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FDA U.S. FOOD & DRUG ADMINISTRATION

US FDA and Health Canada Joint Regional Consultation on the International Council for Harmonisation (ICH)

April 3, 2020

Today's Agenda

I. Overview of ICH

II. Topics Recently Reaching Step 4 of the ICH Process (final guideline)
- Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- E9(R1) Addendum: Statistical Principles for Clinical Trials
- M9 Biopharmaceutics Classification System-based Biowaivers
- S5(R3) Revision on Detection of Toxicity to Reproduction for Human Pharmaceuticals

III. Update on Electronic Standards Topics and MedDRA

IV. Overview of Ongoing Topics

V. Question and Answer

VI. Closing Remarks

Overview of ICH

Joan Blair, M.A.
Senior Advisor for International Affairs
FDA, Center for Biologics Evaluation and Research
April 3, 2020

30th Anniversary of ICH

- 2020 marks 30th anniversary of ICH
- A commemorative conference to be held Saturday, 14 November 2020 in Athens, Greece – in advance of the bi-annual ICH meeting
- Will look at ICH's evolution since inception in 1990, current efforts and future directions
- Open registration after an initial invitation to key former ICH participants

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

- Unique harmonization project involving the regulators and research-based industries
- Begun in 1990 involving US, EU and JP
- 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**
- Accomplish through the development and implementation of harmonized Guidelines and standards

The ICH Process for Guideline Development has 5 Steps

Sampling of Major Topic Areas Addressed by ICH Guidelines

Safety

- Carcinogenicity studies
- Genotoxicity studies
- Toxicokinetics and Pharmacokinetics
- Toxicity testing
- Reproductive toxicology
- Biotechnology products
- Pharmacology studies
- Immunotoxicology studies
- Nonclinical evaluation for anticancer pharmaceuticals
- Photosafety evaluation

Efficacy

- Clinical safety
- Clinical study reports
- Dose-response studies
- Ethnic factors
- Good clinical practice
- Clinical trials
- Clinical evaluation by therapeutic cat.
- Clinical evaluation
- Pharmacogenomics
- Multi-regional clinical trials

Quality

- Stability
- Analytical validation
- Impurities
- Pharmacopoeias
- Quality of biotechnology products
- 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
- Data elements and standards for drug dictionaries
- Gene therapy
- Genotoxic impurities

ICH Work Products

- Over 60 Guidelines on technical requirements on:
  - Quality
  - Safety
  - Efficacy
  - Multidisciplinary (including for electronic submissions)
- Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B)
- MedDRA (standardized medical terminology)

ICH Reform - Establishment of Non-Profit Association

- The new ICH Association was officially established on October 23, 2015.
- The new ICH Association is a non-profit legal entity under Swiss Law with the aim to focus global pharmaceutical regulatory harmonization work in one venue
- More involvement from regulators around the world is welcomed and expected

ICH Articles of Association:
http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisational_changes/ICH_Articles_of_Association_Adopted_by_Founding_ICH_Members_October_23_2015_for_publication.pdf

Goals of the ICH Reform

- Better prepare ICH to face the challenges of global pharmaceutical development and regulation
- Expand ICH beyond the current Members
- More involvement from regulators around the world and wider inclusion of global industry sectors affected by ICH harmonization
- Focus global pharmaceutical regulatory harmonization work in one venue
- Continue to harmonize and streamline the global drug development process for the benefit of patients around the world
- Maintain efficient and well-managed operations and harmonization work processes

