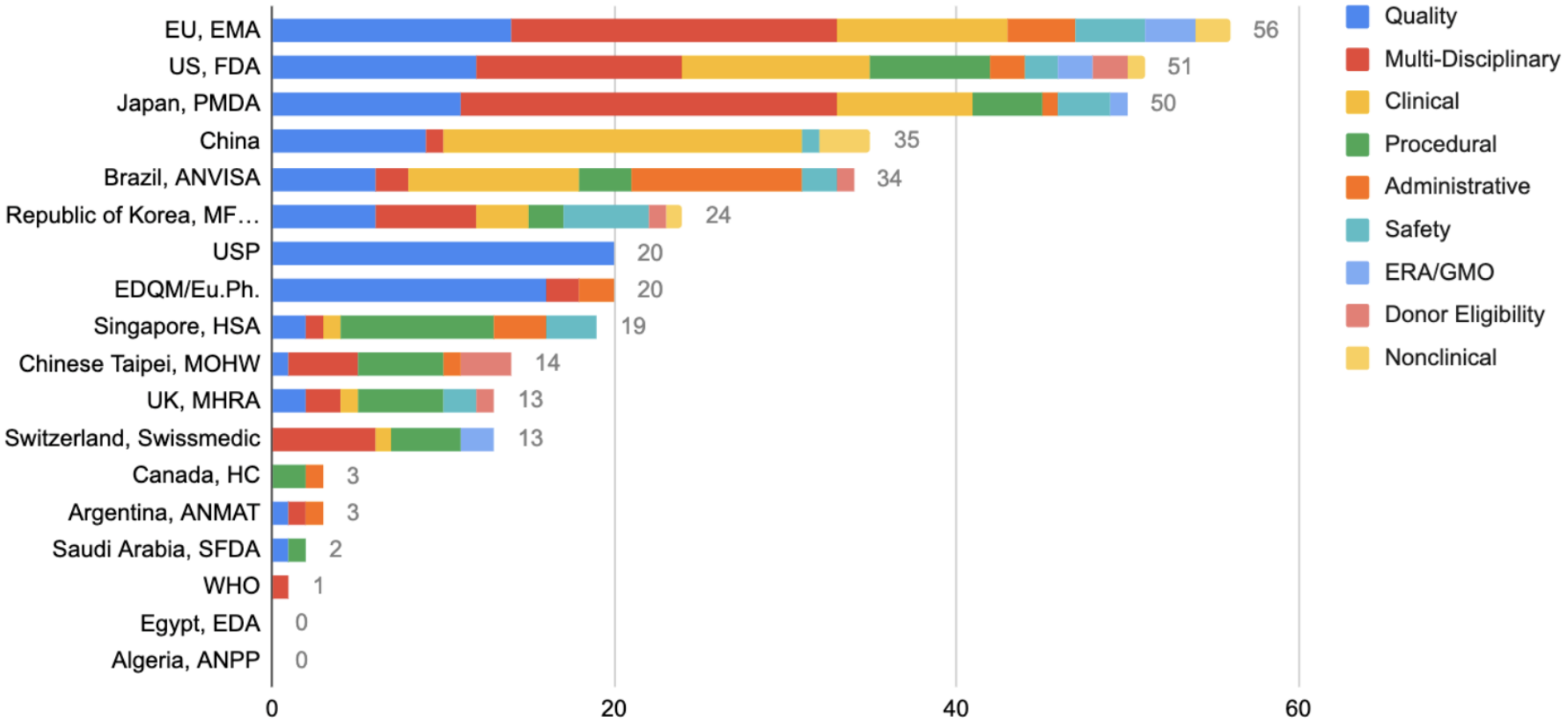
- ✓ Reviewed and verified global map of ATMP-specific regulations.
- ✓ Approximately 400 national/regional guidelines currently

- ❖ Inter-agency meeting held among regulators
- ❖ Identified areas of divergence or gaps.

ATMP Global Regulatory Framework

ICH CGT DG Member Existing Regulations and Guidances on ATMPs

Data analyzed from IPRP, Health Authority websites, and third party databases. (n = 359 regs and guidances)



Nearly 400 ATMP-specific guidelines and regulations across regulatory agencies participating in CGT DG (as of November 2024)

Identified Areas of Divergence: Industry

- Identified areas of divergence in regulatory expectations – industry perspective (BIO, EFPIA, IFPMA, IGBA, JPMA, and PhRMA) using surveys to trade associations

- Inter-association meeting to align on approach to gather info (Feb 2024).

- Compile information gathered by trade groups (Feb - May 2024).

- Divergence that developers encountered while trying to conduct global clinical trials and/or commercialize ATMPs in multiple globally.

