Health Canada Santé Canada

ICH Member

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA – Health Canada ICH Public Meeting

May 14, 2021

Agenda

- Welcome and Opening Remarks
- Overview of ICH
- Topics Recently Reaching ICH Milestones
- E6 Principles
- Q12 Implementation
- Model Informed Drug Development
- Patient Focused Drug Development
- Q&A/Comment Period

FDA and Health Canada

Regional ICH Consultation

Opening Remarks

May 14, 2021

Theresa M Mullin, PhD
Associate Director for Strategic Initiatives
FDA Center for Drug Evaluation and Research

Our regional meeting supports the original aims of 2015 ICH Reforms

Goals for ICH Reform in 2015

1. Focus global pharmaceutical regulatory harmonisation work in **one venue.**
2. Create a venue that gives to all key pharmaceutical regulatory authorities and industry stakeholders the **opportunity to be more actively involved** in pharmaceutical harmonisation work.
3. **Maintain efficient and well-managed operations** and harmonisation work processes.

The ICH Association, established in October 2015, is a non-profit legal entity under Swiss law with the aim to focus global pharmaceutical regulatory harmonisation work in one venue. http://www.ich.org/about/articles-procedures.html

Regional Meetings provide another opportunity for ICH and stakeholder engagement

- Since ICH reforms:
  - Growing participation of regulators and industry in work to harmonize scientific and technical standards for human drugs
  - Increasing recognition of need for external stakeholder engagement and consultation
  - Expanding opportunities for public input via EWG **workshops**, **publication of Reflection Papers** for public comment (e.g., GCP Renovation paper)

Significant Global Growth in the Number and Diversity of ICH Participants

ICH Members & Observers

MEMBERS

Founding Regulatory Members

- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan

Founding Industry Members

- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members

- Health Canada, Canada
- Swissmedic, Switzerland

MEMBERS (continued)

Regulatory Members

- ANVISA, Brazil
- HSA, Singapore
- MFDS, Republic of Korea
- NMPA, China
- TFDA, Chinese Taipei
- TITCK, Turkey

Industry Members

- Global Self-Care Federation
- IGBA
- BIO

OBSERVERS

Standing Observers

- IFPMA
- WHO

OBSERVERS (continued)

Legislative or Administrative Authorities

- ANMAT, Argentina
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- CPED, Israel
- INVIMA, Colombia
- JFDA, Jordan
- MMDA, Moldova
- MOPH, Lebanon
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SFDA, Saudi Arabia
- TGA, Australia

OBSERVERS (continued)

Regional Harmonisation Initiatives (RHIs)

- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

International Pharmaceutical Industry Organisation

- APIC

International Organisation regulated or affected by ICH Guideline(s)

- Bill & Melinda Gates Foundation
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

Approach to promoting ICH standards globally

- Guideline Relevance
  - Focus harmonized guideline work on topics directly relevant to the quality and efficiency of drug development, regulatory review, manufacturing, post-approval oversight
- Scientific Rigor
  - Focus on data-driven consensus-based scientific standards, with work processes that are inclusive and transparent
- Implementation
  - Support through training and continued monitoring progress and challenges in implementation

FDA and Health Canada Regional ICH Consultation -- Presentations

- **Overview of ICH**
  - *Jill Adleberg, FDA*
- **Guidelines Recently Reaching ICH Milestones (S1 and Q3C)**
  - *Alisa Vespa, Health Canada*
- **Guideline Work On-going: ICH E6 GCP Principles**
  - *Khair ElZarrad, FDA*
- **Guidelines in Implementation: ICH Q12**
  - *Ashley B. Boam, FDA*
- **ICH Discussion Groups: Model Informed Drug Development**
  - *Scott Marshall, PhRMA (Pfizer)*
- **ICH Reflection Papers: Patient Focused Drug Development**
  - *Robyn Bent, FDA*
- **Q&A/Comment Period**

Thank you

ICH Overview

Jill Adleberg
ICH Coordinator
International Programs, Office of the Center Director
CDER | US FDA

FDA/HC ICH Regional Public Meeting – May 14, 2021

ICH Overview

- The International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) is a unique harmonization organisation involving regulators and the pharmaceutical industry.
- Launched in 1990 by the US, EU, and Japan. Canada, Swissmedic and WHO as observers.
- Well-defined objectives:
  - **To improve efficiency of new drug development and registration processes**
  - **To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness**
- Accomplished through development of harmonized, technical guidelines and standards that are implemented by regulatory authorities.

ICH Association

Reformed as a non-profit legal entity under Swiss Law in 2015 to promote public health through international harmonization that contributes to:

- Focus global pharmaceutical regulatory harmonization work in a single forum for constructive dialogue on scientific issues
- Promote more involvement from regulators around the world and wider inclusion of global industry sectors
- Continue to harmonize and streamline the global drug development process for the benefit of patients around the world
- Facilitate greater adoption of new and improved research and development approaches, common standards, and therapeutic advances
- Maintain efficient and well-managed operations

ICH Members and Observers

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- FDA, US
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- PhRMA
- JPMA

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- INVIMA, Colombia
- JFDA, Jordan
- MMDA, Moldova
- MOPH, Lebanon
- National Ctr, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SFDA, Saudi Arabia
- TGA, Australia

Regional Harmonization Initiatives
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

Int'l Pharmaceutical Industry Organizations
- APIC

Int'l Orgs regulated by or affected by ICH guidelines
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- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

ICH Products

- ~70 guidelines on technical requirements related to human drugs
- Electronic Standards for the Transfer of Regulatory Information (CTD/eCTD, ICSRs)
- Medical Dictionary for Regulatory Activities (MedDRA) -- standardized medical terminology to facilitate regulatory information sharing

Major ICH Topic Areas

Safety

- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and Pharmacokinetics
- Duration of chronic toxicity testing
- Reproductive toxicology
- Safety pharmacology studies
- Immunotoxicology studies
- Nonclinical evaluation for anticancer pharmaceuticals
- Photosafety evaluation
- Nonclinical pediatric safety

Efficacy

- Clinical safety
- Clinical study reports
- Dose-response studies
- Good clinical practice
- Clinical trials
- Clinical evaluation by therapeutic category
- Clinical evaluation
- Pharmacogenomics

Quality

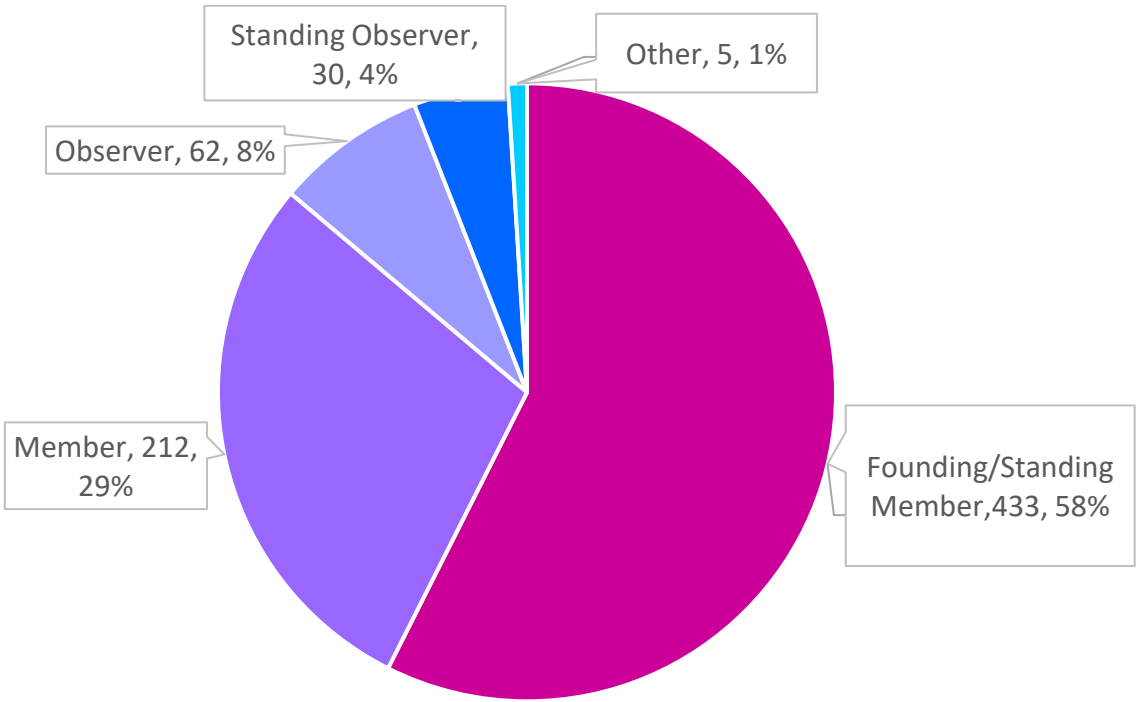
- Stability
- Analytical validation
- Impurities
- Pharmacopoeias
- Specifications
- Good manufacturing practice
- Pharmaceutical development
- Quality risk management
- Pharmaceutical quality system
- Development and manufacture of drug substances

Multidisciplinary

- MedDRA terminology
- Electronic standards
- Nonclinical safety studies
- CTD and eCTD
- Bioanalytical Method Validation
- Biopharmaceutics Classification System-based Biowaivers
- Data elements and standards for drug dictionaries
- Gene therapy
- Mutagenic impurities
- Drug Interaction Studies
- Bioequivalence for IR solid