Governance of new ICH Association

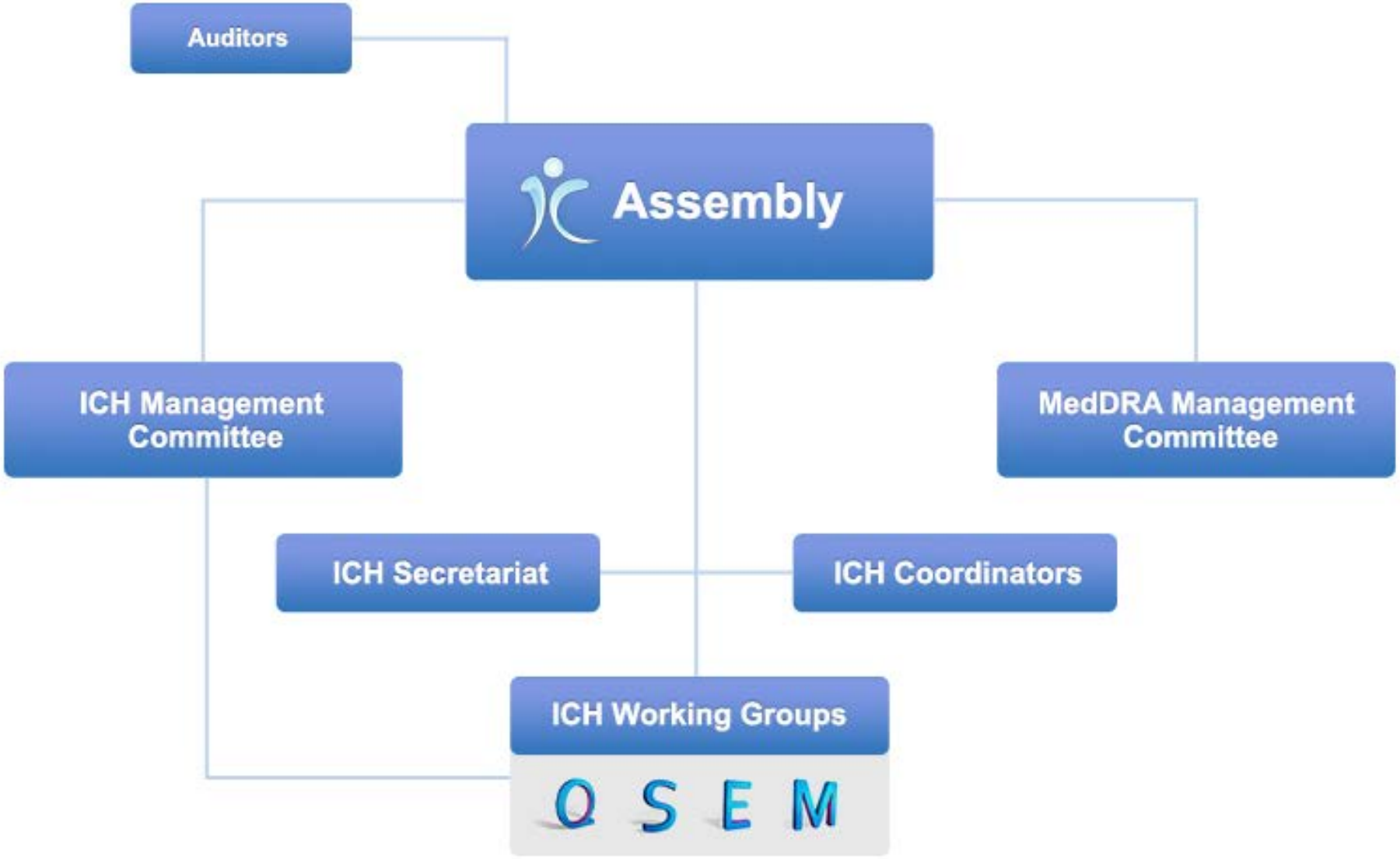
Assembly

- The overarching body of the Association that makes decisions regarding the Articles of Association and its Rules of Procedures, Admission of new Members, Election of Elected Management Committee representatives, Guideline work plan, Adoption of ICH guidelines, Approval of budget, etc.
- **Includes all ICH Members and Observers**

Management Committee

- The body that 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



Membership in the Assembly—Eligibility Criteria for Regulators

Recognized Authority

- Has a legal personality
- Responsible for the regulation of pharmaceutical products 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

- Implementation of the following ICH Guidelines at minimum, upon application for membership:
  - Q1: Stability Testing guidelines
  - Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
  - E6: Good Clinical Practice Guideline

Membership in the Assembly—Eligibility Criteria for Industry

Recognized Authority

- Has a legal personality
- Represents members from several countries in at least three continents
- Is regulated by all of some of the ICH Guidelines

Engagement in the ICH Process

- Has participated in ICH as an Observer
- Past appointment of experts in at least 2 Working Groups

ICH Members Have a Vote in the Assembly

- All ICH Members have a voice and may vote in the Assembly on decisions related to[1]:
  - Selection and nomination of new topics for harmonization
  - Approval of the annual and multi-annual strategic plan
  - Adoption, amendment, or withdrawal of ICH Guidelines
  - Approval or rejection of membership/observer admission

1 See ICH Articles of Association for more details:
http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisational_changes/ICH_Articles_of_Association_Adopted_by_Founding_ICH_Members_October_23_2015_for_publication.pdf

ICH Members can Propose New Topics for Harmonization

Annual topic submission and review process:

- Each ICH Member can propose topics for harmonization
- The ICH Management Committee provides a recommendation to the Assembly on selection of new topics
- The ICH Assembly makes a decision at each June meeting on new topics for harmonization

ICH Members and Observers *

Members

Founding Regulatory Members
- EC, Europe
- FDA, US
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members
- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- HSA, Singapore
- MFDS, Republic of Korea
- NMPA, China
- TFDA, Chinese Taipei

Industry Members
- BIO
- IGBA
- GS-CF

**As of April 2020*

Observers

Standing Observers
- IFPMA
- WHO

Authorities
- ANMAT, Argentina
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- CPED, Israel
- INVIMA, Colombia
- JFDA, Jordan
- MMDA, Moldova
- National Ctr, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SFDA, Saudi Arabia
- TFDA, Chinese Taipei
- TGA, Australia
- TITCK, Turkey

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
- BMGF
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

Summary

- ICH has achieved international harmonization of technical guidelines, with engagement of regulators and industry
- ICH uses a science- and consensus-based process following 5 transparent steps in the ICH process for Guideline development
- ICH has clear governance and increasingly global membership following ICH reform
- Recent reforms have expanded global participation in regulatory harmonization

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Questions?

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Ashley B. Boam, MSBE
Director
Office of Policy for Pharmaceutical Quality
FDA/Center for Drug Evaluation and Research

Guideline Objectives

- …Harmonize management of post-approval CMC changes…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…

Key Principles

- Provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner
- Presents a number of harmonised regulatory tools and enablers with associated guiding principles
- Demonstrates how increased product and process knowledge can contribute to a more precise and accurate understanding of which post-approval changes require regulatory submission
- Emphasizes the importance of an effective pharmaceutical quality systems in the management of changes during the product lifecycle

Scope

- Pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorisation
- Drug-device combination products that meet the definition of a pharmaceutical or biological product
- Does not include changes needed to comply with Pharmacopeial monographs

Table of Contents – Core Guideline

Table of Contents - Annex

- Annex I – Illustrative Examples
  - Identification of Established Conditions for the Manufacturing Process - Chemical Medicinal Product
  - Identification of Established Conditions for the Manufacturing Process - Biological Medicinal Product
  - Identification of Established Conditions for Analytical Procedures
  - PACMP Example 1
  - PACMP Example 2
  - Product Lifecycle Management Document - Illustrative Example
- Annex II - Structured Approach to Analytical Procedure Changes

Key Tools and Enablers

- **Established Conditions (ECs)** – provide a clear understanding between the Marketing Authorisation Holder (MAH) and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed
- **Post-Approval Change Management Protocol (PACMP)** – provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority
- **Product Lifecycle Management Document** – serves as a central repository for ECs, reporting categories for changes to ECs, PACMPs, and any post-approval CMC commitments

Key Tools and Enablers

- **Structured Approaches for Frequent CMC Post-Approval Changes** – a simplified approach to accomplish certain CMC changes through the use of immediate or other post-implementation notification for products whose marketing authorization did not involve identification of ECs and reporting categories
- **Stability Data Approaches to Support the Evaluation of CMC Changes** – additional science- and risk-based approaches that are relevant to strategies for confirmatory stability studies to enable more timely implementation of CMC changes

An effective PQS as described in ICH Q10 (Pharmaceutical Quality System) and compliance with regional GMP requirements are necessary to gain full benefit from the guideline

Timeline Highlights

• September 2014	Concept paper endorsed
• June 2017	Step 1 reached
• November 2017	Steps 2a/2b reached
• December 2018	End of public consultation period
• February 2019	Interim meeting, Tokyo
• June 2019	F2F meeting, Amsterdam
• November 2019	Steps 3 and 4 reached, Singapore
• February 2020	Step 4 presentation online
• February 2020 →	Step 5 regional publication ongoing
• April 2020	Formation of IWG in progress for development of training materials

Considerations

- The ICH Q12 guideline should be applied in conjunction with other ICH “Q” guidelines, including Q8(R2), Q9, Q10, and Q11
- MAHs wishing to use the tools and enablers described in ICH Q12 should consult publicly available information provided by regulatory authorities (e.g., see regulators’ websites) about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations

Acknowledgements

Nanna Abby Kruse, EC, Regulatory Chair
Rebecca McKnight, FDA, Rapporteur Supporter
Moheb Nasr, PhRMA, Rapporteur, Steps 1-2

E9(R1) ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

Catherine Njue, PhD

Biostatistics Advisor

Office of Biostatistics

Centre for Regulatory Excellence, Statistics and Trials (CREST)

Biologic & Radiopharmaceutical Drugs Directorate (BRDD)
Health Products and Food Branch (HPFB)

Health Canada

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

- Background
  - An Addendum was proposed to provide clarification on the E9 guideline developed in 1998 to provide greater clarity on **estimands** (the property to be estimated in the context of a scientific question of interest) and **sensitivity analyses** (analyses performed in addition to the primary statistical analysis).

