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ADMINISTRATION

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

Great Room, White Oak Campus

FDA, Center for Drug Evaluation and Research

April 29, 2019

Agenda

- I. Overview of ICH
- II. Topics Recently Reaching Step 3 of the ICH Process (draft guideline)
 - E8(R1) Revision on General Considerations for Clinical Trials
 - E19 Optimization of Safety Data Collection
 - S11 Nonclinical Safety Testing in Support of Drug Development of Paediatric Medicines
 - M10 Bioanalytical Method Validation
- III. Update on Electronic Standards Topics and MedDRA
- IV. Overview of Ongoing Topics
- V. Public Comment
- VI. Closing Remarks

Overview of ICH

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Senior Advisor for International Affairs

FDA, Center for Biologics Evaluation and Research

April 29, 2019



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



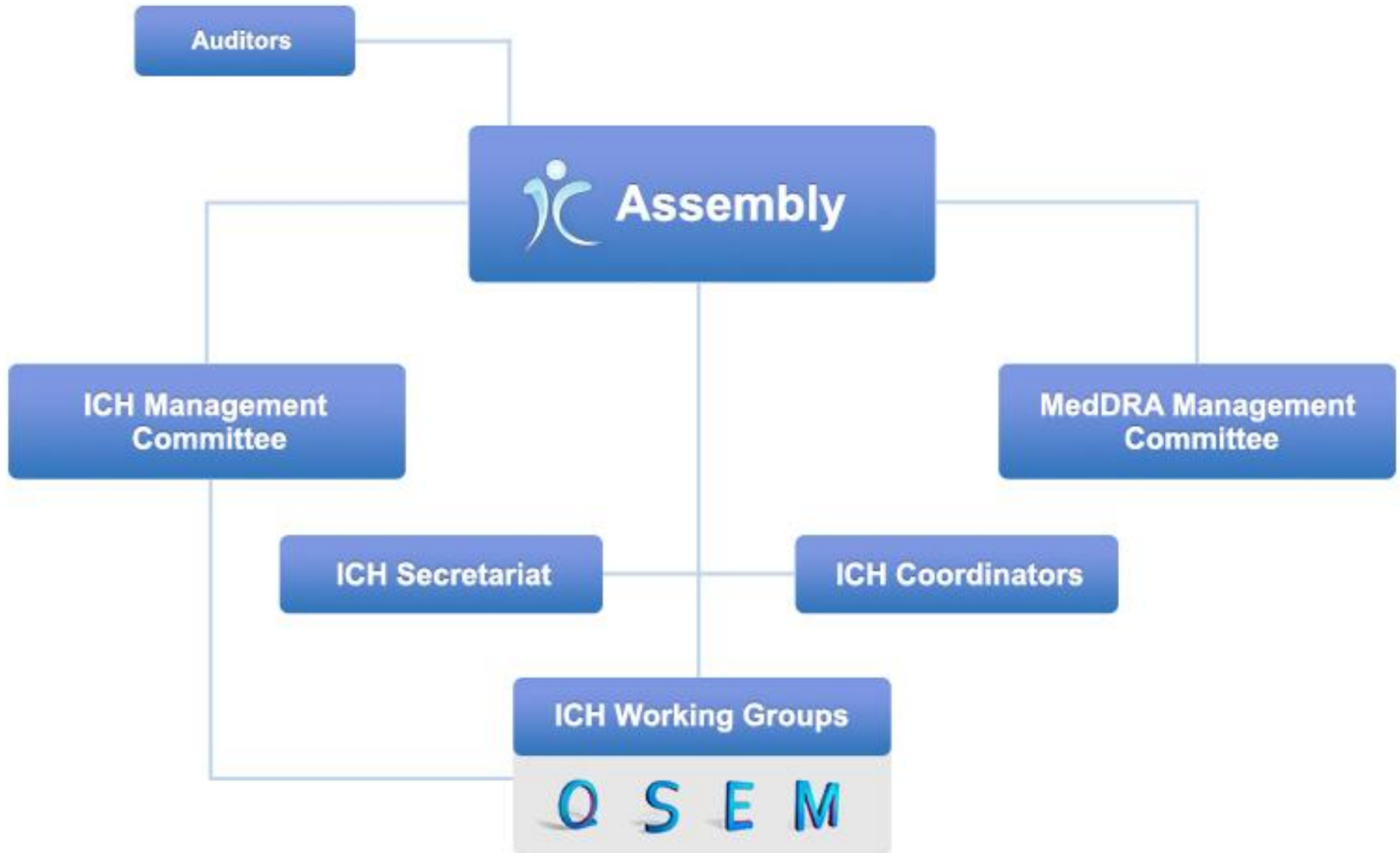
Assembly

- 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**

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 to¹:
 - 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
- WSMI

Observers

Standing Observers

- IFPMA
- WHO

Authorities

- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- INVIMA, Columbia
- MMDA, Moldova
- National Ctr,
Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor,
Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- 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

**As of April 2019*

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

Questions?

TOPICS RECENTLY REACHING STEP 3 OF THE ICH PROCESS

ICH E8 (R1)

Revision of General Considerations for Clinical Trials

Lisa LaVange, PhD

Rapporteur

Expert Working Group

US FDA and Health Canada

Regional Public Consultation

Silver Spring, MD

April 29, 2019

Outline

- Background
- Objectives and scope
- Key principles
- Content
- Timeline

- ICH Reflection paper
- Published Jan 2017
- Proposal to
 - Revise E8
 - Renovate E6

ICH
harmonisation for better health

Home About ICH Work Products Meetings Training **Newsroom** RSS

ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 / News / Newsroom / Home

12 January 2017

ICH is inviting public review and comment on a reflection paper on Good Clinical Practice (GCP) “Renovation”, which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6(R2).

The reflection paper is available for download via the following link:

- [Reflection paper on GCP Renovation](#)

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. ICH's decision to invite stakeholder comment on the proposed renovations at this early stage, ahead of guideline development efforts, recognises the considerable stake and relevant expertise in the research community beyond ICH.

The seeking of stakeholder comment on the current reflection paper is seen as a first step in an enhancement of the ICH process with respect to public consultation for the revision of ICH E8 and E6. The GCP Renovation reflection paper outlines additional steps that are also being considered to enhance stakeholder engagement.