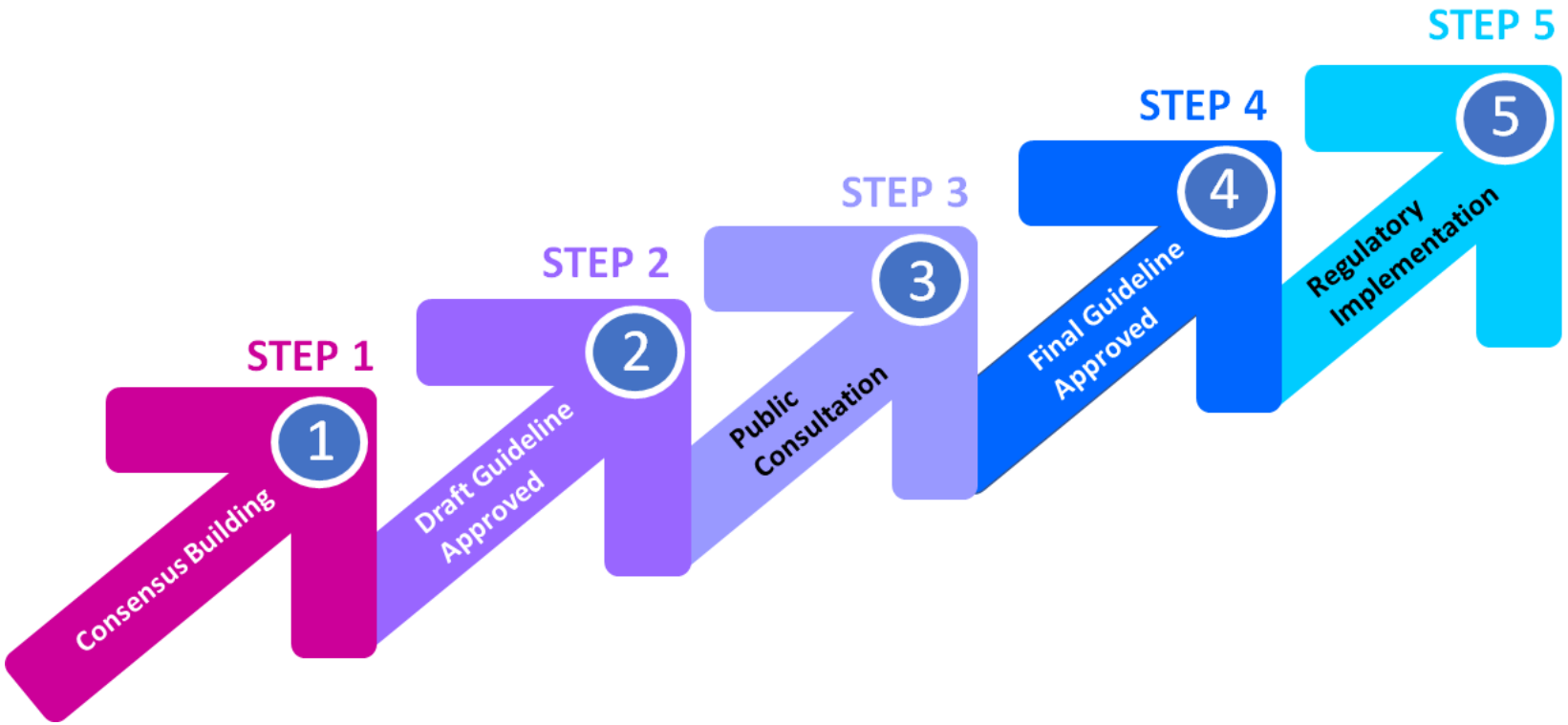
Composition of ICH Working Groups

Over 700 experts in 34 working groups



ICH Guideline Development

5 Step Process



ICH Training

Guideline Training:

- ICH is working to ensure that high quality training is available based upon scientific and regulatory principles outlined in its guidelines.

Efforts include:

- Development of a Training Library on the ICH website with access to all training materials including Step 4 working group presentations.
- Funding support for training programs organized by ICH regulatory members and observers.
- ICH Recognized Training Programs hosted by a variety of organizations, associations, regulatory authorities and academia. Offered in-person, virtually, and online. Information available on the ICH website.
- Online training materials development including some translations.

ICH Governance

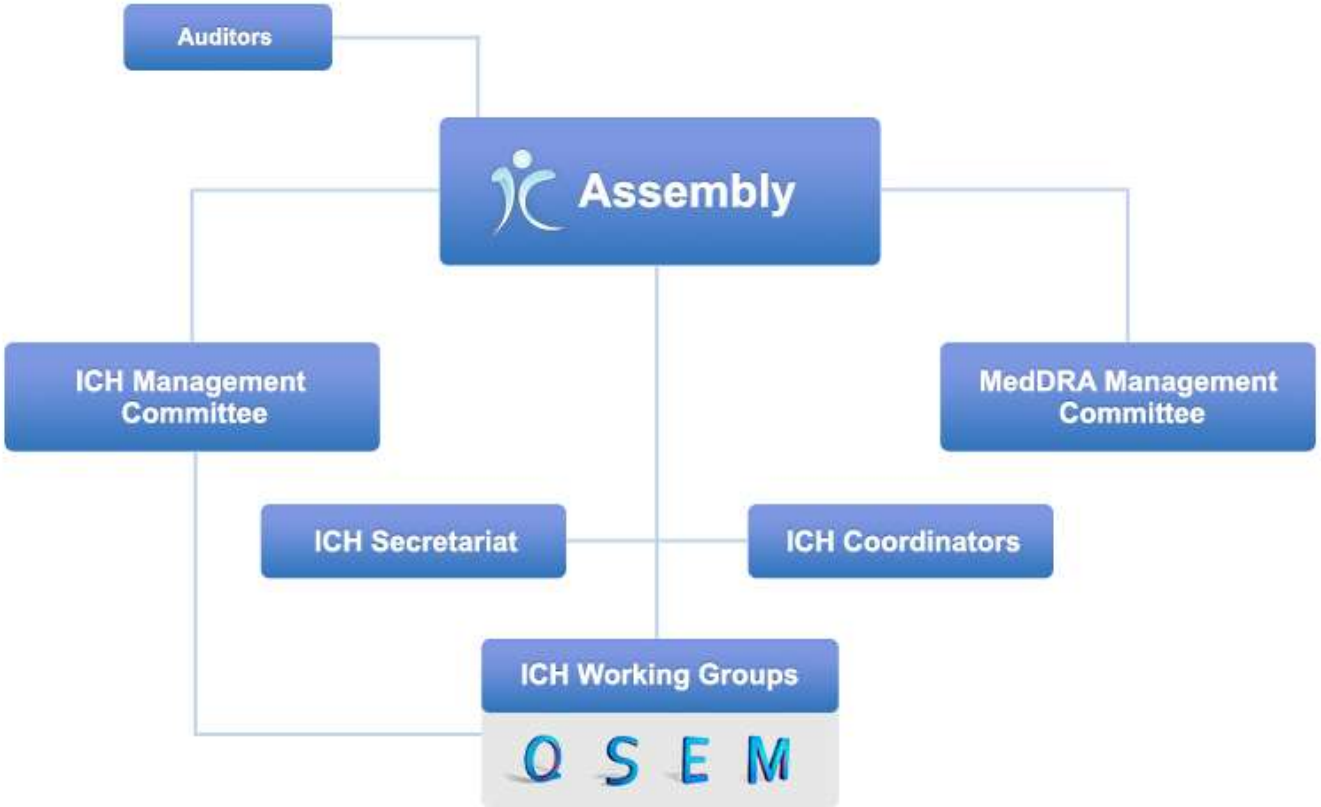
Assembly

- The overarching body, comprised of all ICH Members and Observers, that makes decisions regarding the Articles of Association and its rules and procedures, admission of new members, election of Management Committee representatives, adoption of ICH guidelines, etc.

Management Committee

- Oversees operational aspects on behalf of all members of the Association, including administrative and financial matters and oversight of WG operations.
- Financial responsibilities include preparation of the ICH budget and, during a transition period, ensure funding of ICH operations.
- Includes Permanent and Standing Members, and Elected Members

ICH Governance



Eligibility Criteria: Regulators

Recognized Authority

- Has a legal personality
- Responsible for regulation of pharmaceuticals for human use

Engagement in the ICH Process

- Past regular attendance in at least 3 ICH meetings during the previous 2 consecutive years
- Past appointment of experts in at least 2 working groups

Application of ICH Guidelines

At minimum, implemented the following guidelines:

- Q1: Stability Testing
- Q7: Good Manufacturing Practices for Active Pharmaceutical Ingredients
- E6: Good Clinical Practice

Eligibility Criteria: Industry

Recognized Authority

- Has a legal personality
- Represents members from several countries in at least three continents
- Organization or its members regulated by ICH guidelines

Engagement in the ICH Process

- Has participated in ICH as an observer
- Past regular attendance in ICH meetings
- Past appointment of experts in 2+ working groups

Summary

ICH:

- Draws on expertise of regulators and industry to achieve international harmonization of technical guidelines to enhance public health
- Uses a transparent, science- and consensus-based process for guideline development including opportunities for public comment
- Includes commitment of regulators to implement guidelines
- Has expanded global participation and engagement through recent reforms