- Goal
  - Develop regulatory guidance which :
    - Promotes harmonized standards on the choice of estimands in clinical trials
    - Describes an agreed framework for planning, conducting and interpreting sensitivity analyses of data from clinical trials

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Key Milestones

- Concept paper endorsed by the ICH Steering Committee on 23 October 2014
- EWG (Expert Working Group) subsequently formed and met for the first time in November 2014 at the ICH meeting in Lisbon, Portugal
- 2017: Step 1 and Step 2a/b - Finalisation of the Technical Document (draft addendum), sign-off by Topic Leaders and adoption by Assembly Members and by Assembly Regulatory Members

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Key Milestones

- August 2017: Step 3 - Draft addendum published
- April 2018: Step 3 - Public comments received in all ICH regions
- August 2018: Publication of Step 2b training material slide decks on the ICH website
- 2018/2019: Step 3 - Discussed comments received during the public consultation period and consolidated the draft addendum

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Key Milestones

- 2019: Step 3 and Step 4 - Finalisation of the addendum and sign-off by topic leaders of the ICH Regulatory Parties and by the ICH Regulatory Parties
- November 20, 2019: Adoption of E9 (R1): ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Purpose and scope of the addendum to ICH E9

- Provides a framework for describing with precision a treatment effect of interest
- Precision in describing a treatment effect of interest is facilitated by constructing the “estimand”
- Estimand: A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Purpose and scope of the addendum to ICH E9

- Clarity requires a thoughtful envisioning of “intercurrent events” such as discontinuation of assigned treatment, use of an additional or alternative treatment and terminal events such as death
- Intercurrent Events: Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
- It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Purpose and scope of the addendum to ICH E9

- Addendum introduces strategies to reflect different questions of interest that might be posed
- Attributes used to construct the estimand are also introduced in the addendum
- Addendum clarifies the definition and the role of sensitivity analysis
- Sensitivity Analysis: A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Strategies for addressing intercurrent events

- Treatment policy strategies: The occurrence of the intercurrent event is considered irrelevant
- Hypothetical strategies: A scenario is envisaged in which the intercurrent event would not occur
- Composite strategies: This strategy relates directly to the variable of interest, and an intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Strategies for addressing intercurrent events

- While on treatment strategies: Response to treatment prior to the occurrence of the intercurrent event is of interest
- Principal stratum strategies: This strategy relates directly to the population of interest

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Estimand attributes

- Treatment: The treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made
- Population: Patients targeted by the clinical question
- Variable (or endpoint): Obtained for each patient and required to address the clinical question
- Population level summary: Provides a basis for comparison between treatment conditions for the variable

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Other important topics covered

- Construction of estimands
- Impact on trial design and conduct
- Impact on trial analysis
  - Main estimation
  - Sensitivity analysis
  - Supplementary analysis
- Documenting estimands and sensitivity analysis

ICH E9 (R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials

Next steps

- Implementation of the addendum across the different regions
- Planning training and implementation activities
- Updating the Step 2b training material slide decks on the ICH website to reflect the Step 4 document, and publishing the updated slides as soon as they are finalised
- A sub-team comprising of ICH E9 (R1) EWG members and ICH M11 EWG members have been having regular discussions on how to incorporate the estimand framework into CeSHarP (Clinical electronic Structured Harmonised Protocol)

M9: Biopharmaceutics Classification System (BCS) - based Biowaivers

Mehul Mehta, Ph.D.
Director, Division of Neuropsychiatric Pharmacology
Office of Clinical Pharmacology, OTS, CDER, FDA

Outline

I. Regional BCS guidances and M9 History
II. BCS Concept
III. M9 Contents
IV. M9 Implementation
V. Summary
VI. Acknowledgments

Outline

I. Regional BCS guidances and M9 History

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I. Regional Guidances and M9 History

- **FDA** BCS Guidance "*Waiver of In-vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*" was issued in year 2000
- **EMA** BCS Guideline was issued in 2010, followed by **Health Canada**, **WHO** and **ANVISA**
- FDA revised it's guidance in 2015 and issued the final guidance in December 2017

I. Regional Guidances and M9 History

- **The ICH M9 Guideline:** *Biopharmaceutics Classification System-Based Biowaivers*
  - This document was developed based on a Concept Paper (7 October 2016) and Business Plan (7 October 2016)
  - This document has been signed off as Step 4 document (20 November 2019) to be implemented by the ICH Regulatory Members
  - Currently at Step 5: Implementation by ICH members
- M9: *Questions and Answers Annex*
  - Also signed off on 20 November 2019
  - The ICH M9 Q&A provides clarity to support the implementation of the ICH M9 Guideline on BCS based biowaivers in ICH Regulatory Member countries/regions
  - Currently at Step 5: Implementation by ICH members

Outline

I. Regional BCS guidances and M9 History

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II. BCS Concept

- When the blood level profile of the same drug from two different formulations is shown to be similar, using strict statistical criteria, the two formulations are called bioequivalent, and such a study is called in vivo bioequivalence (BE) study.
- Pretty much all generics are approved based on a BE study and BE assessment plays an important role in the pre- and post-approval space of innovator drugs also.
- BCS framework allows waiving the need for the in vivo BE study (biowaiver) and provides assurance of in vivo BE based on fundamental properties of the drug substance and drug product, and extensive comparative in vitro characterization (comparative dissolution)

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Information in subsequent slides is extracted from ICH M9 Training Slides, M9 Guidance Step 4, and M9 Q/A, Step 4

https://database.ich.org/sites/default/files/M9_Step_4_Presentation_2020_0302.pdf

III. M9 Content

Guideline Objectives:

- The BCS-based biowaiver approach is intended to reduce in vivo bioequivalence studies.
- **This Guideline**
  - Provides recommendations on the biopharmaceutics classification of drug substances, and to support BCS-based biowaivers for drug products.
  - Aims to harmonize current regional guidances, reduce in vivo bioequivalence studies, and support streamlined global drug development.