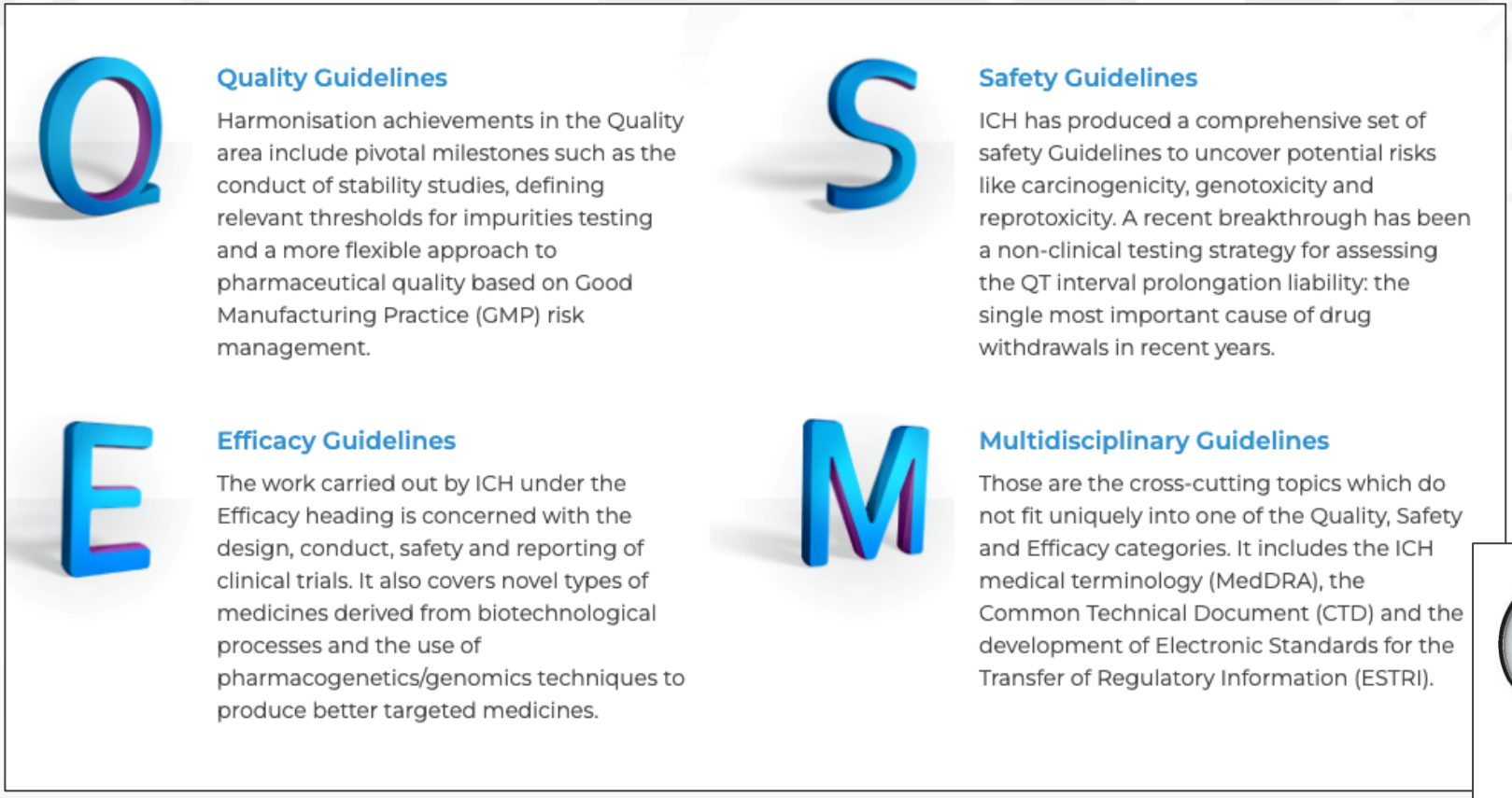
Brought Perspectives Together

- CGT DG collectively discuss topics for harmonization: identified and prioritized by regulators and industry/trade associations.

- Key step in identifying topics for harmonization and their readiness and priority, based on collective experience of DG members.

- Consolidate and prioritize areas for harmonization.

Mapping priority ATMP issues to existing ICH guidelines



Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

- Large PDF consolidation created keyword-searchable files, aiding in topic mapping process. Includes: All Guidelines, Q&As, consideration documents, and drafts available as of September 2024. (2,765 total pages)
- Assess applicability of ICH guidelines to ATMPs

Holistic Roadmap

- Generate holistic CGT roadmap with prioritized areas for harmonization: June, 2025.

- Recommend staggered approach to address these areas.

- Recommend revisions to existing ICH guidelines and/or new guideline development.

Recommendation Paper

- Summarize high level principles and strategic roadmap in Recommendation Paper

- Submit to ICH MC for review and endorsement by October, 2025.