Health Canada Santé Canada

Topics Recently Reaching Step 3 or 4 of the ICH Process: ICH Q3C(R8) & Addendum to ICH S1B(R1)

14 May 2021

Alisa Vespa, Ph.D.
Office of Risk Management
Bureau of Medical Sciences
Therapeutic Products Directorate, Health Canada

Presentation outline

- Q3C(R8): Impurities: Guideline for Residual Solvents
  - Permitted daily exposures (PDEs) for 3 new solvents

- S1B(R1): Testing for Carcinogenicity of Pharmaceuticals
  - Addendum to S1B
  - Expands the testing scheme for assessing human carcinogenic risk of small molecule pharmaceuticals

ICH Q3C(R8): Guideline for residual solvents

PDEs for 2-methyltetrahydrofuran, cyclopentyl methyl ether, and tertiary-butyl alcohol

ICH Q3C(R8): Guideline for residual solvents

Purpose of the ICH Q3C guideline

- To recommend Permitted Daily Exposure (PDE) levels of residual solvents in pharmaceuticals to ensure patient safety

ICH Q3C(R8): Guideline for residual solvents

Document history

- ICH Q3C core guideline adopted by ICH in June 1997
- In 1999, maintenance expert working group formed to:
  - Revise existing PDEs as new toxicity data becomes available
  - Develop monographs and derive PDEs for new solvents when adequate toxicity data is available
- ICH Q3C has undergone several revisions over the past 20 years

ICH Q3C(R8): Guideline for residual solvents

Timeline of current update

- Consensus reached in May 2017 to develop monographs and derive PDEs for the following solvents:
  - 2-Methyltetrahydrofuran
  - Cyclopentyl methyl ether
  - Tertiary-butyl alcohol
- Step 1 draft document endorsed by ICH Assembly (March 2020)
- Step 3 regulatory consultation, EWG discussion, document revision (April 2021)
- Step 4 adoption of the guideline by ICH Assembly (April 2021)

https://database.ich.org/sites/default/files/ICH_Q3C-R8_Guideline_Step4_2021_0422_1.pdf

ICH Q3C(R8): Guideline for residual solvents

2-Methyltetrahydrofuran (2-MTHF): Summary of toxicity data

- Genotoxicity
  - No evidence of genotoxic potential
- Carcinogenicity
  - No data available
- Reproductive toxicity
  - No reliable studies for PDE calculation
- Repeat dose toxicity
  - Two 3-month oral rat studies available
  - One of the studies was appropriate calculating PDE

ICH Q3C(R8): Guideline for residual solvents

2-Methyltetrahydrofuran (2-MTHF): Derivation of PDE

- Male and female rats orally dosed with 2-MTHF at 80, 250, 500 and 1000 mg/kg/day for 3-months

- NOEL = 250 mg/kg/day

$$PDE = \frac{250 \text{ mg/kg/day} \times 50 \text{ kg (weight adjustment)}}{5 \times 10 \times 5 \times 1 \times 1 \text{ (modifying factors)}} = 50 \text{ mg/day}$$

ICH Q3C(R8): Guideline for residual solvents

Outcome of regulatory consultation

- Monograph updated to include results of an OECD 414 & GLP-compliant rat developmental toxicity study
- No change to PDE

2-Methyltetrahydrofuran (2-MTHF)

- PDE = 50 mg/day
- Placed into Class 3 “solvents with low toxic potential”

ICH Q3C(R8): Guideline for residual solvents

Cyclopentyl methyl ether (CPME): Summary of toxicity data

- Genotoxicity
  - No evidence of genotoxic potential
- Carcinogenicity
  - No data available
- Reproductive toxicity
  - No reliable studies for PDE calculation
- Repeat dose toxicity studies in rats
  - Two oral (28-day, 90-day) and one 90-day inhalation study
  - NOEL from 28-day oral study considered most appropriate for PDE calculation

ICH Q3C(R8): Guideline for residual solvents

Cyclopentyl methyl ether (CPME): Derivation of PDE

- Male and female rats orally dosed with CPME at 15, 150 and 700 mg/kg/day for 28 days

- NOEL = 150 mg/kg/day

$$PDE = \frac{150 \text{ mg/kg/day} \times 50 \text{ kg (weight adjustment)}}{5 \times 10 \times 10 \times 1 \times 1 \text{ (modifying factors)}} = 15 \text{ mg/day}$$

ICH Q3C(R8): Guideline for residual solvents

Outcome of regulatory consultation

- Minor editorial revisions made to the monograph
- No change to PDE

Cyclopentyl methyl ether (CPME)

- PDE = 15 mg/day
- Placed into Class 2 “solvents to be limited”

ICH Q3C(R8): Guideline for residual solvents

Tertiary-butyl alcohol (TBA): Summary of toxicity data

- Genotoxicity
  - No evidence of genotoxic potential
- Reproductive and developmental toxicity
  - Evidence of TBA-induced effects at maternal dose of 1000 mg/kg/day (e.g., ↑ pup mortality and # stillborn pups)
  - NOAEL = 400 mg/kg/day

ICH Q3C(R8): Guideline for residual solvents

Tertiary-butyl alcohol (TBA): Summary of toxicity data

- Repeat dose toxicity: Two 13-week drinking water studies

Rats:

  - Mortality at high dose
  - Adverse effects in the kidney (nephropathy) and urinary bladder (inflammation) in both sexes
  - LOEL = 176 mg/kg/day

Mice:

  - Mortality at high dose
  - Adverse effects in the urinary bladder (hyperplasia/inflammation) in both sexes
  - NOEL = 1786 mg/kg/day

ICH Q3C(R8): Guideline for residual solvents

Tertiary-butyl alcohol (TBA): Summary of toxicity data

- Carcinogenicity: Rat and mouse drinking water studies (NTP)
  - Primary targets of toxicity and carcinogenicity were the kidney in rats; thyroid gland and urinary bladder in mice
  - NTP conclusion: "some evidence of carcinogenic activity" in male rats and female mice
- The 2-year carcinogenicity studies were considered the most appropriate to support calculation of the PDE
- A PDE was calculated for each carcinogenicity study
  - $PDE_{mice} > \boxed{PDE_{rats}}$

ICH Q3C(R8): Guideline for residual solvents

Tertiary-butyl alcohol (TBA): Derivation of PDE

- Rats orally dosed with TBA at 85, 195 and 420 mg/kg/day (males) and 175, 330, 650 mg/kg/day (females)

- LOEL = 175 mg/kg/day based on nephropathy in females

$$PDE = \frac{175 \text{ mg/kg/day} \times 50 \text{ kg (weight adjustment)}}{5 \times 10 \times 1 \times 1 \times 5 \text{ (modifying factors)}} = 35 \text{ mg/day}$$

ICH Q3C(R8): Guideline for residual solvents

Outcome of regulatory consultation

- Minor editorial revisions made to the monograph
- No change to PDE

Tertiary-butyl alcohol (TBA)

- PDE = 35 mg/day
- Placed into Class 2 “solvents to be limited”

ICH S1B(R1):
Addendum to the Guideline on Testing for Carcinogenicity of Pharmaceuticals

ICH S1B(R1): Carcinogenicity Testing - Addendum

Purpose of the ICH S1B guideline

- Provides guidance on approaches for evaluating the carcinogenic potential of pharmaceuticals

Document history

- ICH S1B guideline adopted by ICH in July 1997

ICH S1B(R1): Carcinogenicity Testing - Addendum

Current options for carcinogenicity testing

Option 1

- 2-year study in one rodent species (e.g., rat)
- Short- or medium-term *in vivo* rodent study (e.g., RasH2-Tg)

Option 2

- 2-year study in one rodent species (rat)
- 2-year study in 2nd rodent species (mouse)

ICH S1B(R1): Carcinogenicity Testing - Addendum

Work process and timeline

- Concept paper and business plan developed (November 2012)
- Prospective evaluation study launched (August 2013)
  - Regulatory Notice document (RND) posted on ICH website
  - Several status reports posted on ICH website
- EWG consensus on Step 1 draft Addendum reached (March 2021)
- Step 1 draft Addendum endorsed by ICH Assembly (April 2021)
- Step 3 regulatory consultation to be initiated shortly

ICH S1B(R1): Carcinogenicity Testing - Addendum

Purpose of the Addendum

- Expands testing scheme for assessing human carcinogenic risk of small molecule pharmaceuticals
  - Weight-of-evidence (WoE) approach to determine if a 2-year rat study adds value
  - Does not replace existing S1B guideline

- Includes a plasma exposure ratio endpoint for high dose selection in rasH2-Tg mouse model

ICH S1B(R1): Carcinogenicity Testing - Addendum

Possible conclusions following WoE assessment

- Likely to be carcinogenic in humans
- Likely not to be carcinogenic in humans

→ 2-year rat study will not add value

- Carcinogenic potential in humans uncertain

→ 2-year rat study will add value

ICH S1B(R1): Carcinogenicity Testing - Addendum

Factors to consider for WoE assessment

- Drug target biology & primary pharmacologic mechanism
  - Carcinogenicity data for compounds in drug class
- Off-target potential (e.g., secondary pharmacology screens)
- Histopathology data from repeat-dose toxicity studies
  - Long-term rat study most informative
  - Include exposure margin assessment
- Evidence of hormonal perturbation
- Genetic toxicology data (ICH S2(R1))
- Evidence of immune modulation (ICH S8)