III. M9 Content

Key Principles:

- This multidisciplinary Guideline addresses the BCS based waivers of bioequivalence studies (biowaivers).
- This Guideline provides recommendations on how to determine the biopharmaceutics classification of drug substances.
- In addition, the Guideline provides recommendations to support the waiver of bioequivalence studies for BCS Class I and III drugs.

III. M9 Content

Key Principles (continued):

- The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver the drug to the systemic circulation.
- Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver.
- Fixed-dose combination products are considered eligible for a BCS-based biowaiver in cases where all the active drug substances fulfill the criteria.

III. M9 Content

Table of Guideline Contents

III. M9 Content

- The BCS is a scientific approach based on the aqueous **solubility** and intestinal **permeability** characteristics of the drug substance, resulting in four classes:
  - Class I: high solubility, high permeability
  - Class II: low solubility, high permeability
  - Class III: high solubility, low permeability
  - Class IV: low solubility, low permeability

III. M9 Content

- BCS-based biowaiver is only applicable to BCS Class I and III immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation.
  - BCS Class I: Applicants must demonstrate high solubility and high permeability of the drug substance. Applicants must also demonstrate that both the test and reference formulations show rapid (i.e., at least 85% in 30 minutes or less) and similar dissolution. Excipients in the proposed formulation should be evaluated for their potential effects on absorption.

III. M9 Content

- BCS Class 3: Applicants must demonstrate high solubility of the drug substance. Applicants must also demonstrate that both the test and reference formulations show very rapid (i.e., at least 85% in 15 minutes or less) dissolution. Excipients in the proposed formulation should be qualitatively the same and quantitatively very similar to those in the reference formulation.

III. M9 Content

Annexes

Annex I: Caco-2 cell permeability assay method considerations

- Covers how probe compounds should be selected, testing of the monolayer integrity and passive transport of test drug
- Includes a listing of Examples of model drugs for permeability assay method validation;

Annex II: Further information on the assessment of excipient differences

- Includes flow charts to guide BCS-based biowaivers
- Includes examples of acceptable differences in amount of excipients

- Separate clarification annex in Question and Answer format
  - Addresses questions received during the public consultation
  - Includes exceptions to the Guideline and how they should be handled

Outline

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IV. M9 Implementation

- **ANVISA, Brazil** - In the process of implementation; Reference: RDC 37/2011
- **EC, Europe** - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/493213/2018
- **MFDS, Republic of Korea** - In the process of implementation; Date: 1 January 2021; Reference: Regulation on Standard on Pharmaceuticals Equivalence Test (MFDS Notification No. 2019-141, December 30, 2019)
- **MHLW/PMDA, Japan** - In the process of implementation;
- **NMPA, China** - In the process of implementation;
- **Swissmedic, Switzerland** - In the process of implementation;
- **TFDA, Chinese Taipei** - Implemented; Date: 11 August 2016; Reference: BCS biowaiver guideline for Generics

IV. M9 Implementation

FDA:

- **Train key internal stakeholders:** scheduled for 4/14/2020
- **Assessment of changes on in-house work:** on going
- **Internal Communications**
- **External Communications**
  - Federal Register Notice (FRN): Publication will signal official implementation by Agency (predicted to publish approximately 3 to 4 months).
  - Simultaneous to publication, the M9 Guidance will replace the current FDA BCS guidance on the external FDA website and will be considered a Final Guidance.

Outline

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V. Summary

1. BCS is a scientific framework that provides assurance of in vivo bioequivalence (BE) for certain dosage forms using the fundamental properties of the drug substance and drug product and extensive in vitro comparative dissolution.
2. ICH M9 EWG, within a relatively short period of ~3 years, has developed the M9 guideline and taken it through all the clearance steps; M9 is now at Step 5, i.e., implementation.
3. M9 guideline is expected to reduce unnecessary in vivo BE studies and facilitate faster availability of quality drug products globally.

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IV. M9 Implementation

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VI. Acknowledgments

VI. Acknowledgments

- Paul Seo
- Ethan Stier
- Utpal Munshi
- Amanda Roache
- Theresa Mullin

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Thanks!

S5(R3) Revision of Detection of Toxicity to Reproduction for Human Pharmaceuticals

Ronald Wange, PhD
FDA Topic Lead for ICH S5(R3)
Associate Director for Pharm/Tox
Office of New Drugs, CDER, FDA

S5(R3) Detection of Developmental and Reproductive Toxicity for Human Pharmaceuticals

Ronald Wange, PhD
FDA Topic Lead for ICH S5(R3)
Associate Director for Pharm/Tox
Office of New Drugs, CDER, FDA

Outline

- Purpose of the Guidance
- Objectives of Guidance Revision
- Timeline
- Overview of Significant Changes from S5(R2)

Purpose of ICH S5 Guidance

- Provide harmonized guidance on approaches that can be used for assessing the reproductive and embryofetal development risk associated with exposure to a given drug, biologic or vaccine.

Objectives of Revision (1)

- Align with other ICH guidances (e.g., M3(R2), S6(R1), S9)
- Establish alternative dose selection endpoints (beyond MTD)
- Emphasize the use of relevant existing data (WoE)
- Provide approaches to defer definitive DART studies
  - preliminary embryofetal development study (enhanced)
  - alternative assays

Objectives of Revision (2)

- Integrate testing strategies for assessing reproductive toxicity across treatment modalities (drugs, biologics & vaccines)
- Provide guidance on regulatory use of alternative assays:
  - Necessary performance criteria
  - Qualification for context of use
  - Scenarios where alternative assays could be appropriate
  - Integration in risk assessment
- Reduce unnecessary animal use

Objectives of Revision (3)

- The revised ICH S5 Guideline is intended to provide human safety assurance at least equivalent to that provided by current testing paradigms.