Background

- 1997 ICH E8 guideline describes:
 - Protection of clinical trial participants
 - Scientific approach to study design and conduct
 - Phases of drug development
- 2017 ICH Reflection Paper
 - Proposed revision of E8 as 1st step towards a broader GCP renovation
- E8 Revision to focus on:
 - Adopting a quality-by-design framework for clinical studies
 - Expanding the scope to include a broader range of study designs and data sources

Background

- Expert working group (EWG) formed
 - 30 representatives from 14 ICH members and observers
 - Multiple disciplines represented
 - 3 in-person meetings plus conference calls to date
- Draft guideline shared with internal stakeholders in December 2018
- Step 1 guideline completed and signed off by EWG members in April 2018

E8 (R1) EWG Members

ANVISA, Brazil

Ms. Miriam Motizuki Onishi
Ms. Flávia Regina Souza Sobral

EC, Europe

Dr. Fergus Sweeney
Dr. Andreas Kirisits

FDA, United States

Dr. Lisa M. LaVange
Ms. Robyn Bent
Dr. Mark Levenson
Dr. Philip Krause

IGBA

Dr. Aletta van Beek
Dr. Sigrid Balsler

MHLW/PMDA, Japan

Mr. Hiroshi Sakaguchi
Dr. Mutsuhiro Ikuma
Dr. Yuki Ando

PhRMA

Dr. Joanne Palmisano
Ms. Melissa Mudrick

TFDA, Chinese Taipei

Dr. Hsiao-Yun Chen
Ms. Mei-Chen Huang

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Dr. Kerstin Koenig
Prof. Dr. Byron Jones

Health Canada, Canada

Dr. Carole Légaré
Dr. Fuhu Wang

JPMA

Mr. Mitsuhiro Kondo
Dr. Yasuyuki Matsushita

NMPA, China

Dr. Shuang Lu
Dr. Tao Wang

Swissmedic, Switzerland

Dr. Christine Haenggeli
Prof. Thomas Kleppisch

IFPMA

Dr. Angela Yan (Hui)

Guideline Objectives

1. Describe internationally agreed upon principles and practices to facilitate regulatory acceptance
2. Provide guidance on the consideration of quality in the design and conduct of clinical studies, including:
 - Identification of factors critical to the quality of the study
 - Management of risks to those factors during study conduct
3. Provide an overview of the types of clinical studies performed during the product lifecycle, including
 - Aspects that support the determination of quality factors critical to ensuring the protection of study subjects and ability to meet the study objectives
4. Provide a guide to the ICH efficacy documents

Key Principles

- Protection of clinical study subjects is a shared responsibility (investigators, sponsors, IRBs)
 - Emerging data should be reviewed to assess impact on safety
- Clinical studies should be designed, conducted, and analysed according to sound scientific principles and reported appropriately
- Results of prior studies should inform the plan of later studies

Key Principles

- Quality by design sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes
- A basic set of factors relevant to ensuring study quality should be identified for each study
 - Emphasis should be given to those factors that stand out as critical to study quality
- Consulting with patients and/or patient organisations helps ensure that all perspectives are captured

E8 (R1) Table of Contents

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Summary of Guideline Content

- Guideline objectives (Section 1) and general principles (Section 2)
- Designing quality into clinical studies (Section 3)
- Planning a clinical development programme, including types of studies important at different points in the programme (Section 4)
- Elements of clinical study design (Section 5)
- Study conduct and reporting, and safety considerations (Section 6)
- Identifying critical to quality factors (Section 7)

Summary of Guideline Content

- Annex 1: Type of studies, study objectives, and examples
- Annex 2: ICH Efficacy Guidelines
- Annex 3: Examples of quality factors mapped to ICH E guidelines where they are discussed

ICH E family of guidelines – need to be read together

E8 General Considerations for Clinical Trials

Design and analysis:

E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

Conduct and reporting:

E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:

E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:

E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

Genetics/genomics:

E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

Timeline

- Guideline developed based on a Concept Paper (14 Nov 2017) and a Business Plan (14 Nov 2017)
- Reached *Step 1* sign-off by Expert Working Group members in April 2019
- Expect to reach *Step 2b* in early May 2019 and be issued by the ICH Regulatory Members for public consultation
- External Stakeholders Public Meeting planned for November 2019 at FDA
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system in June 2020

E8 (R1) EWG
Kobe, Japan
June 2018



Questions?

E19 Optimization of Safety Data Collection

Mary Thanh Hai, MD

Director, Office of Drug Evaluation II, Office of New Drugs

FDA, Center for Drug Evaluation and Research

Outline of Presentation

- **Objective of E19**
- **Scope of E19**
- **Contents of E19**
- **ICH Timelines for E19**
- **Conclusions**

Objective of Guideline

- E19 is proposed to provide harmonized guidance on when it would be appropriate to use a selective approach to safety data collection in some late-stage pre-marketing or post-marketing studies, and how such an approach would be implemented.
- Optimization of safety data collection using a selective approach may improve the efficiency of clinical studies while reducing burden to study participants
- Built off the principles outlined in an FDA Guidance issued April 2016 titled, “Determining the Extent of Safety Data Collection Needed in Late-Stage Preapproval and Postapproval Clinical Investigations”
<https://www.fda.gov/downloads/drugs/guidances/ucm291158.pdf>
- Adoption of an internationally harmonized approach to selective data collection may facilitate global participation in clinical studies

Scope of E19

- When the safety profile of a medicinal product is well-understood, principles of E19 are:
 - Applicable to late-stage development of medicinal products in interventional and non-interventional studies
 - Most often, post-approval studies
 - But in specific cases, can also be applied in pre-approval studies
- Selective safety data collection under E19 does not alter local/regional safety reporting requirements and sponsors and investigators should still ensure that routine patient care is not compromised.

Contents of E19

I. Introduction

1.1 Objectives

1.2 Background

1.3 Scope

2. General Principles

2.1 Types of safety data for which selective collection may be appropriate (2.1.1, 2.1.2, 2.1.3)

2.2 When may safety data collection be considered? (2.2.1, 2.2.2)

2.3 Examples where selective safety data collection may be considered

2.4 Ensuring patient safety within studies

2.5 Changes in approach to safety data collection

2.6 Early consultation with regulatory authorities

3. Methods of Implementation

3.1 Selective safety data collection for all patients in the study

3.2 Comprehensive safety data collection for a specific subset(s) of the population, with selective safety data collection for other patients

3.3 Comprehensive safety data collection in a representative subset of the population, with selective safety data collection for other patients

3.4 Comprehensive safety data collection for the initial portion of the study, with selective data collection thereafter

4. Relationship with other guidelines/regulations

ICH Meetings for E19

- **Montreal, Canada June 2017**
 - Final concept paper endorsed by ICH Management Committee in July 2017
- **Geneva, Switzerland November 2017**
 - Refined objectives and scope – replaced targeted safety data collection with selective safety data collection
 - Group discussion/editing
- **Kobe, Japan June 2017**
 - Group discussion/editing
- **Charlotte, North Carolina, US November 2017**
 - Near final technical document
 - Goal for Step 1 finalization by January 31, 2019
 - EWG concurrence in February 2019

ICH Timelines for E19

- Currently reached Step 3
 - https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E19/E19EWG_Step2_DraftGuideline_2019_0403.pdf
- EWG plans to meet in Fall 2019 to review public comments
- Spring/Fall 2020 - Continue to revise document based on public comments
- Anticipate Finalization Step 3/Step 4 Adoption June 2021

Conclusions

- Adoption of E19 is an important advance in global medicinal product development
- When appropriate, selective safety data collection may facilitate the conduct of larger studies that can provide important information on long-term efficacy and safety of a therapy without compromising the quality or integrity of the study results

Thank you from E19 EWG!