ICH S1B(R1): Carcinogenicity Testing - Addendum

If WoE factor(s) are inconclusive or indicate a concern

- Additional investigations may be needed to inform human relevance of potential risk:
  - Conduct additional investigational studies
  - Analyze specimens collected from prior studies
  - Clinical data to inform human mechanistic relevance at therapeutic exposures

ICH S1B(R1): Carcinogenicity Testing - Addendum

Integration of WoE factors

- Integrated analysis determines whether or not 2-year rat study will add value to the assessment of human carcinogenic risk
  - Case studies in Appendix 1

- Novel drug targets (i.e., first-in-class) eligible for a WoE approach
  - Higher evidentiary standard to demonstrate no cause-for-concern

ICH S1B(R1): Carcinogenicity Testing - Addendum

Mouse carcinogenicity studies

- Remains recommended component of carcinogenicity testing plan

- Exception in the EU:
  - When WoE assessment indicates a 2-year rat study does not add value, a mouse carcinogenicity study is not recommended

ICH S1B(R1): Carcinogenicity Testing - Addendum

High dose selection for RasH2-Tg carcinogenicity studies

- 25-fold plasma AUC exposure ratio (rodent:human) can be used for high dose selection in 2-year rodent studies [ICH S1C(R2)]
  - Does not apply to 6 month RasH2-Tg study

- Retrospective assessment of RasH2-Tg studies indicates no value in exceeding a 50-fold plasma AUC exposure ratio (rodent:human)
  - Manuscript to be published by Hisada et. al.
  - Does not apply to other transgenic mouse models

ICH S1B(R1): Carcinogenicity Testing - Addendum

Next steps

- Public consultation in the ICH regions to be initiated
- Comments can be submitted as follows
  - Health Canada: hc.ich.sc@canada.ca
  - US FDA: www.regulations.gov
    (once Addendum is published in the federal register)
- Discuss comments received in each regulatory region
  - Revise Addendum as appropriate
- Finalization of the Addendum as a Step 4 document planned for summer 2022

Acknowledgements

- ICH Q3C expert working group
- ICH S1 expert working group

Questions?

ICH E6(R3) Guideline for Good Clinical Practice

An Important Global Standard for Clinical Trial Conduct

M. Khair ElZarrad

Deputy Director -Office of Medical Policy
CDER | US FDA

FDA and Health Canada Regional
ICH Consultation

May 14, 2021

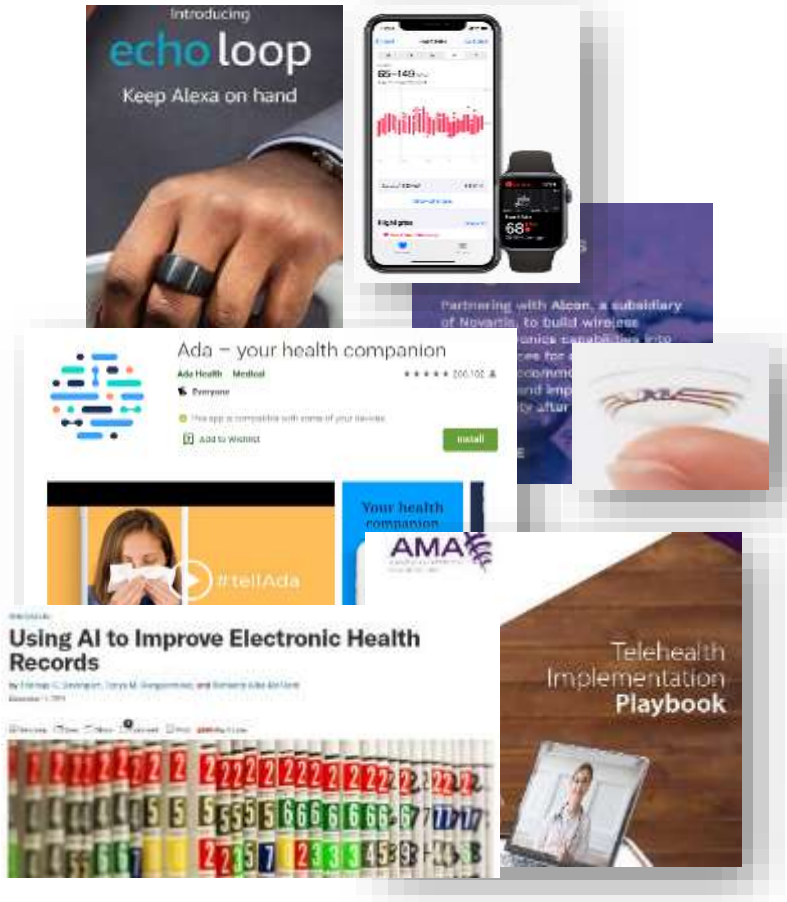
For today…

- Rapidly evolving evidence generation ecosystem
- Description of ICH-E6(R3) Expert Working Group (EWG) approach
  - ❑ ICH E6(R3) development strategy
  - ❑ Analysis of public input
  - ❑ Stakeholder engagement
- Published draft E6(R3) introduction and principles
  - ❑ Overview of draft introduction
  - ❑ Overview of draft principles
- Invitation to the EWG web-conferences on May 18 & 19.

We Need to be Responsive to a Rapidly Evolving Ecosystem

Advancing Evidence Generation Paradigm*

Increasingly Digital World*



Innovative Clinical Trial Designs*

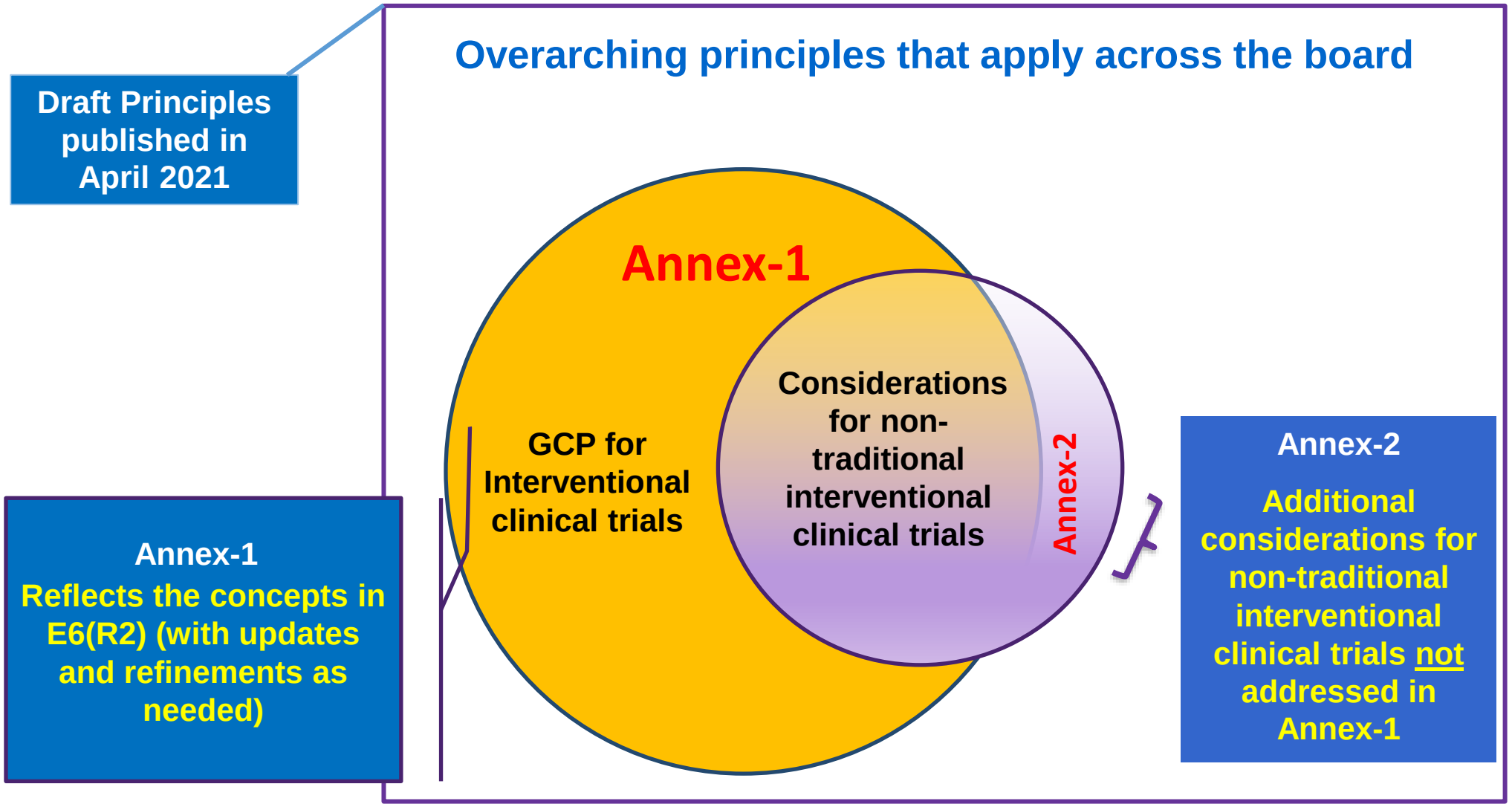
* Examples – not fully inclusive

ICH E6 - Guideline for Good Clinical Practice

- E6: Good Clinical Practice (GCP) – finalized in 1996
- Describes the responsibilities and expectations of stakeholders in the conduct of clinical trials
- E6 covers aspects of monitoring, reporting, and archiving clinical trials
- E6 (R2) – finalized in 2016
  - Addendum to encourage implementation of more efficient GCP approaches
  - Updated standards for electronic records