Timeline

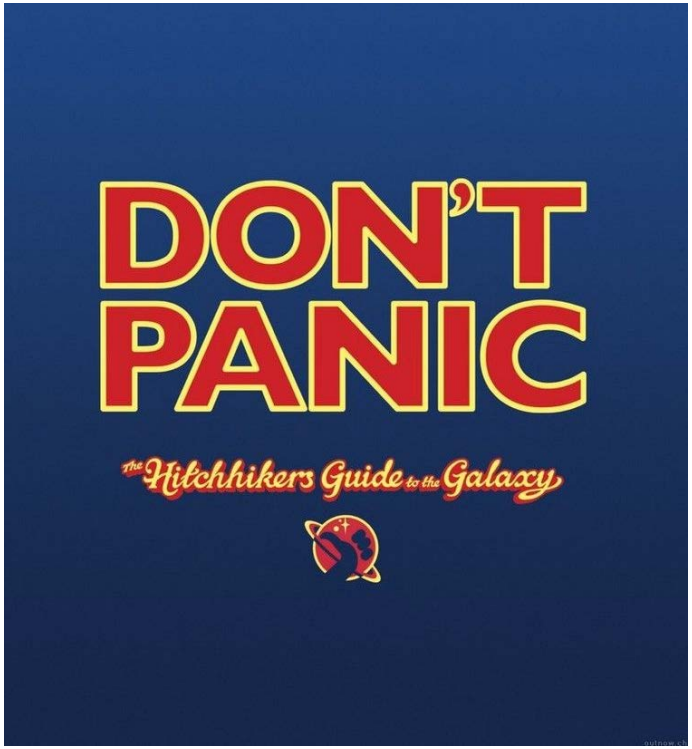
- Concept Paper endorsed (Spring 2015)
- Step 2 draft endorsed (Spring 2017)
- Federal Register Notice published (13 Nov 2017)
- FDA public comment period closed (12 Feb 2018)
- Substantive comments received by all regions
- EWG determined that a major revision of the Step 2 draft would be required to address public comments
- Step 4 document signed-off on February 18, 2020

By the Numbers

R2	R3
21 pages	120 pages

78 pages are dedicated to providing Reference Compound data for aiding in qualification of alternative assays

Still, with Annexes, twice as long



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Factors to Consider in Developing an Overall Integrated Testing Strategy

- The intended patient population and conditions of use
- The known role of the pharmaceutical target and downstream biology in reproduction or development
- Clearly positive results in an EFD study (pivotal or DRF/pEFD) in one species at clinically relevant exposures at the maximum recommended human dose (MRHD)

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Deferral of Definitive EFD Studies (Outside of USA)

1) A qualified alternative assay that predicts the outcome in one species can be combined with a pEFD from a second species to enable the limited inclusion of WOCBP (up to 150 WOCBP for up to 3 months).

2) A modified GLP pEFD/DRF study (increased group size + fetal skeletal examinations) in a pharmacologically relevant species, when combined with a pEFD study in a 2nd species, allows for enrolment of an unlimited number of WOCBP in clinical trials through Phase 2.

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High Dose Selection Criteria

- Toxicity: maximally tolerated dose
- Saturation of systemic exposure
- Maximum feasible dose
- Limit dose (1 g/kg/day)
- Clinically relevant multiple to human exposure
  - >25-fold the exposure in humans at the MRHD
    - Exposure in pregnant animals
    - GLP-compliant pEFD or definitive study
  - For biologics, >10-fold human exposure at the MRHD or saturation of target engagment (maximum PD effect)

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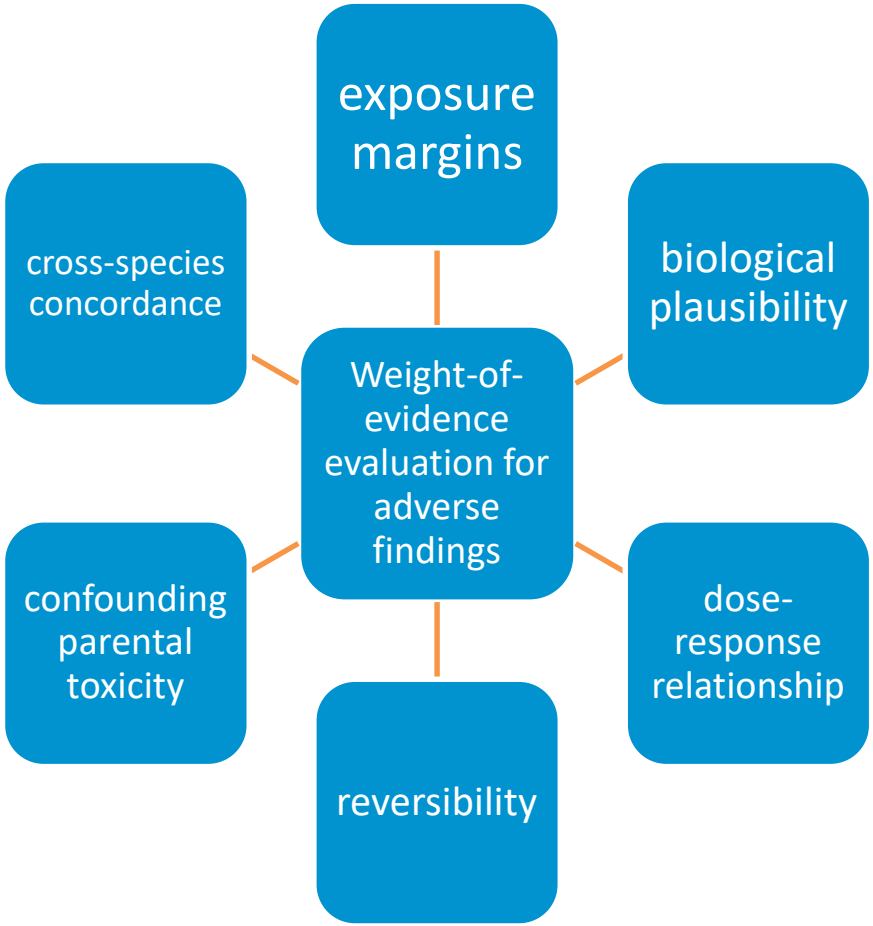
Principles of Risk Assessment

Should include all available data.

Address any limitations, uncertainties and data gaps.

Definitive *in vivo* studies carry more weight than those from alternative assays or preliminary studies.

For rare malformations, the absence of increased frequency with dose does not always alleviate concern.