Questions?

S11 Nonclinical Safety Testing in Support of Development of Paediatric Medicines

Karen Davis Bruno, PhD

*Associate Director for Pharmacology/Toxicology Staff
Office of New Drugs*

FDA, Center for Drug Evaluation and Research

Background

- This document has been signed off as a *Step 2* document (September, 2018) and issued by the ICH Regulatory Members for public consultation
- This document was developed based on a Concept Paper and a Business Plan (both approved November, 2014)
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: November 2019

Concept Paper - 2014

- Several regional guidelines/guidances on nonclinical testing in support of development of pediatric guidances, no harmonised guideline
- **Specific issues identified**
 - Lack of harmonized criteria for determining when all previous animal data (juvenile and adult) and human safety data are considered sufficient to support pediatric clinical trials
 - Lack of harmonization of the design of juvenile animal studies
 - No guidelines describe in detail the nonclinical studies that need to be conducted to support a pediatric-only development

Business Plan - 2014

- What are the benefits to the key stakeholders of generating a new guideline?
 - Guideline will streamline the drug development
 - Unnecessary use of animals will be minimized (3Rs)
 - Guideline will provide a harmonized approach on the need and design of juvenile animal studies
 - data from juvenile animal studies will be of higher quality and more informative to the safety of pediatric clinical trials
- Planned timeline was to reach *Step 2b* in 2016 - delayed due to complexity of issues
- See also S11 Business Plan:
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S11/S11_Final_Business_Plan_10_November_2014.pdf

Gathering the underlying data

- Collection and evaluation of existing nonclinical data for pediatric development (blinded data)
 - industry survey from Japan, US and EU
 - EMA analysis of CNS and oncology drugs¹
 - FDA analysis of all therapeutic areas
- Comprehensive literature review

Table of Contents

- Section 1 Introduction: objectives, scope and general principles
- Section 2 Determining the need for additional nonclinical safety investigations: weight of evidence approach
- Section 3 Design of nonclinical juvenile animal studies: core and additional endpoints
- Section 4 Considerations for pediatric-first/ only development
- Section 5 Other considerations: excipients and combined drugs
- Appendix A, B and C

Section 1: Objectives and Scope

- Objective: Support development of safe pediatric medicines, 3Rs, facilitate pediatric clinical trials.
- Scope
 - Drugs intended for pediatric use
 - ICH S9 determines need for nonclinical information for pediatric anticancer pharmaceuticals, S11 provides study design considerations
 - Excluded: tissue-engineered products, gene and cellular therapies, and vaccines

Section 1: General principles

- Pediatric patients are not small adults - they are a different population compared with adults.
- Understanding of the overall clinical development plan is needed to design an appropriate and efficient nonclinical program.
- Think about changing the design and/ or timing of the traditional nonclinical program → e.g. use of data from reproductive toxicity studies.
- Prior to each pediatric clinical trial: weight of evidence (WoE) evaluation should be conducted → would additional nonclinical investigations have added value?

Section 2: Determining the need for additional nonclinical safety investigations

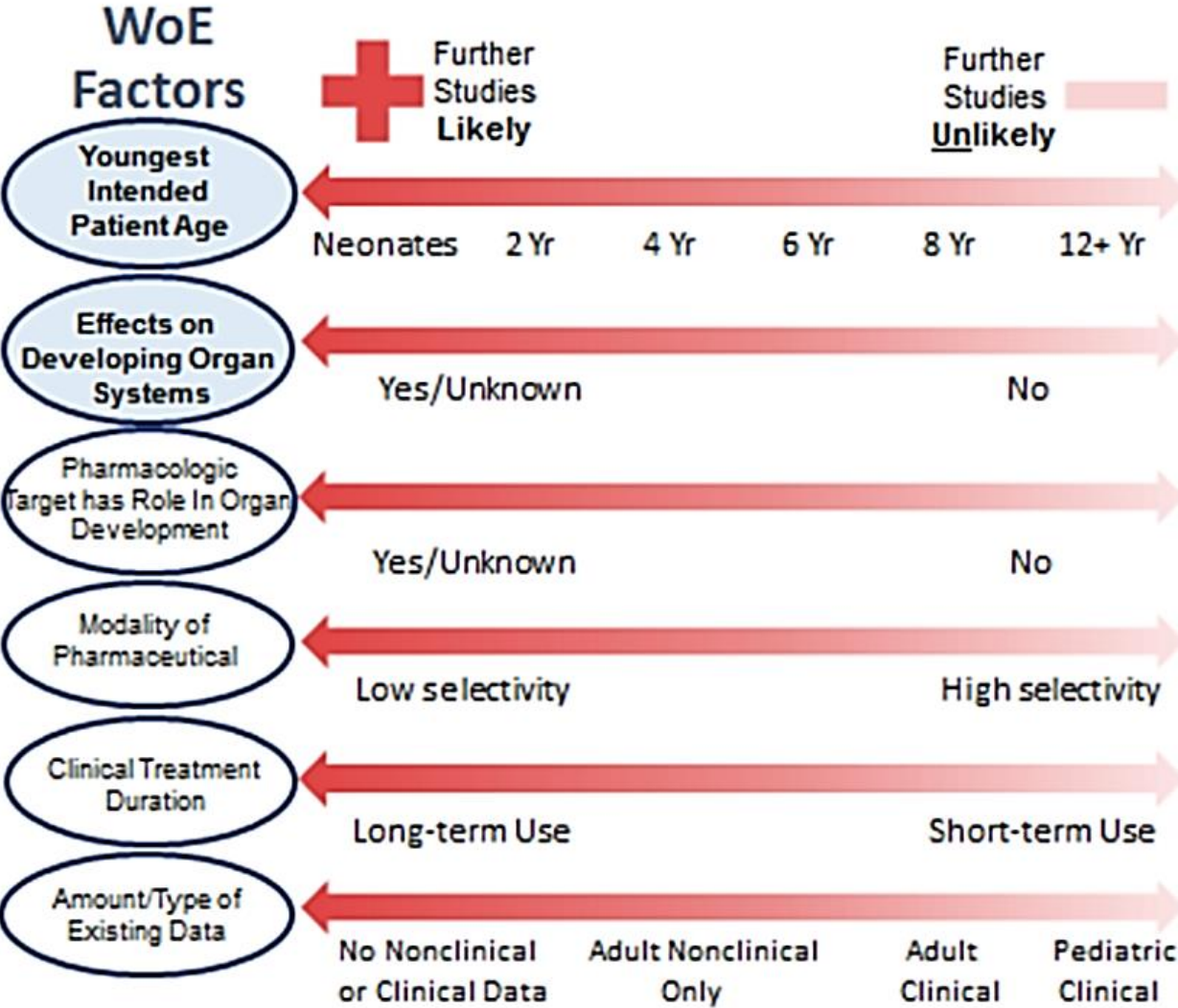


- Weight of evidence (WoE) approach = integrated assessment

Based on:

- clinical context: indication, intended pediatric age group, and treatment regimen
- Pharmacology and Pharmacokinetics (ADME)
- Existing nonclinical (*in vitro* and *in vivo* animal data) and clinical safety data

Application of the WoE approach (II)



Section 3: Design of JAS (I)

- **Guideline recommends a customized JAS:** core and additional endpoints are driven by identified safety concerns.
- JAS design including all additional endpoints is not recommended without a rationale.
- Understanding the level of maturity and function of organ systems across species during their development is needed (see Appendix A)
 - to design an appropriate JAS
 - for the translation of nonclinical toxicity findings to a specific human age range

Section 3: Design of JAS (II)

- Dose-Range-Finding (DRF) studies
- Species selection - Appendix A: advantages/disadvantages of species use in JAS
- Age of animals at dosing
- Off-treatment period: should be included to understand persistence, progression, reversibility or delayed onset of a specific effect
- Route of administration
- Dose selection: a dose-response relationship and a no-observed adverse effect level (NOAEL) should be established

Section 3: Design of JAS (III)

- **Core endpoints:** general standard for a JAS (mortality and clinical signs, growth (body weight + long bone length), food consumption, sexual development, clinical pathology (serum chemistry and haematology), anatomic pathology (gross pathology, organ weights, histopathology), and toxicokinetics
- **Additional endpoints:** driven by identified safety concerns e.g. ophthalmologic examinations, CNS and reproductive assessments
- Allocation of animals to study groups - examples provided in Appendix C

Section 4: Paediatric-first/ Paediatric-only

- Special criteria are described when drug will be administered to paediatric patients without any prior adult data: two JAS are recommended (rodent and non-rodent)
- Juvenile primate study to be conducted only in exceptional cases e.g. Biologics: when primates are the only relevant species
 - Technical feasibility - limiting factor is the age of the juvenile primates

Section 5: Other considerations

- Excipients
 - **Separate studies generally not recommended, but safety should be assessed.**
- Combination pharmaceuticals
 - **Considerations similar to those for supporting combinations in adults.**
 - **Studies of combination only or of combination in an additional arm of a study of individual drug may be sufficient if warranted.**

Appendices

- Appendix A
 - Overview of age-dependent development of organ systems by species
 - Principle advantages and disadvantages of mammalian species for use in juvenile animal studies
- Appendix B: Case studies applying the weight of evidence approach
- Appendix C: Example of an approach to rodent preweaning litter allocation

Conclusions

- Agreement on limited request for JAS (based on WoE)
- Core study with additional endpoints (if applicable)

Timeline

Anticipated Completion Date	Milestone
August 2018	Step 1 sign-off
August 2018	Step 2a/b ICH Assembly endorsement
September 2018	Start public consultation period
April-June 2019	TCs to review comments
June 2019	F2F to discuss revisions
June-November 2019	TCs to prepare final document
November 2019	F2F to finalize Step 4 document





Contact

- For any questions please contact the ICH Secretariat:

admin@ich.org

Questions?

M10 Bioanalytical Method Validation

Brian Booth, PhD

*Deputy Director, Division of Clinical Pharmacology V
Office of Translational Sciences*

FDA, Center for Drug Evaluation and Research

Objectives:

Recommendations for the validation of bioanalytical assays for chemical and biological drug quantification and their application in the analysis of study samples.

The objective of the validation of a bioanalytical assay is to demonstrate that it is suitable for its intended purpose.

Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development.

It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

Scope:

This guideline describes the method validation that is expected for bioanalytical assays that are submitted to support regulatory submissions.

Applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples

- (e.g., blood, plasma, serum, other body fluids or tissues)
- Nonclinical Toxicokinetic/pharmacokinetic studies
- All phases of clinical trials

The bioanalysis of biomarkers and assessment of immunogenicity are not within the scope of this guideline.

Topics:

General Principles of Method Development & Validation

Chromatographic Assay Validation

- Reference Standards
- Validation Parameters
- Study Sample Analysis Expectations

Ligand Binding Assay Validation

- Key Reagents
- Validation Parameters
- Study Sample Analysis Expectations

Incurred Sample Reanalysis

Partial & Cross Validation

- Definitions/conditions

Topics (cont'd):

Additional Considerations

- Endogenous Compounds
- Parallelism
- Recovery
- Minimum Required Dilution
- Commercial Kits
- New Technologies

Documentation

- Bioanalytical site,
- Validation report,
- Bioanalytical Report

Work Plan: Key Milestones

Expected Completion date	Deliverable
November 2018	<ul style="list-style-type: none"> • Technical Document v5-draft preparation
December 2018- January 2019	<ul style="list-style-type: none"> • Step 1 ICH M10 EWG guideline sign-off/acceptance • Step 2a endorsement by Assembly • Step 2b endorsement by Assembly Regulators
February 2019	<ul style="list-style-type: none"> • ICH M10 Draft Guideline posted
March- September 2019	<ul style="list-style-type: none"> • Regional Public Comment Period
November 2019	<ul style="list-style-type: none"> • ICH M10 EWG meetings
November 2020	<ul style="list-style-type: none"> • Step 3 sign-off and Step 4 adoption planned

ICH M10 Regional Public Consultation



	From	To	Period	URL
ICH	02/2019			https://www.ich.org/products/open-consultation.html
EMA	03/14/2019	09/01/2019	5.5 months	https://www.ema.europa.eu/en/news-events/open-consultations
FDA	pending		3 months	
MHLW/ PMDA	under translation		~3 months	
Health Canada	04/03/2019	06/30/2019	3 months	https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/notice-step2-m10-bioanalytical-validation-method.html
Swissmedic	02/2019			https://www.ich.org/products/open-consultation.html
ANVISA	04/17/2019	08/14/2019	4 months	http://portal.anvisa.gov.br/propostas-regulatorias#/visualizar/394860
MFDS	05/21/2019	07/20/2019	2 months	pending
NMPA	04/12/2019	07/31/2019	3.5 months	http://www.cde.org.cn/ichWeb/news/getNewsDetail/2/1022/1
TFDA	04/01/2019	06/30/2019	3 months	https://www.fda.gov.tw/TC/siteListContent.aspx?sid=10742&id=29181



Thank you!