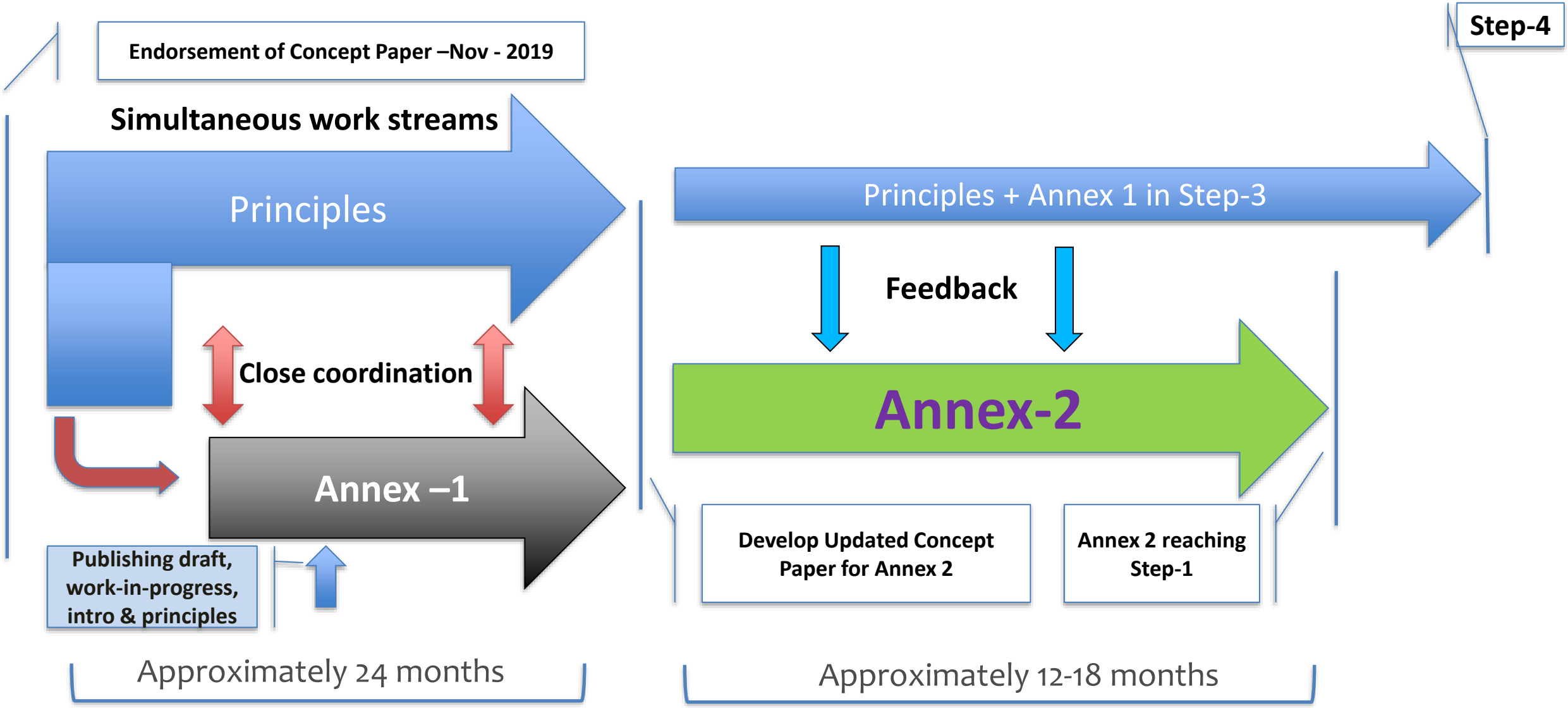
ICH E6: An Important Global Standard

Conceptual Representation of the Approach to ICH E6(R3)



Approach to E6(R3) Development

Simultaneous work on the principles & Annex-1



E6(R3) development is informed by the results of an extensive analysis of stakeholder input and by consistent engagement with stakeholders.

E6(R3) Expert Working Group (EWG) Analysis

- Analysis is comprised of two approaches:
  - An analysis of stakeholder comments on E6(R2)
  - An analysis of select ICH guidelines to help align between relevant guidelines whenever appropriate
- Goals of this analysis
  - Identify opportunities for improvement in E6(R3) and provide the EWG with potential options on how and where to apply the modifications

Sample of Resources Used to Inform the Analysis

Stakeholder Comment Analysis

- **Academic feed Responses**
  - Open letters & published articles
- **CTTI "Informing the Renovations to the ICH E6" Project**
  - Stakeholder Survey, In-depth Interviews, Open Comments
- **Public Engagement Materials**
  - Americas Engagement Meeting
  - Europe Engagement Meeting
  - Japan Engagement Meeting

ICH Guideline Analysis

- All Efficacy Guidelines + M11
- Peer-review publications

Examples of Areas Identified for Potential Updates

- **Data Management** (e.g., consider digitization of data ecosystems)
- **Responsibilities** (e.g., consider variable roles, clarity of tasks, delegation)
- **Monitoring** (e.g., consider highlighting further the importance of risk-based approaches, variety of monitoring approaches)

Engagement is Essential to Inform EWG Work

- Acknowledging the wide impact of E6 and the many stakeholders who are affected by this guideline, the ICH Management Committee approved an engagement plan* for the E6(R3) EWG.
- The engagement plan includes:
  - Public engagements, such as conducting web-conferences, and publishing updates. As a part of the EWG continuous transparency and engagement efforts, the EWG published draft, work-in-progress principles and is organizing a web-conference for May 18 & 19 (https://www.ctti-clinicaltrials.org/briefing-room/meetings/ich-e6-guideline-good-clinical-practice-%E2%80%93-update-progress)
  - Direct EWG engagement with academic experts during the EWG meetings as the work on the guideline proceeds

*ICH E6 Summary Engagement Plan - https://admin.ich.org/sites/default/files/2020-05/E6-R3_PublicEngagemenSummary_2020_0421.pdf

EWG Stakeholder Engagement

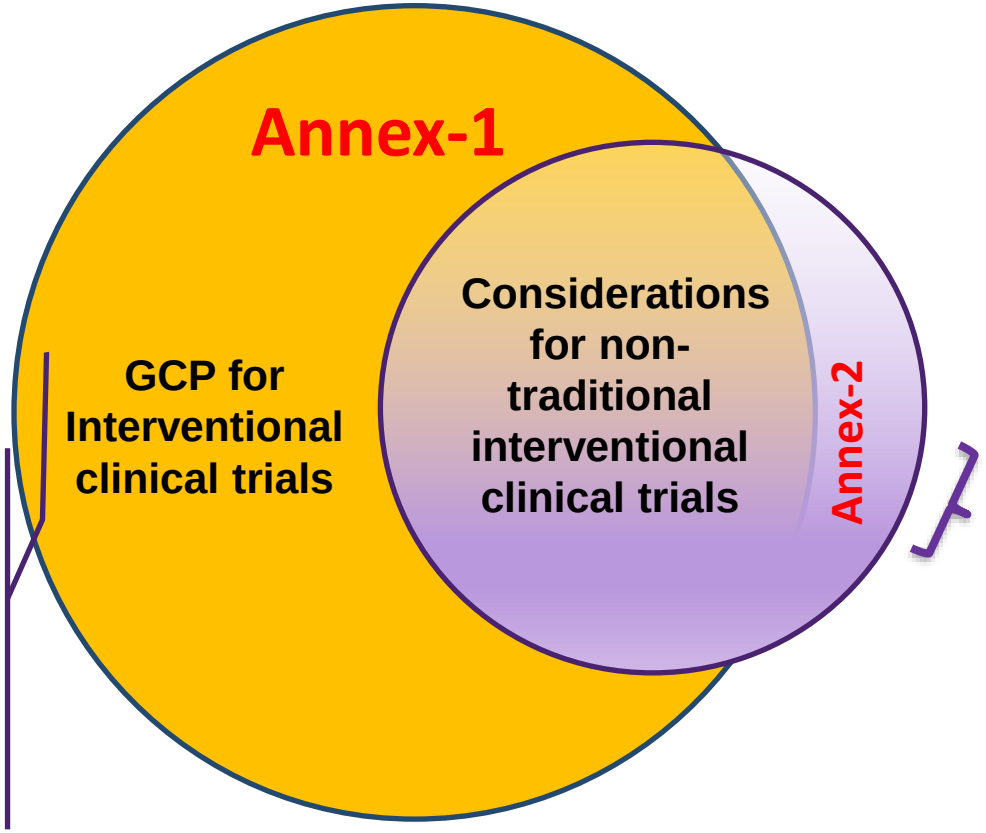
Nominated stakeholders that engage directly with the EWG as the work evolves

Organization Name	Representative Name
Society of Clinical Trials (USA)	Pamela Tenaerts, MD
Network of Networks (Canada)	Lisa Johnston, RN
Healthcare Professionals Working Party (EU)	Martin Landray, PhD
Brazilian Society of Clinical Research Professionals (Brazil)	Vivienne Castilho, PharmD
Chinese Pharmaceutical Association (China)	Haiyan Li, MD
The Clinical Research Core Hospital (Japan)	Kenichi Nakamura, MD, PhD

ICH E6(R3) Introduction and Principles

Draft Introduction & Principles published in April 2021

Overarching principles that apply across the board



Annex-1
Reflects the concepts in E6(R2) (with updates and refinements as needed)

Annex-2
Additional considerations for non-traditional interventional clinical trials not addressed in Annex-1

ICH E6(R3) Introduction and Principles

Draft E6(R3) Introduction & Principles published in April 2021

Overarching principles that apply across the board

- Comprehensive principles that remain relevant as technology evolves and clinical trial design advances
- Leveraging and facilitating an increasingly digital ecosystem
- Risk-based approach and proportionality
- Thoughtful process throughout clinical trial conception, design, conduct and analyses

ICH E6(R3) Introduction

- Clinical trials are a fundamental part of clinical research that support the development of new medicines or uses of existing medicines.
- The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials.
- The principles and E6(R3) in general are being developed to encourage thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial.
- The principles are intended to support improved and more efficient approaches to trial design and conduct. For example, innovative digital health technologies may expand the possible approaches to trial conduct. Such technologies can be incorporated in existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials.