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Annex 1: In Vivo Study Designs

- Tabular listing of the principle advantages and disadvantages of various routine and non-routine test species for DART testing
  - NHP is to be considered a non-routine for the testing of drugs
    - Often only relevant species for biologics
- Granular recommendations on group sizes, endpoints to be collected and timing of collection
- Subject to a maintenance procedure, so that it can be updated as the state of the science evolves, without re-opening the entire guidance

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Annex 2: EFD Alternative Assays

1 of 4

Under limited circumstances qualified alternative assays can be utilized to support hazard identification and risk assessment:

- Circumstances where there is evidence indicating an adverse effect on EFD is likely
- Toxicity in animal species precludes attaining systemic exposures relevant to the human exposures under conditions of use
- As support for a weight of evidence assessment of equivocal findings
- As partial support for clinical trials including up to 150 WOCBP for up to 3 months duration
- Pharmaceuticals being developed for certain severely debilitating or life-threatening diseases or late-life onset diseases

Annex 2: EFD Alternative Assays

2 of 4

- No specific assays are recommended, rather basic scientific principles are included to assist in assay qualification for regulatory use

- Subject to a maintenance procedure, so that it can be updated as the state of the science evolves, without re-opening the entire guidance

Annex 2: EFD Alternative Assays

3 of 4

Qualification of AAs for Prediction of Malformations or Embryo-Fetal Lethality (MEFL)

Should include:

- A thorough description and justification of the predictive model
- An evaluation of the biological plausibility of the model
- An assessment of the accuracy and ability for the alternative assay to detect MEFL
- Definition and justification of the threshold for molecular and metabolic markers predicting MEFL
- The details of the algorithm employed for determining positive and negative outcomes *in vivo*
- Details of algorithm used to relate *in vitro* concentrations to *in vivo* exposure

Annex 2: EFD Alternative Assays

4 of 4

Reference Compound List

- Contains data for 29 compounds that have been shown to induce MEFL in nonclinical studies (rats or rabbits) and/or humans
  - Define NOAEL and LOAEL exposures for MEFL
  - Reversible or minor manifestations of developmental toxicity were not used for this assessment.
- Negative controls are also required to assess assay specificity
  - Reference Compound List contains data from 3 compounds that were clearly negative in animals at >25-fold human exposure.
- The compounds in this list as well as others (with justification) can be used to support qualification of an alternative assay or battery of assays.

Summary of Guideline Content

This R3 revision of ICH S5

- Provides a focus on application to human risk assessment
- Offers additional dose selection endpoints
- Emphasizes the use of existing data
- Describes integrated testing strategies for assessing DART, including for biologics and vaccines
- Outlines guidance on qualification of alternative assays for use in risk assessment for regulatory purposes

Update on Electronic Standards Topics and MedDRA

Mary Ann Slack
Director Office of Strategic Programs
FDA, Center for Drug Evaluation and Research
April 3, 2020

Topics

- eCTD v4 and E2B(R3) Updates
- M2 Updates
- MedDRA and MedDRA Points to Consider Updates

Updates on eCTD and E2B(R3)

ICH M8 eCTD v4.0 Status Update

- **ICH eCTD v4.0 Assessment**
  - Assessment: June 2019 – November 2019
  - Assessment activities included:
    - Review of the eCTD v4.0 requirements
    - Risks and Benefits Analysis
    - Vendor Readiness Survey
    - HL7 RPS Support
    - FHIR Mapping & Analysis
  - Recommendation to Implement eCTD v4.0
- **Implementation**
  - ICH M8 regulatory authorities are moving forward with implementation
  - Initial regional implementations are planned for 2021 - 2023
- **ICH eCTD v4.0 website (https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v40)**
  - ICH eCTD v4.0 Implementation Package v1.3
  - Links to regional eCTD v4.0 webpages
  - Change Control – Submit questions and change requests

ICH E2B R3 Updates

- **ICH E2B R3 Regional Requirement**
  - Defined all regional data elements
  - Conducted 3 public meetings to communicate the regional data elements
  - Regional data elements and forward compatibility published at the public meeting
- **Implementation**
  - Core ICH and regional data elements setup in FAERS II and under testing
  - R3 regional data element for similar device for combo product under construction
  - Validator tool to validate E2B R3 regional specs available to public by end of 2020
  - E2B R3 regional submission planned in 2021
  - Update to E2B R3 Regional Technical Specification underway
- **ICH Activities**
  - Training material development underway

M2 Updates

M2's Charge

ICH Topic Assessment & Consultative Support

- Perform technical evaluation of EWG guidelines for technical risk and opportunities; make recommendations on electronic exchange, format and security of information.
- Provide technical/consultative support to EWGs (e.g., terminology list maintenance).

Project Opportunities

- Identify, evaluate and propose technically oriented new topic opportunities with good potential to the ICH MC.

Technology and Regulatory Trends

- Monitor technology and regulatory trends for impact on ICH areas of interest.
- Manage relationships with Standards Development Organizations (e.g., HL7, ISO/TC215, EDQM)

Technical Recommendations

- Publish technical recommendations and implementation status for regulatory submissions (ESTRI)

M2 Updates

Recent Accomplishments and Activity

- Identified and elaborated potential project opportunity for developing electronic standards for product quality, chemistry and manufacturing controls data
- M2 is collaborating with M11 to develop a technical specification for clinical trials protocol; the joint effort is defining an innovation framework for continued support and improvement that could apply to electronic standards more broadly.
- Completed the evaluation of FHIR and risk assessment of implementing new HL7 v3 electronic standards
  - Collaborated with M8 to evaluate risk/benefit of implementing eCTD v4 (based on HL7 v3 standard) and options if not. Conclusion made to continue with implementation
  - Establishing baseline documentation of tools and information supporting potential changes needed for HL7 v3 messages (eCTD and E2B(R3))
  - Continuing to monitor HL7 FHIR maturity growth for ICH-relevant purposes
- Drafted considerations for a modified standards development process that interleaves with the ICH process and recognizes the swift technology pace of change; these are currently under review.

MedDRA and MedDRA Points to Consider (PtC) Updates

ICH MedDRA

- MedDRA (Medical Dictionary for Regulatory Activities): standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for drugs, vaccines and drug-device combination products
- MedDRA Management Committee: governance body providing technical and financial oversight of the MedDRA terminology and the MedDRA maintenance organization. Under the governance of the ICH MedDRA Management Committee, MedDRA is continuously enhanced to meet the evolving needs of regulators and industry around the world.
- ICH MedDRA Points to Consider Working Group: develops guides for harmonized MedDRA usage (coding and retrieval guidelines)
- MSSO (Maintenance and Support Services Organization): contracted by ICH to maintain, develop and distribute MedDRA. The terminology is free for all regulators worldwide, academics, and health care providers while paid subscriptions are on a sliding scale linked to annual turnover of companies