Dr. Anna Edmison-

Senior Clinical Assessment Officer-Health Canada

Dr. Akiko Ishii-Watabe-

MHLW/PMDA-*ICH M10 rapporteur*

ICH M10 Expert Working Group

Questions?

Update on Electronic Standards Topics and MedDRA

Mary Ann Slack, MS

Director Office of Strategic Programs

FDA, Center for Drug Evaluation and Research

April 29, 2019

Topics

- **E2B (R3) – ICH next-gen Individual Case Safety Report**
- **M8 eCTD v4.0 – ICH next-gen electronic Common Technical Document**
- **M2 and ESTR1 – ICH electronic standards Activities**
- **MedDRA and MedDRA Points to Consider**

E2B (R3) Update

ICH E2B R3 Updates

Recent Accomplishments

- **Business rule and data element template**
 - Template listing ICH core data elements and their business rules published on Sept 2018
- **Q&A**
 - Published ver.2.2 on Sep. 2018

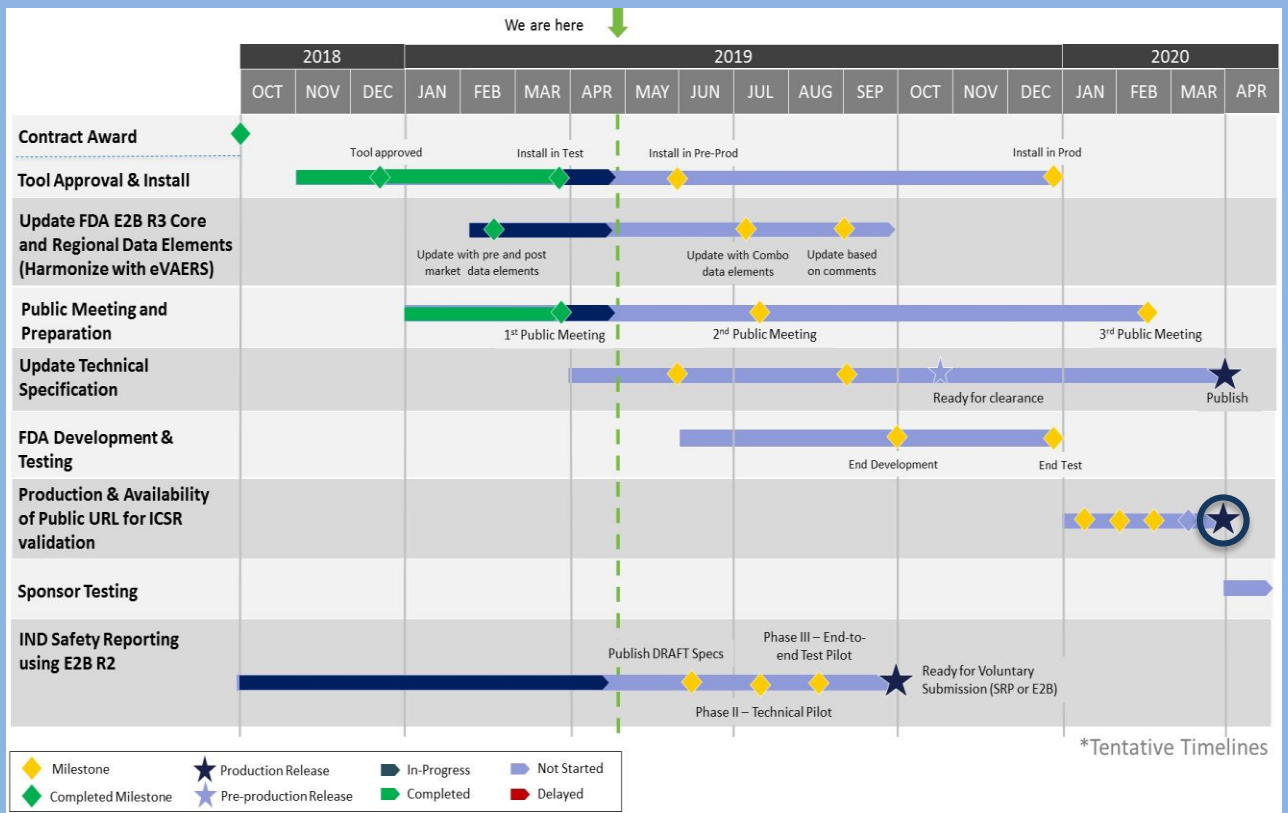
Work Item(s) for June ICH meeting in Amsterdam

- **Training**
 - Development of ICH E2B(R3) training materials
- **Route of Administration (RoA) Mapping**
 - Preparing mapping for RoA between E2B(R2) and EDQM terms
- **EDQM API**
 - Prepare business requirements for API to extract dosage form and route of administration directly from EDQM

FAERS II – FDA’s R2 to R3 Roadmap

- FAERS II - a mission critical system for CDER/CBER
- Provide a modernized system for:
 - surveillance of **pre-market** and **post-market** safety reports along with **product quality defect** reports
 - one-stop shop solution for intake, triage and case processing
 - allows for **enhanced and unified data analytics** and **signal management lifecycle solution**
- Achieve compliant with data standards - ICH E2B R3

FAERS II contract awarded on Sept 30th 2018



M8 eCTD v4.0 Update

ICH M8 (eCTD v4.0) Status Update

- Current ICH eCTD v4.0 Implementation Package (v1.3)

Document	Version	Format
eCTD v4.0 Implementation Guide	1.3	PDF
eCTD v4.0 Controlled Vocabularies	3.0	Spreadsheet
eCTD v3.2.2 Transition Mapping Message Controlled Vocabularies	2.0	Spreadsheet
Genericcode Files	-	Folder and files
Schema Files	-	Folder and files
Implementation Package History	1.3	PDF

- - ICH signoff June 2018
 - General update with additional functionality (e.g. Study Group Order)

ICH eCTD v4.0 Supplemental Documents

- Support Documentation
 - Overview of the eCTD v4.0 Implementation Package
 - Target audience is business and technical personnel
 - Updated in accordance with Implementation Package updates
- Orientation Material
 - Provides an outline of eCTD v4.0 concepts from business perspective
 - Target audience is business personnel and management
 - Updated in accordance with Implementation Package updates
- ICH eCTD v4.0 website (<http://estri.ich.org/new-eCTD/index.htm>)
 - Implementation Package
 - Links to regional eCTD v4.0 webpages
 - Change Control – Submit questions and change requests

M2 and ESTR1 Update

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 project opportunity CeSHarP accepted as new ICH topic (M11); identified project opportunity Common Clinical Trial Submission submitted as a New Topic Proposal (WSMI); identified project opportunity electronic Trial Master File submitted as a new topic proposal (JPMA)
- Finalized terminology list management process
- Confirmed ICH liaison approach with ISO
- White paper on HL7's FHIR standard and considerations for ICH under development; joint discussions with M8 and E2B

Work Item(s) for June ICH meeting in Amsterdam

- Face to face working meeting with HL7 CTO on HL7 V3 support, FHIR roadmap, and potential transition of ICH standards in future; validate assumptions and considerations
- Joint meetings with E2B and M11 on technical questions and support
- Review technical opportunities/risks for current ICH topics

MedDRA and MedDRA Points to Consider (PtC) Update

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

MedDRA Updates

- The Innovative Medicines Initiative's sponsored project to establish sustainable MedDRA-SNOMED crosswalk is progressing well; positive outcomes anticipated in 2019
- MedDRA is now subscribed to by over 5000 organizations in 110 countries
- The MSSO has staffed to provide local support in several additional areas – Central America, Republic of Korea, China and India. In addition to local support, this will enable training to be provided in the local languages.
- The Russian MedDRA translation has been completed; Korean translation underway with anticipated completion this year, bringing total translations to 13.
- The MedDRA MC and MSSO are collaborating with WHO to support countries transitioning from WHO-ART to MedDRA for pharmacovigilance activities
- A new SMQ (Hyperkalemia) was included in MedDRA v22, and another is expected for the September update.

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 2019 for MedDRA version 22.0
 - *Points to Consider Companion Document*, with a focus on data quality and medication errors, v1.1 update will be in 2019
 - Condensed version of PtC documents, released in 9 MedDRA languages in 2018: Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese and Spanish (English and Japanese remain in full)

Questions?

Overview of Ongoing ICH Topics

Amanda Roache, MPP

FDA, Center for Drug Evaluation and Research

April 29, 2019

Topics for Discussion

I. Efficacy Topics:

- E9(R1) Addendum: Statistical Principles for Clinical Trials
- E11A Pediatric Extrapolation
- E14/S7B Questions & Answers: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential

II. Multidisciplinary Topics:

- M9 Biopharmaceuticals Classification System-based Biowaivers
- M7(R2): Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals to Limit Potential Carcinogenic Risk
- M11 Clinical electronic Structured Harmonized Protocol (CeSHarP)

III. Safety Topics:

- S1(R1) Revision of S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals
- S5(R3) Revision of S5 Detection of Toxicity to Reproduction for Human Pharmaceuticals

IV. Quality Topics:

- Q3C(R8) Maintenance of Guideline for Residual Solvents
- Q3D(R1)/(R2) Maintenance of Guideline for Elemental Impurities
- Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- Q13 Continuous Manufacturing of Drug Substances and Drug Products
- Q2(R2)/Q14 Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

V. Additional topics forthcoming

EFFICACY TOPICS

E9(R1) Addendum: Statistical Principles for Clinical Trials



Identified Problem:

- Incorrect choice of estimand and unclear definitions lead to problems in relation to clinical trial design, conduct and analysis
- Absence of a framework for planning, conducting and interpreting sensitivity analyses may lead to inconsistencies in inference and decision making within and between regulatory regions

Objective:

- Establish a framework for translating trial objectives into a precise definition of the treatment effect that is being estimated
- Clarify existing E9 document and expand upon it

Timeline for Development:

- Topic initiated in October 2014
- Draft Guideline was released for public comment in August 2017
- Final Guideline is anticipated by the end of 2019

E11A Paediatric Extrapolation

Identified Problem:

- In many cases, there is a long gap (between 7-10 years) between the initial adult approval and the inclusion of pediatric-specific information in product labeling
- The use of pediatric extrapolation has advanced substantially as an approach to improve the efficiency and success of pediatric drug development. However, there is variability in the interpretation and application of extrapolation across regulatory authorities.

Objective:

- 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 trials

Timeline for Development:

- Guideline proposed by FDA and PhRMA and initiated in October 2017
- Draft guideline anticipated November 2020



E14/S7B Questions and Answers: Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential

Identified Problem:

- ICH E14 and S7B describe non-clinical and clinical risk assessment strategies to inform the potential risk of proarrhythmia for a test substance
- The way E14 and S7B have been used in practice has been to sometimes drop compounds or drugs that prolong the QT interval from development, which may not always be appropriate.
- Science has evolved and new technologies are available that can provide improved insight into which QT prolonging drugs are proarrhythmic and which are not

Objective:

- Streamline clinical development for drugs that prolong the QT interval but are found to have low proarrhythmic risk and result in fewer products being dropped from development
- Provide a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential
- Define drug effects on multiple human cardiac currents, characterize integrated electrical responses using in silico reconstructions of human ventricular electrophysiology, and verify effects on human stem-cell derived ventricular myocytes.
- Provide clarity on how new technologies can be applied and a harmonized approach to implementation

Timeline for Development:

- Q&A initiated in 2018
- First stage of Q&As are anticipated to be finalized in June 2020

MULTIDISCIPLINARY TOPICS

M9 Biopharmaceutics Classification System-based Biowaivers

Identified Problem:

- The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability
- BCS can be used to request waiver of an in vivo bioavailability study or bioequivalence study requirement
- BCS-based biowaivers may be applicable to Class I (high solubility – high permeability) and Class III (high solubility – low permeability) drugs; however, BCS-based biowaivers for these two classes are not recognized worldwide which can lead to additional studies unnecessarily being conducted in the patient population

Objective:

- Provide recommendations to support:
 - Biopharmaceutics classification of medicinal products
 - Waiver of bioequivalence studies
- Harmonize current regional guidelines/guidance and supporting streamlined global drug development
- Prevent unnecessary exposure of mostly healthy volunteers to medicinal products
- Reduce the costs and time for pharmaceutical development when in vivo studies to prove the biopharmaceutical quality of the medicinal product are unneeded

Timeline for Development:

- Guideline initiated in 2016
- Draft guideline issued in June 2018
- Final guideline anticipated 2019

M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk



ICH M7 Addendum: Calculation of Compound-Specific Acceptable Intakes

- ICH M7 provides a framework to limit mutagenic impurities and potential carcinogenic risk in drug products and substances
- An Addendum was finalized in 2017 to summarize known mutagenic impurities commonly found or used in drug synthesis. The intent of this Addendum is to provide useful information regarding the acceptable limits of known mutagenic impurities/carcinogenic and supporting monographs.
- The M7(R2) EWG is currently undertaking a maintenance of the Guideline to expand the Addendum

Development of M7 Question and Answer Document

- Clarify and address quality and safety issues and concerns that have been identified from experience through implementation of M7-based control strategies for mutagenic impurities since its finalization in 2014
- Aims to facilitate communication between applicants and assessors
- Topics include:
 - Additional clarification on the justification of control strategy for mutagenic impurities in the marketing authorization dossier
 - Organization and depth of information reporting of individual mutagenic impurities
 - Quantitative structure-activity relationship (QSAR) systems
 - Other safety-related information
- Draft version anticipated in 2019

M11 Clinical electronic Structured Harmonised Protocol (CeSHarP)



Identified Problem:

- Currently there is no internationally harmonized standard template for the format and content of the clinical protocol document to support consistency across sponsors and exchange of protocol information.
- Contributes to inefficiencies and difficulties in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders.

Objective:

- Create a template to include identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange
- Establish a technical specification that uses an open, nonproprietary standard to enable electronic exchange of clinical protocol information

Timeline for Development:

- Topic approved by the ICH Assembly in November 2018
- Draft Guideline is anticipated in June 2020



SAFETY TOPICS

S1(R1): Revision of S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals



Background:

- Prospective evaluation study is being conducted where sponsors voluntarily submit Carcinogenicity Assessment Documents (CADs) to regulatory authorities - initiated in August 2013
- CADs address carcinogenic potential of investigational pharmaceutical using a weight-of-evidence (WOE) approach. Based on level of certainty of carcinogenic risk and its potential human relevance, a company is expected to indicate the need for and additional value of conducting a 2yr rat study
- Regional drug regulatory authorities independently review CADs and rationale for sponsors assessment
- As 2 year rat studies are completed, the results are submitted to the regulatory authorities – the study outcome is then checked against the WOE assessment in the respective CAD
- Results on accuracy of the prospective assessments and degree of agreement among regulatory parties will be used to determine whether a WOE approach can be used to characterize carcinogenicity risks without conducting a 2-year rat carcinogenicity study
- CADs were accepted until Dec 2017

Objective:

- This may result in a revision to the current S1 Guideline on rodent carcinogenicity testing to introduce a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of pharmaceuticals
- Expected to clarify and update, without compromising safety, the 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:
 - 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
 - Reduction in animal use

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



Identified Problem:

- The S5(R2) Guideline on Reproductive Toxicity was finalized in 2000. Since then:
 - Experience has been gained with the testing of pharmaceuticals using the current and novel testing paradigms
 - Scientific, technological and regulatory knowledge has also significantly evolved
- Opportunities exist for modernizing testing paradigms to enhance human risk assessment, while also potentially reducing animal use
- There are areas in which the guideline could be revised or amended for greater clarity or usefulness as well as to align more fully with other guidelines, e.g. ICH M3(R2), ICH S6(R1) as well as ICH S9

Objective:

Establish harmonized guidance on:

- Appropriate multiples above human exposure and other endpoints that could be used for dose selection in reproductive toxicity studies
- Criteria for species selection taking into account relevance to humans
- Basic principles for possible regulatory acceptance of in vitro, ex vivo, and non-mammalian in vivo Embryo Fetal Development (EFD) assays
- Design of optional integrated testing strategies involving an in vivo mammalian EFD assessment and in vitro, ex vivo and non-mammalian in vivo EFD assays and circumstances under which such testing strategies would be considered

Timeline for Development:

- Topic endorsed in March 2015
- Draft guideline was finalized in August 2017
- Final guideline anticipated November 2019

QUALITY TOPICS

Q3C(R8) Maintenance of Guideline for Residual Solvents

Objective:

- 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
- Originally finalized in 1997, a maintenance procedure was developed for this guideline in 1999 to add PDEs for new solvents and to revise existing PDEs as new toxicological data for solvents become available
- In 2017, the ICH Assembly approved development of Permitted Daily Exposures for three new compounds:
 - 2-methyltetrahydrofuran
 - cyclo pentyl methyl ether
 - tert-butanol

Timeline for Development:

- Work on the three solvents began in early 2017
- Draft guideline anticipated by end of 2019

Q3D(R1)/(R2) Maintenance of Guideline for Elemental Impurities

- Establishes a global policy to limit metal impurities in drug products and ingredients
- Q3D includes Permitted Daily Exposures (PDEs) for 24 Elemental Impurities for drugs administered by the oral, parenteral and inhalation routes of administration (ROA)
- PDEs for new elemental impurities are added as new toxicological data become available
 - **Q3D(R1):** Revision of PDE for Cadmium by the inhalation ROA – **finalized March 2019**
 - **Q3D(R2):** Work is currently ongoing to include PDEs for the subcutaneous and transdermal route of administration – **draft anticipated in 2019**

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management



Identified Problem:

- Currently there is a lack of harmonized requirements for pharmaceutical lifecycle management
 - One post-approval change can take 3-5 years to implement across all regions, resulting in additional costs and potential supply disruption due to need for multiple inventories
 - Disincentive for firms to implement manufacturing improvements to increase process robustness
- Opportunities for “operational flexibility” offered by the science and risk based approaches in ICH Q8-Q11 have not been fully realized

Objective:

- Provide guidance on a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle
- Address technical and regulatory gaps related to the implementation of ICH Q8-Q11 and also address the commercial phase of product lifecycle
- Allow regulators (assessors and inspectors) to better understand the firms Pharmaceutical Quality Systems (PQSs) for management of post-approval CMC changes
- Promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments

Timeline for Development:

- Topic was initiated in September 2014
- A draft Guideline was issued in November 2017
- Final version is anticipated in 2019

Q13 Continuous Manufacturing of Drug Substances and Drug Products

Identified Problem:

- Regulatory agencies have seen an increase in the development and implementation of Continuous Manufacturing (CM) by industry
- Lack of regulatory guidance can make industry implementation, regulatory approval, and drug lifecycle management challenging, particularly for products intended for commercialization internationally

Objective:

- Reduce barriers to the adoption of CM technology
- Capture key technical and regulatory considerations that are specific for CM or may differ from batch processing: (e.g. Current Good Manufacturing Practices (CGMP) elements specific to CM, CM-related definitions and regulatory concepts, key scientific approaches)
- Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for small molecules and therapeutic proteins for new and existing products
- Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies

Timeline for Development:

- Topic initiated in June 2018
- Draft Guideline is anticipated in June 2020



Q2(R2)/Q14 Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Q14 Analytical Procedure Development

Identified Problem:

- Lack of exiting guidance results in submissions with performance evaluations that are missing analytical development outcomes, applicants typically only report analytical validation results, this makes regulatory communication ineffective especially when non-conventional analytical procedures (for example, real time release testing) are employed.
- Can preclude the applicant from an opportunity to present scientific basis for flexible regulatory approaches to post-approval Analytical Procedure changes.

Objective:

- The new guideline will harmonize the scientific approaches of Analytical Procedure Development and provide principles relating to the description of Analytical Procedure Development process.
- Intended to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures.



Q2(R2)/Q14 Analytical Procedure Development and Revision of Q2(R1) Analytical Validation

Q2(R2) Revision of Analytical Validation

Identified Problem:

- Current version (Q2(R1)) does not cover more recent application of analytical procedures (e.g. Near Infrared (NIR), Raman, Nuclear Magnetic Resonance, and Mass Spectroscopy)
- Lack of guidance for these analytical procedures can lead to submissions with inadequate validation data, resulting in repeated information requests and responses, which can delay application approval. It can also impede implementation of CM that may require these procedures.

Objective

- Define common validation characteristics for procedures like NIR and NMR and hyphenated techniques; address procedures reliant on multivariate methods used to compare measurements between test and reference samples
- Continue to provide a general framework for the principles of analytical procedure validation

Q2(R2)/Q14 Timeline for Development:

- Topic initiated in June 2018
- Draft Guideline is anticipated June 2020

ICH Informal Discussion Groups



- **Informal Quality Discussion Group**

- Established in February 2019
- Serves as a 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 emphasizing an integrated approach to quality risk management and science
- For more information:
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Reflection_Papers/ICH_AdvancingPharmaceuticalQualityStandards_2018_1122.pdf

- **Informal Generic Drug Discussion Group**

- Established April 2019
- Technical discussion group for issues relevant to harmonization of scientific and technical standards for generic drugs. The IGDG will recommend areas for harmonization under ICH and assess feasibility of harmonization of various topic areas within existing regional regulatory frameworks.
- For more information:
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Reflection_Papers/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

New Topics to be Initiated June 2019

- **M12 Drug Interaction Studies**

- Harmonize approaches to designing, conducting, and interpreting drug-drug interaction (DDI) studies that are conducted to evaluate the potential for DDI during the development of a therapeutic product
- Harmonize regulatory expectations with respect to evaluation of in vitro and in vivo DDI studies

- **E20 Adaptive Clinical Trials**

- Harmonize regulatory perspective on the planning, conduct, and regulatory review of adaptive clinical trial designs
- Define a set of principles for adaptive trial designs that guide all aspects of design, conduct, analysis and interpretation

Thank you for your attention

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

- www.ich.org
- <https://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm>
- <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation.html>



Questions?

Public Comment Period

S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines, ICH

Comments submitted by the International
Council on Animal Protection in
Pharmaceutical Programs

ICAPPP
pharmaceutical programmes

Presented by Laura Alvarez
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Science Advisor
Cruelty Free International



About ICAPPP

ICAPPP works to promote animal welfare protection in pharmaceutical testing guidelines developed by the ICH and VICH

Cruelty Free International is currently serving as ICAPPP's Secretariat



ANIMAL WELFARE
ACADEMY

EUROGROUP
FOR ANIMALS



PETA INTERNATIONAL
SCIENCE CONSORTIUM, LTD.



S11 key objective: to promote reduction in animal use in accordance with 3Rs

ICAPPP has some serious concerns regarding:

1) Lack of examples and limited guidance provided on nonclinical testing methods other than juvenile animal studies (JAS)



Guideline title is 'nonclinical safety testing in support of development of pediatric medicines' and NOT 'juvenile animal testing in support of pediatric medicines'. Therefore, more guidance on other nonclinical testing methods that should be considered before recommending JAS is needed.

2) **Unsubstantiated support for JAS as a standard approach, rather than as a last resort option**



There are not enough clear-cut examples in the available literature to determine whether JAS are useful or necessary to support pediatric development. Where reviews into their utility have been conducted, the results are far from satisfactory.

ICAPPP's proposed changes

1) Limited guidance on other nonclinical testing methods

❖ A section should be added in between Section 2 and Section 3 to provide guidance on the design and use of other nonclinical testing methods including:

- ➔ Biosimulation studies e.g. physiologically-based PK models from in vitro-in silico data
- ➔ In vitro models e.g. in vitro gastrointestinal tract models to study drug bioavailability in children
- ➔ Ex vivo models e.g. use of tumour cells and biopsies
- ➔ Recent innovations in personalised medicine for the identification of effective drug regimes
- ➔ Adult clinical data for evaluating safe starting doses for children

❖ Guideline should promote use of advanced tools such as these within an integrated package, ensuring JAS are considered as an absolute last resort

ICAPPP's proposed changes

2) Unsubstantiated support for JAS as standard approach

- ❖ References from key reviews on the utility of JAS should be included to guide and better inform industry and regulators.
- ❖ The use of JAS, especially multiple JAS in one or more species or those with multiple complex endpoints, should be discouraged.

If data from adult humans is not enough to predict safety in human children, it is difficult to see how extrapolation of data from young animals to young humans can be meaningful, especially considering the vast species differences (e.g. shorter lifespan, varying developmental schedules etc.) that must be accounted for.

Serious consideration should be given to the conduct of a multi-national review on the true value of JAS to inform pediatric risk assessment to avoid further waste of time and money on JAS that could be better used in more effective testing methods, which could accelerate drug development.

Key references from literature

Novel toxicity was only observed in 4 out of 39 (10%) JAS compiled, one of which could have been predicted from pharmacology data. JAS contributed to pediatric clinical trials in only 20% of cases and to product label in only 30% of cases (Bailey & Marien, 2009).

Out of 241 JAS, 75% and 85.7% of all rat and dog studies, respectively, were predictable from either pharmacology or adult toxicity data. JAS only contributed new data in less than 25% of cases (Bailey & Marien, 2011).

Despite increasingly being used in drug product labels, “it is unclear how a health care professional would use the presented study findings (often in technical jargon) when considering prescribing the drug to a child” and “what the differences actually mean when compared with adult animal results” (Baldrick, 2018).

“JAS are not needed in order to safely conduct Phase I trials in pediatric subjects, either for selecting the starting dose or informing on potential toxicities that may be unique to a pediatric population [...] In the absence of case examples showing that findings of JAS allowed clinical catastrophes to be avoided, we do not believe that JAS provide any value” (Visalli et al., 2018)

Concluding remarks

JAS should not be performed as a 'tick-box' exercise or default option for addressing safety concerns.

Based on the available evidence, it is difficult to understand why regulators seem to be encouraging the use of JAS and why the draft S11 guideline places so much emphasis on the design of a study that runs counter to the 3Rs.

Instead of promoting unreliable and inhumane science, the S11 guideline should aim to steer regulators and drug developers in the right direction and deter unnecessary requests for additional experiments in young animals, which are difficult to justify from a cost-benefit point of view.



Thank you for listening!



Laura.alvarez@crueltyfreeinternational.org



CrueltyFreeInternational.org



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Health
Canada

Santé
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U.S. FOOD & DRUG
ADMINISTRATION

Thank you for attending!

The public docket will remain open until May 20,
2019:

[https://www.regulations.gov/document?D=FDA-
2019-N-0444-0001](https://www.regulations.gov/document?D=FDA-2019-N-0444-0001)

Visit the ICH website for more information on the
work of ICH:

www.ich.org