ICH E6(R3) Introduction

- The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the trial design.
- The use of innovative technologies may help enable those designing and conducting a trial to include relevant patient populations.
- The process of building quality into the design of the trial may be supported by participation of those directly involved. These may include a broad range of stakeholders, including patients and treating physicians.
- This guideline is intended to be media neutral to enable the use of different technologies for the purposes of documentation.

ICH E6(R3) Introduction

- Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results.
- Clinical trial designs and processes should be proportionate to the risks inherent in the trial and the importance of the data being collected.
- Trial designs and processes should be evaluated to minimize unnecessary complexity and burden.

ICH E6(R3) Principles

- The overarching principles provide a flexible framework for clinical trial conduct.
- They are structured to provide guidance throughout the lifecycle of the clinical trial.
- These principles are applicable to trials involving human participants, i.e., healthy volunteers or patients.
- The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results.

ICH E6(R3) Principles

1. **Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and applicable regulatory requirement(s).**

ICH E6(R3) Principles

2- Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.

ICH E6(R3) Principles

3- Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants are well-informed.

ICH E6(R3) Principles

4- Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).

ICH E6(R3) Principles

5- Clinical trials should be scientifically sound for their intended purpose, and based on robust and current scientific knowledge and approaches.

ICH E6(R3) Principles

6- Clinical trials should be designed and conducted by qualified individuals.

ICH E6(R3) Principles

7- Quality should be built into the scientific and operational design and conduct of clinical trials.

ICH E6(R3) Principles

8- Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.

ICH E6(R3) Principles

9- Clinical trials should be described in a clear, concise, and operationally feasible protocol.

ICH E6(R3) Principles

10- Clinical trials should generate reliable results.

ICH E6(R3) Principles

11- Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately.

ICH E6(R3) Principles

12- Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.

Summary

- Well designed and conducted clinical trials are essential
- The EWG shares the perspective that trials should be efficient and robust to inform the decisions of many stakeholders
- ICH E6(R3) is being developed as a robust and responsive guideline that facilitates innovation while protecting trial participants
- The EWG is actively working on Annex-1 and will continue to focus on a risk-based approach to GCP.
- Please join us for May 18 & 19 web-conferences
  (https://www.ctti-clinicaltrials.org/briefing-room/meetings/ich-e6-guideline-good-clinical-practice-%E2%80%93-update-progress)

ICH E6 Expert Working Group (EWG) Members

Rapporteur: Dr. Khair ElZarrad (FDA, United States)

Regulatory Chair: Dr. Fergus Sweeney (EC, Europe)

ANVISA, Brazil - Dr. Carla Abrahao Brichesi, Ms. Miriam Onishi

CDSCO, India - Mr. Arun Kumar Pradhan

EC, Europe - Ms. Lisbeth Bregnhøj, Ms. Gabriele Schwarz

EFPIA – Ms. Susanne Nørskov, Ms. Rebecca Stanbrook

FDA, United States - Dr. Celia Witten, Dr. Kassa Ayalew

Health Canada, Canada – Dr. Carole Légaré

HSA, Singapore – Ms. Sumitra Sachidanandan

IFPMA – Mr. Guodong FANG

IGBA – Dr. Gerald Beuerle, Dr. Manjunath Krishnappa

JPMA – Mr. Mitsuaki Aoyagi, Mr. Eiji Kawakatsu

MHLW/PMDA, Japan – Ms. Kanako Ito, Ms. Eriko Yamazaki

NMPA, China – Ms. Zhimin Yang

PhRMA – Ms. Deborah Driscoll

PIC/S – Ms. Gail Francis

Roszdravnadzor, Russia – Mr. Dmitrii Gorenkov

TFDA, Chinese Taipei – Ms. Yi-Ting Chen

TGA, Australia – Dr. Nitin Bagul

TITCK, Turkey – Ms. Nihan Burul Bozkurt

WHO – Dr. Ray Corrin

ICH E6(R3) EWG Members

ICH Q12 Implementation

Ashley B. Boam, MSBE
Director, Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality
CDER | US FDA

FDA and Health Canada Regional ICH Consultation – March 14, 2021

Overview

- Objectives and scope
- Regulatory tools
- Status of the guideline
- Implementation Working Group activities
- FDA Implementation

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

ICH Q12 Objectives

- Objectives* include:
  - …**Harmonize change management**…in a more transparent and efficient manner…across ICH regions
  - …Facilitate **risk-based regulatory oversight**…
  - Emphasize…**control strategy** as a key component of the…dossier
  - Support **continual improvement** and facilitate introduction of **innovation**
  - Enhance use of regulatory tools for **prospective change management**…enabling **strategic management of post-approval changes**…

*From the ICH Q12 concept paper

Scope

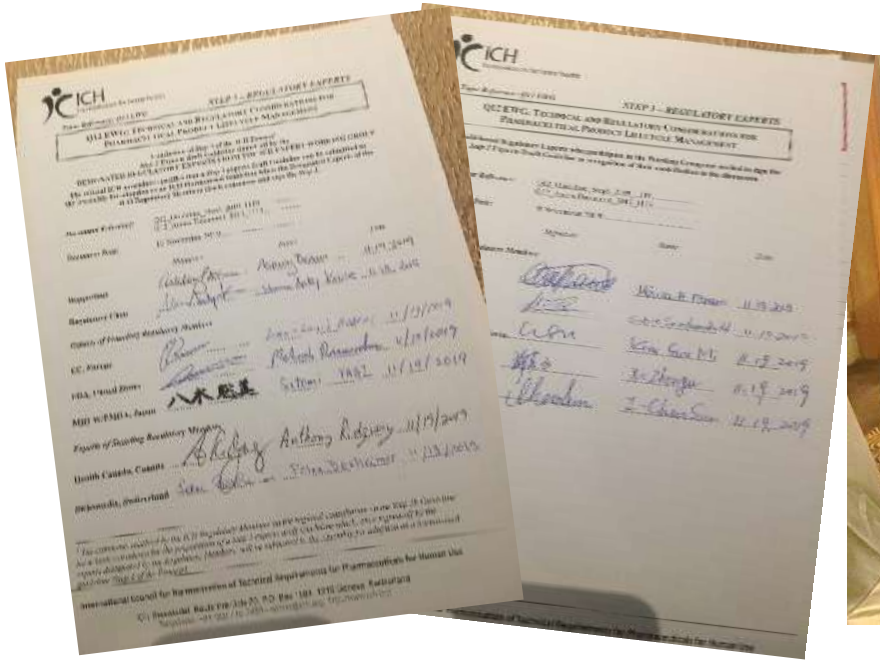
- Pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorization
  - includes innovators, generics, biosimilars
- Drug-device combination products that meet the definition of a pharmaceutical or biological product
  - In the US, this includes CDER- and CBER-led drug-device and biologic-device combination products
- Does not include changes needed to comply with Pharmacopeial monographs

Tools in Q12

- Established Conditions
- Post-approval Change Management Protocols
- Product Lifecycle Management Document
- Structured Approaches for Frequent CMC Post-Approval Changes

ICH Q12 Status

Step 4 reached in November 2019 (Singapore)



Implementation

- Regions are beginning implementation
  - Regulatory Members of ICH are encouraged to provide publicly available information, preferably on their website, about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations
- Formation of the Implementation Working Group (IWG)
  - Concept paper approved in March 2020
  - IWG developing global training materials
  - ICH pilot with PIC/S to develop training materials for inspectorates

Q12 IWG

Training materials

- For ICH and non-ICH regions
- Modules addressing each section of guideli
  - Slides for 8 modules to be posted on ICH website
- Case studies with additional examples and narrative text
  - Based on input provided during public consultation period
- Examples include:

ECs for API	ECs for vaccine product	ECs for analytical method	PACMP
PQS	Drug-device combination		PLCM

Q12 IWG

- Ongoing regional implementation
  - Shared experiences and lessons learned from implementation
  - Both regulators and industry
    - FDA Established Conditions pilot

ICH Q12 – FDA Implementation

- FDA adoption and publication
  - Replaces 2015 draft guidance - Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products
- Draft guidance on considerations for ICH Q12 implementation awaiting publication
  - Intended to clarify how to implement Q12 within US regulatory system
- CDER MAPP on implementation of ICH Q12 in progress
- Significant training executed (2018-present)
  - Developed and initiated a multi-phase strategy to build awareness and capability within FDA staff

FDA – Established Conditions (ECs) Pilot

- FDA initiated a pilot in 2019 to evaluate EC proposals
- Accepted nine applications into the pilot
  - Mixture of small and large molecule, originals and supplements, innovator and generic
- Experience and learnings have informed FDA's ICH Q12 implementation guidance and MAPP

ICH Q12 – FDA Training

- Phase 1:
  - Created awareness and clarity on ICH Q12 (goals, content, scope, core elements)
  - Utilized theoretical examples to illustrate concepts and practice the identification of established conditions
- Phase 2:
  - Augmented understanding of pharmaceutical quality systems, CGMP, and their role in ICH Q12 implementation

ICH Q12 – FDA Training

- Phase 3:
  - Driven by assessment teams from the established conditions pilot
  - Utilized real world examples to demonstrate implementation
  - Teams shared their experiences assessing proposals and working with applicants
- Phase 4: To be implemented
  - ICH Q12 support team to work with assessors to help answer questions, provide oversight to guide consistency, etc.