ICH MedDRA Updates

- ICH and SNOMED International have developed a bi-directional SNOMED-MedDRA mapping as an outcome of the Innovative Medicines Initiative WEB-RADR2 project.
  - Early testing will be conducted through September 2020
  - A draft MOU is under review that covers the maintenance and distribution of the mapping
- ICH and IMDRF have entered into a MOU that outlines the maintenance efforts by both parties to ensure a robust mapping of overlapping MedDRA terms and IMDRF device adverse event terms to facilitate interoperability. This benefits health professionals, industry and regulators as they will be able to efficiently and effectively communicate a patient's condition multiple times using only one set of terms.
- Most recently, a number of terms were added with more anticipated to support coding and reporting COVID-19 related events. These supplemental terms may be viewed in the MSSO's Web-Based Browser, and will be included in subsequent releases of MedDRA.
- The initial Korean MedDRA translation was released in September 2019.
- The Brazilian Portuguese translation is on track to be released this spring.
- Four new SMQs were developed:
  - Sepsis – released in MedDRA v22.1, September 2019
  - Opportunistic Infections – released in MedDRA v23, March 2020
  - Progressive Multi-focal leukoencephalopathy and Immune-mediated/autoimmune disorders – to be released in MedDRA v23.1, September 2020

ICH MedDRA Points to Consider working group (M1 PtC)

- **Author and update Points to Consider (PtC) documents for consistent use of MedDRA:**
  - MedDRA Term Selection (MTS:PtC), MedDRA Data Retrieval and Presentation (DRP:PtC)
  - Update released in March 2020 for MedDRA version 23.0, frequency conversion from six-monthly to an annual release
  - MedDRA Points to Consider Companion Document: update / release of second edition in April 2020
  - Developing new section of Companion Document on product quality issues
    - Due to numerous new members and the difficult topic, agreed to meet at the next ICH face-to-face meeting (virtual meeting 26 - 27 May 2020)

Overview of Ongoing ICH Topics

Amanda Roache, MPP
FDA, Center for Drug Evaluation and Research
April 3, 2020

Topics for Discussion

I. ICH Strategic Themes:
- Good Clinical Practices (GCP) Renovation
- Harmonization of Standards for Generic Drugs
- Strategic Approach to Enhance Standards for Pharmaceutical Quality
- Harmonization of Standards for Pharmacoepidemiological Studies

II. Ongoing ICH Harmonization Projects:
- Efficacy Topics
- Quality Topics
- Safety Topics
- Multidisciplinary Topics

III. Conclusion

ICH STRATEGIC THEMES

ICH GCP Renovation

ICH STRATEGIC THEME

FDA

ICH
harmonisation for better health

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Reflection Papers

GCP Renovation

ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

This Reflection Paper was endorsed by the Assembly in January 2017.

The ICH Reflection Paper on Good Clinical Practice (GCP) "Renovation" contains the ICH proposal for further modernisation of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the renovation includes the revision of the current E8 General Considerations for Clinical Trials, and the further revision of the E6 Guideline for Good Clinical Practice, which had last been revised in November 2016 as E6(R2).

For the E8(R1) Concept Paper and Business Plan, please refer to the E8(R1) page.

The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain.

Reflection Paper on GCP

ICH Global Meeting on ICH E8(R1) Guideline on General Considerations for Clinical Trials

GCP Renovation Step 1

ICH STRATEGIC THEME

Revision of ICH E8 General Considerations for Clinical *Studies*

- Address a broader range of trial designs and data sources
- Identify a basic set of critical-to-quality factors that can be adapted to different types of trials to support the meaningfulness and reliability of trial results and to protect human subjects
- Provide an updated cross-referencing of all other relevant ICH Guidelines that should be referred to when planning clinical studies

ICH Global Meeting on E8(R1) held October 2019 (see https://www.ich.org/page/reflection-papers)

Timeline:

- Draft Guideline issued in May 2019
- Public comment period May – October 2019
- *Final Guideline anticipated in 2020*

GCP Renovation Step 2

ICH STRATEGIC THEME

Revision of ICH E6(R2) Good Clinical Practices

- Address application of GCP principles to the increasingly diverse trial types and data sources being employed to support regulatory and healthcare related decision making on drugs, and provide flexibility, when appropriate, to facilitate the use of technological innovations in clinical trials
  - Refinement of E6 principles in overarching principles and objectives document
  - Annex I Interventional clinical trials – address use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants and collection of trial data
  - Annex 2 Additional considerations for non-traditional interventional clinical trials - designs such as pragmatic clinical trials and decentralized clinical trials, as well as those trials that incorporate real world data sources

Timeline:

- Draft General Principles Guideline and Annex I anticipated December 2021

Harmonization of Standards for Generic Drugs

- **Reflection Paper endorsed November 2019, *Further Opportunities for Harmonisation of Standards for Generic Drugs***
  - Outlines approach for developing and enhancing ICH Guidelines to support harmonization of scientific and technical standards for generic drugs
  - Intended to streamline drug development across regulatory jurisdictions and increase patient access to high quality affordable pharmaceuticals

- **ICH Generic Drug Discussion Group**
  - Technical discussion group for issues relevant to harmonization of scientific and technical standards for generic drugs

- **M13 Guideline on Bioequivalence for Immediate Release Solid Oral Dosage Forms**
  - Topic endorsed November 2019
  - First ICH Guideline on standards for demonstrating bioequivalence to address study design and data analysis

ICH Reflection Paper:

Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches

- Strategic approach to enhance the portfolio of ICH Quality-related Guidelines to support continual improvement and innovation in biopharmaceutical manufacturing technologies and approaches
- Advance ICH Quality Vision to develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science

ICH Approved Topics Recommended through Quality Reflection Paper

- **Q2(R2)/Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation**
  - New Q14 Guideline on *Analytical Procedure Development* to harmonize scientific approaches and provide principles related to the description of the analytical procedure development process
  - Revision to ICH Q2(R2) Guideline on *Validation of Analytical Procedures* to include validation principles that cover analytical use of spectroscopic or spectrometry data and provide general framework for the principles of analytical procedure validation
  - *Draft anticipated in 2020*

- **Q13 Continuous Manufacturing**
  - Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of continuous manufacturing technologies
  - Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate continuous manufacturing for small molecules and therapeutic proteins for new and existing products
  - *Draft anticipated in May 2020*

ICH Quality Discussion Group

- Technical discussion forum for issues relevant to the ICH Quality Vision to develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product
- Current activities:
  - Review need for new ICH quality-related harmonization work
  - Survey of existing ICH Quality guidelines to identify and recommend those that need revision
  - Review and recommend training needs to promote consistent implementation of ICH guidelines globally

ICH Reflection Paper

Strategic Approach to Harmonisation of Technical Scientific Requirements for Pharmacoepidemiological Studies

- Reflection Paper endorsed in June 2019
  - Proposes a strategic approach to harmonization of technical standards for pharmacoepidmiological study data submitted to regulatory agencies

- Pharmacoepidemiology Discussion Group
  - Supports advancement of harmonization of scientific and technical requirements related to pharmacoepidemiological studies
  - Identify a priority list and overall structure of potential guidelines

EFFICACY TOPICS

E14/S7B Questions & Answers: Clinical and non-Clinical Evaluation of Qt/QTc Interval Prolongation and Proarrythimic Potential

- Guidance on how to apply new technologies that can offer improved insight into which QT prolonging drugs are proarrhytmic and which are not
- Streamline clinical development for drugs that prolong the QT interval but are found to have low proarrhytimic risk and result in fewer products being dropped from development
- Two stages of Q&As are being developed:
  - Stage 1: E14 Q&As on in vitro, in silico and in vivo assay standardization and application, while considering the impact of these recommendations on clinical situations where current E14 methodology is problematic and an S7B Q&A on principles for proarrthymia risk prediction models.
  - Stage 2: Q&A(s) for S7B and E14 on how to use the proarrythmia prediction algorithms or model results

Stage 1 final Q&As anticipated 2020

E19 Optimization of Safety Data Collection

- Harmonized guidance on when it is appropriate to use a targeted approach to safety data collection in some late-stage pre-marketing or post-marketing studies, and how such an approach would be implemented.
- Avoid unnecessary data collection, minimize burden to patients and promote greater efficiency

Timeline

- Draft Guideline issued April 2019
- Comment period ended Sept. 2019
- Final Guideline anticipated Nov. 2021

E11A Pediatric Extrapolation

- Harmonize methodologies and strategies to incorporate pediatric extrapolation into overall drug development plans
- Improve the speed of access to new drugs for pediatric patients while limiting the number of children required for enrollment in clinical trails
- *Draft guideline anticipated November 2020*

E2D(R1) Post Approval Safety Data Management: Definitions and Standards for Expedited Reporting

- Revision of E2D Guideline to clarify the management of post-approval safety information from new or increasingly used data sources including the need to adapt definitions and standards
- *Draft anticipated October 2021*

E20 Adaptive Clinical Trials

- New guideline on the design, conduct, analysis, and interpretation of adaptive clinical trials that provides a transparent set of principles for regulatory review of these studies in a global drug development program
- *Draft anticipated November 2021*

QUALITY TOPICS

- **Q3C(R7) Maintenance of Guideline for Residual Solvents**
  - Q3C sets pharmaceutical limits for residual solvents in drug products called “Permitted daily exposure” (PDE) and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms
  - PDEs are currently being developed for three new compounds including: 2-methyltetrahydrofuran, cyclo pentyl methyl ether, and tert-butanol
  - *Draft PDEs anticipated April 2020*

- **Q3D(R2) Guideline for Elemental Impurities**
  - Establishes permitted daily exposures (PDEs) to limit elemental impurities in drug products administered by the oral, parenteral and inhalation route of administration
  - The guideline is being revised to incorporate PDEs for the cutaneous and transdermal products
  - *Draft anticipated April/May 2020*

- **Q3E Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics**
  - Harmonize requirements around the evaluation and reporting of extractable and leachables thresholds, and processes to assess leachables within a risk-based framework
  - Topic endorsed Nov. 2019

- **Revision of ICH Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin**
  - Address new biotechnology product types, advances in manufacturing technology, analytical methods for virus testing, and scientific knowledge that have occurred since publication of the original guideline in 1999
  - *Draft anticipated Nov. 2020*

SAFETY TOPICS

- **S1 EWG - Rodent Carcinogenicity Studies for Human Pharmaceuticals**
  - Potential revision to provide a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of pharmaceuticals and clarify criteria for deciding whether the conduct of a two-year rodent carcinogenicity study of a given pharmaceutical would add value to this risk assessment
  - Benefits may include a reduction in 2-year rat carcinogenicity studies where there is regulator and sponsor agreement that a product presents a low risk or likely risk of human carcinogenicity and reduction in animal use
  - *Draft anticipated 2020*

- **S12 EWG - Biodistribution Studies for Gene Therapy Products**
  - Will provide recommendations on the aspects of nonclinical studies performed that include biodistribution assessment to contribute to the streamlined development of gene therapy products, while maintaining scientific rigor and minimizing the unnecessary use of animals
  - *Draft anticipated March 2021*

- **S11 EWG – Nonclinical Safety Testing in Support of Development of Pediatric Medicines**
  - Will recommend standards for the conditions under which nonclinical juvenile animal testing is considered informative and necessary to support pediatric clinical trials, and to provide guidance on the design of the studies
  - This will result in streamlined drug development and higher scientific rigor while minimizing the unnecessary use of animals

  Timeline:

  - Draft issued in September 2018
  - Public consultation ended in April 2019
  - *Final Guideline anticipated April 2020*

MULTIDISCIPLINARY TOPICS

- **M7 (R2) EWG - Addendum to Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk**
  - Provides a framework to limit mutagenic impurities and potential carcinogenic risk in drug products and substances
  - Question and answer document is being developed to provide clarification on the justification of control strategy for mutagenic impurities, organization and depth of information reporting of individual impurities, (Q)SAR systems, and other safety-related information
  - Additional permitted daily exposures are also being determined for new DNA reactive (mutagenic) impurities
  - *Draft anticipated 2020*
- **M12 Drug Interaction Studies**
  - New guideline on drug interaction studies to provide a consistent approach in designing, conducting and interpreting drug-drug interaction studies during the development of a therapeutic product
  - *Draft Anticipated Oct. 2021*
- **M10 Bioanalytical Method Validation**
  - Provides recommendations for bioanalysis and validation of bioanalytical assays for chemical and biological drug quantification and their application in the analysis of study samples
  - *Final Guideline anticipated in 2020*

Conclusion

- ICH has many ongoing working groups developing or revising Guidelines in the areas of Efficacy, Quality, Safety, and Multidisciplinary Areas
- International harmonization aligns technical and scientific requirements for the development and manufacture of pharmaceuticals and leads to more efficient drug development and marketing and increased patient access to pharmaceuticals
- ICH leverages Reflection Papers and Discussion Groups to explore possible new areas for future harmonization
- Public stakeholders can follow the progress of development of new ICH guidelines and revision of existing ICH guidelines and provide comments during public consultation through the ICH website

Thank you for your attention

Visit our websites for more information on the work of ICH:

- www.ich.org
- https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/ich-guidance-documents
- https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation.html

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Health Canada Santé Canada

ICH Member

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you for attending!

The public docket will remain open until April 30, 2020: https://www.regulations.gov/docket?D=FDA-2020-N-0256

Visit the ICH website for more information on the work of ICH:
www.ich.org