Summary

- ICH Q12 includes tools and enablers to facilitate innovation and continual improvement
- Implementation is underway at FDA and with other regulators
- ICH Q12 IWG developing training materials to support global implementation

Questions?

Ashley B. Boam, MSBE
Director, Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality
CDER | US FDA

Model Informed Drug Development (MIDD)

Scott Marshall, PhD, *Executive Director*
Pfizer R&D UK Ltd
& PhRMA MIDD working group
on behalf of ICH MIDD Discussion group

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

"A world without modelling and simulation would be full of unanswered questions…"

Learning objectives

- What is Model Informed Drug Development
- Why is it important for efficient drug development
- Why there is a need for global harmonisation in this area
- The remit of ICH MIDD discussion group

What is Model Informed Drug Development ?

- **Integration of data from multiple sources**

in the form of mathematical and statistical models

- **Application of these models**
  to inform drug development and registration strategies,
  to optimize the design of future clinical studies &
  to address dose-individualization questions

What is Model Informed Drug Development ?

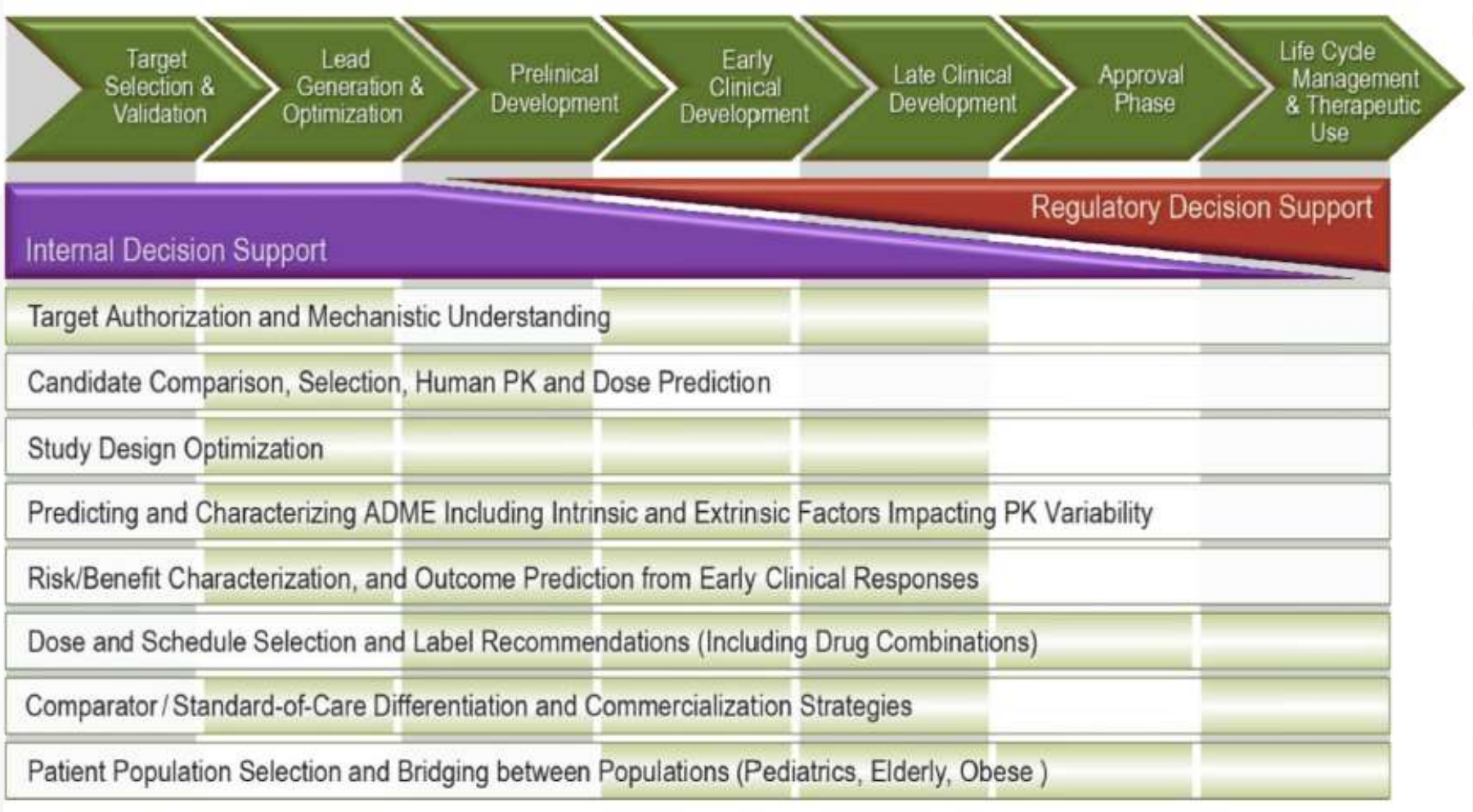
- **Data from multi-sources**
  - Can enrich clinical trial data by utilising non-clinical and Real-World Evidence

- **Mathematical & Statistical Models**
  - Assumptions based on Pharmacology, Physiology & Disease Process

What is Model Informed Drug Development ?

- **Drug development and registration strategies**
  - Probability of acceptable benefit risk & probability of clinical trial/program success
- **Optimize the design of future clinical studies**
  - With respect to the range of possible outcomes
- **Address dose-individualization questions**
  - Optimize for population, sub-population & individual

MIDD has Broad Utility Over the Entire Drug Discovery and Development Continuum



EFPIA workgroup CPT:PSP 2016

MIDD utilization and presentation as part of regulatory Review

"Many regulatory agencies expect to receive, and currently accept MIDD as part of dossier submissions"

MIDD: Current and Future

STATE OF THE ART

Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

[1]Office of Clinical Pharmacology, Office of Translational Sciences, US Food and Drug Administration, Silver Spring, Maryland, USA.
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Received 23 October, 2018; accepted 26 December, 2018. doi:10.1002/cpt.1363

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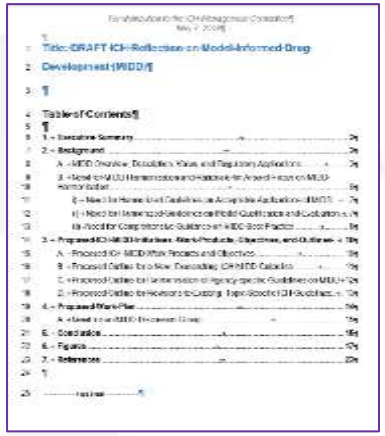
Future:

- **MIDD pilot**
- **Mechanistic models**
- **Machine-learning models**
- **Real-world data/real-world evidence**

Figure 1 Regulatory application of model information drug development.

Growing global interest in MIDD Standardisation

Draft PhRMA MIDD ICH paper(2019)


Title: DRAFT ICH Reflection on Model-Informed Drug Development (MIDD)

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PMDA – Population PK/PD 2019

NMPA – Population PK 2020


Technical Guidelines for Population Pharmacokinetic Study

EMA – PBPK 2019


Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

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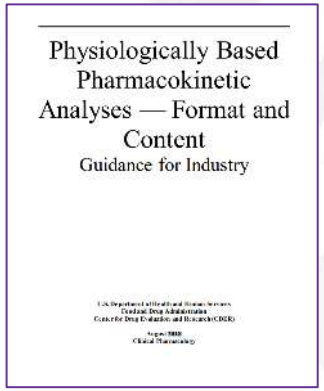
FDA – PBPK 2018


Physiologically Based Pharmacokinetic Analyses — Format and Content

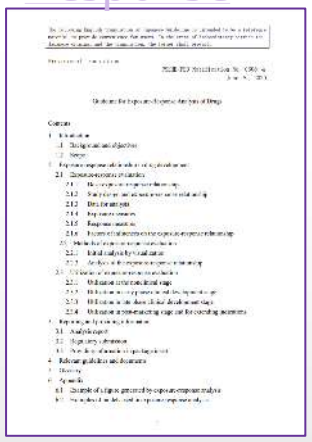
Guidance for Industry

EFPIA MIDD White paper(2016)

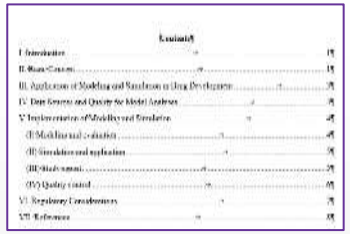

WHITE PAPER

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

Exposure Response 2020



MIDD 2020


Technical Guideline on Model-Informed Drug Development

Extrapolation 2018


EUROPEAN MEDICINES AGENCY

Reflection paper on the use of extrapolation in the development of medicines for paediatrics

MIDD Pilot 2018


Model-Informed Drug Development Pilot Program

What's New

ICH MIDD Discussion Group

FIRST NAME	LAST NAME	PARTY
Malidi	Ahamadi	BIO
Mark	Peterson	BIO
Rubina	Bose	CDSCO, India
Ping	Zhao	Bill and Melinda Gates Foundation
Kristin	Karlsson	EC, Europe
Efthymos	Manolis	EC, Europe
Flora	Musuamba Tshinanu	EC, Europe
Nicolas	Frey	EFPIA
Jörg	Lippert	EFPIA
Million	Tegenge	FDA, United States
Yaning	Wang	FDA, United States
Issam	Zineh	FDA, United States
Sarem	Sarem	Health Canada, Canada
Lucia	Zhang	Health Canada, Canada
Pavel	Farkas	IGBA
Augusto	Filipe	IGBA
Norisuke	Kawai	JPMA
Takayo	Ueno	JPMA

FIRST NAME	LAST NAME	PARTY
Ja-Young	Kim	MFDS, Republic of Korea
Daisuke	Iwata	MHLW/PMDA, Japan
Yasuto	Otsubo	MHLW/PMDA, Japan
Jian	Li	NMPA, China
Ming	Zhou	NMPA, China
Erin	Greene	PhRMA
Scott	Marshall	PhRMA
Amit	Roy	PhRMA
Mohamad	Shebley	PhRMA
Omar	Almazroo	SFDA, Saudi Arabia
Chien-Lung	Tu	TFDA, Chinese Taipei
Observers		
Amanda	Roache	PhRMA ICH Supporter
Anne	Latrive	ICH Secretariat
Nadia	Myers Biggs	ICH Secretariat

Remit of ICH MIDD Discussion Group - 1 Year term

- Finalize the scope of a general principles guideline for MIDD
- Position this proposal with respect to revision of ICH E4
- Develop a multi-year plan for integration of MIDD in existing ICH guidelines & consider potential new guidelines

Impact of lack of harmonisation

- Missed opportunities to fully leverage MIDD
- An over reliance on traditional approaches to answering drug development & review questions
- Inefficient drug development strategies and study designs
- Unnecessary delay in the availability of new innovative medicines

What is the biggest challenges to further implementation of MIDD ?

Choose all that apply

A- Limited opportunity to apply MIDD in drug development

B- The lack of Belief that MIDD can be useful in drug development

C- The lack of common understanding of MIDD between technical and non-technical experts

D- The lack of common standards & understanding of terminology

E- Variable level of integration of MIDD into regulatory submissions

What is the biggest challenges to further implementation of MIDD ?

- x A- Limited opportunity to apply MIDD in drug development
- x B- The lack of belief that MIDD can be useful in drug development
- √ C- The lack of common understanding of MIDD between technical and non-technical experts
- √ D- The lack of common standards & understanding of terminology
- √ E- Variable level of integration of MIDD into regulatory submissions

Summary & Next steps

- **Impact of Model Informed Drug Development**
  - Industry: Make drug development more efficient
  - Regulators: Enhance regulatory review
  - Patients: Reduce unnecessary exposure & provide earlier access to break through medicines
- **ICH MIDD Discussion group is aligned on the need and value of a general principles guideline**
- **An updated ICH MIDD topic proposal is currently underdevelopment**

ICH
harmonisation for better health

Questions?

Patient Focused Drug Development

Robyn Bent, RN, MS
Director, Patient-Focused Drug Development Program
CDER, U.S. FDA

FDA and Health Canada Regional ICH Consultation – 14 May 2021

Overview

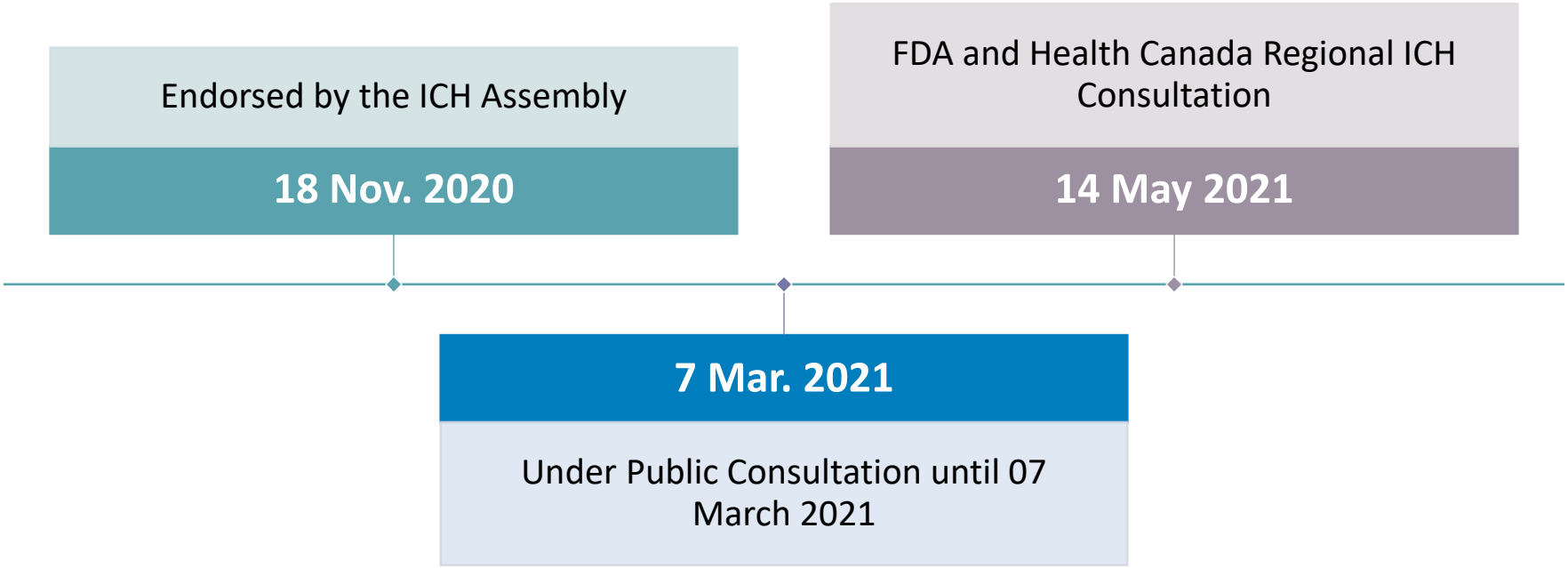
- Background
- Opportunities to incorporate patient experience data
- Possible topics for future ICH Guideline development
- Update on the status of the reflection paper and next steps

Background
PFDD Reflection Paper

identifies key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making.

presents opportunities for development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities.

Background
PFDD Reflection Paper



Background

Patients are experts on what it is like to live with their condition

Patient advocacy and patient engagement is increasing and advancing

There is an opportunity to increase the quality of drug development programs through effective inclusion of patients' perspectives

Methods for identifying, collecting, and analyzing what is meaningful to patients are not standard for harmonized

Background

Regulators and drug sponsors need to employ methods and measures that:

- ensure information collected can be used
- can be deployed in a timely and sustainable way
- will be relevant to patients (and their caregivers)
- reflects concepts that matter and measure changes that would be meaningful
- account for heterogeneity or subgroups.

Incorporating patient experience data

- What are patients' unmet needs that suggest potential drug targets?
- What disease effects and treatment burdens matter most to patients?
- What endpoint are most relevant to patients?

Incorporating patient experience data

Methods and approaches to identify:

- Desirable treatment benefits
- Benefit-Risk tradeoffs

Methodological considerations for sponsor conduct of patient preference studies

Possible topics for future ICH Guideline development

Possible guideline addressing what to measure in a clinical trial

Possible guideline addressing methods for elicitation or collection of assessments looking at patients' perspectives on alternative outcomes or other specified alternative attributes

Updates and Next Steps

Public Consultation-

- Closed 07 March 2021
- Received over 300 comments from over 35 stakeholders
- Overall supportive of the effort moving forward
- Contain recommendations to be considered if new guidelines are developed

Updates and Next Steps

Limited Examples of Related Ongoing Work

- U.S. FDA Patient-Focused Drug Development Guidance Series
  - https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
- IMI PREFER project
  - https://www.imi-prefer.eu/

Updates and Next Steps

Transparency

Reflection paper posted for comment

Any new guidelines will follow an engagement approach like that of ICH E6(R3)

References

- ICH PFDD Reflection Paper
  - https://admin.ich.org/sites/default/files/2020-12/ICH_ReflectionPaper_PFDD_Endorsed-ForConsultation_2020_1118.pdf

Questions?

Robyn Bent, RN, MS
Director, Patient-Focused Drug Development Program
CDER, U.S. FDA

Health Canada Santé Canada

ICH Member

FDA U.S. FOOD & DRUG ADMINISTRATION

Open Q&A begins shortly – type your questions in the Q&A pod now.

Additional questions or comments?
Email: CDERSBIA@fda.hhs.gov

Health Canada Santé Canada

ICH Member

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you for attending!

Additional information on ICH is available at www.ich.org

Additional information on CDER Small Business & Industry Assistance webinars and resources are available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm