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ADMINISTRATION

International Council for Harmonisation US FDA and Health Canada Regional Public Consultation

April 24, 2017

Agenda

- I. Overview of the ICH Process and Reforms
- II. Current Quality Topics
- III. Current Efficacy Topics
- IV. Current Safety Topics
- V. Overview of MedDRA and MedDRA Points to Consider
- VI. Current Electronic Standards Topics
- VII. Industry Perspective on ICH
- VIII. ICH Strategic Discussions: Modernization of ICH E8 and Subsequent Renovation of ICH E6
- IX. Public Comment
- X. Closing Remarks

Overview of the International Council for Harmonisation (ICH) and Reforms

Amanda Roache

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Center for Drug Evaluation and Research

March 29, 2017

International Council for Harmonisation
of
Technical Requirements
for Pharmaceuticals for Human Use (ICH)
<http://www.ich.org>

*Hosted by ICH Secretariat
Geneva, Switzerland*

ICH Background

- Unique harmonisation project involving regulatory authorities and pharmaceutical industry
- Started in 1990
- Well-defined objectives:
 - **To improve efficiency of new drug development and registration processes**
 - **To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness**
- **Accomplished through the development and implementation of harmonized Guidelines and standards**

ICH Reform - **Establishment of a 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 harmonisation work in one venue
- More involvement from regulators around the world is welcomed and expected

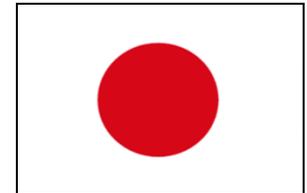
ICH Articles of Association:

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

ICH Members

- **Regulatory Members**

- European Commission (EC)
- US Food and Drug Administration (FDA)
- Ministry of Health, Labour and Welfare of Japan (MHLW) also represented by the Pharmaceuticals and Medical Devices Agency (PMDA)
- Health Canada
- Swissmedic
- Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
- Ministry of Food and Drug Safety (MFDS, Republic of Korea)



- **Industry Members**

- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- International Generic and Biosimilar Medicines Association (IGBA)
- World Self-Medication Industry (WSMI)
- Biotechnology Innovation Organisation (BIO)



ICH Observers

Standing Observers

- The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
- The World Health Organization (WHO)

Observers

- Central Drugs Standard Control Organization (CDSCO, India)
- Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED, Cuba)
- Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- Health Sciences Authority (HSA, Singapore)
- Medicines Control Council (MCC, South Africa)
- National Center for the Expertise of Drugs, Medical Devices and Equipment (National Center, Kazakhstan)
- Roszdravnadzor (Russia)
- Food and Drug Administration (TFDA, Chinese Taipei)
- Therapeutic Goods Administration (TGA, Australia)
- Asia-Pacific Economic Cooperation (APEC)
- Association of Southeast Asian Nations (ASEAN)
- East African Community (EAC)
- Gulf Cooperation Council (GCC)
- Pan American Network for Drug Regulatory Harmonization (PANDRH)
- Southern African Development Community (SADC)
- Active Pharmaceutical Ingredients Committee (APIC)
- Council for International Organizations of Medical Sciences (CIOMS)
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
- International Pharmaceutical Excipient Council (IPEC)
- United States Pharmacopeia (USP)

ICH Work Products: Harmonised Regulatory 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 category
- Clinical evaluation
- Pharmacogenomics

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

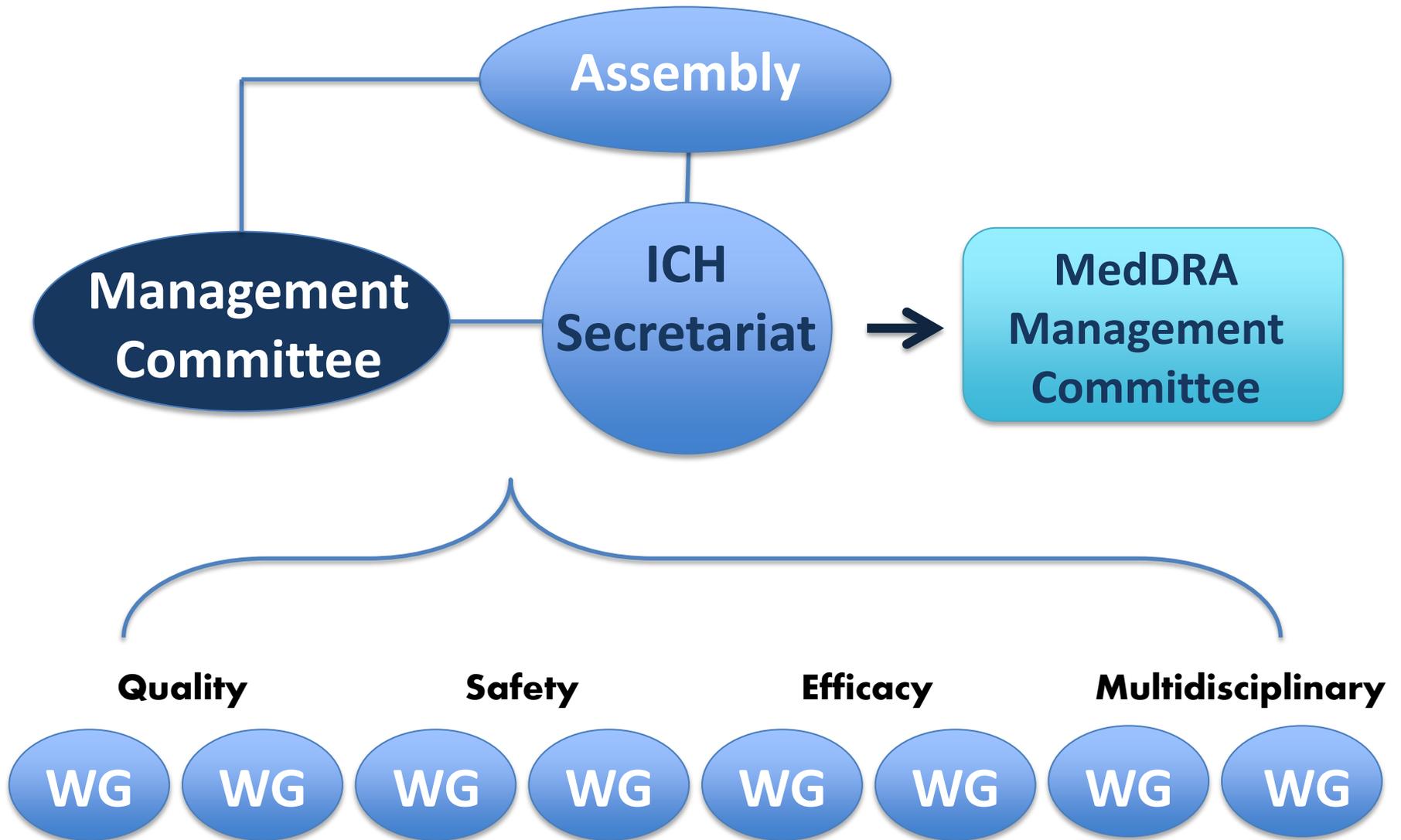
Multidisciplinary

- MedDRA terminology
- Electronic standards
- Nonclinical safety studies
- CTD and eCTD
- Data elements and standards for drug dictionaries
- Gene therapy
- Genotoxic impurities

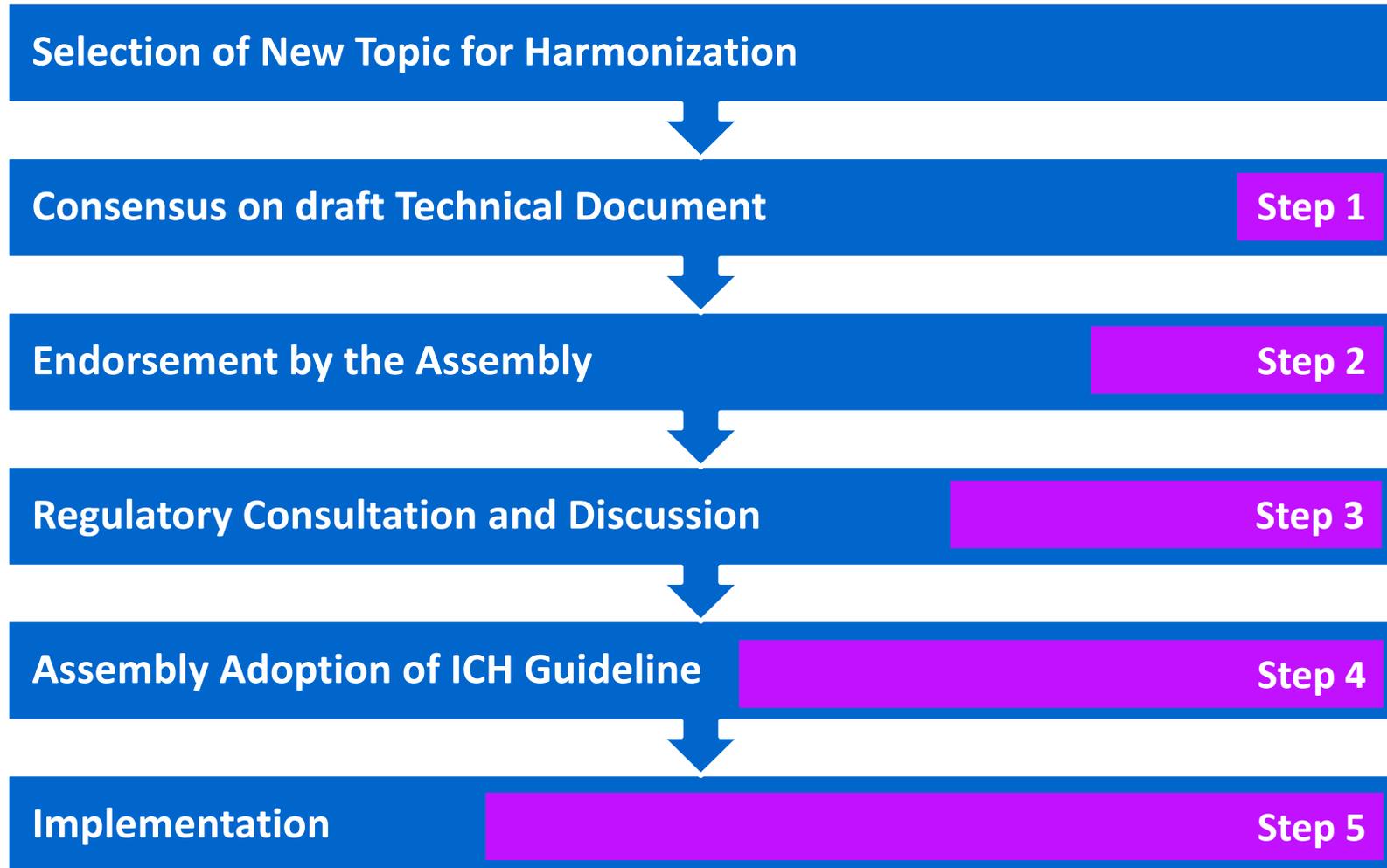
ICH Work Streams

- Formal ICH Process: Development of a new ICH Guideline in areas of Quality, Efficacy, Safety, and Multidisciplinary Areas – Developed by an Expert Working Group (EWG)
- Q&A Document - Developed by an Implementation Working Group (IWG)
- Maintenance Working Groups (Q3C, Q3D, M7)
- Electronic Standards (M2, E2B, M8)
- MedDRA

Governance of ICH Association



ICH Harmonization Process



Thank you for your attention!

Visit the ICH
website:
www.ich.org



The screenshot shows the ICH website header with the logo and tagline "ICH harmonisation for better health". Below the logo is a navigation bar with buttons for Home, About ICH, Work Products, Meetings, Training, and Newsroom. The "Work Products" dropdown menu is open, showing a list of categories: ICH Guidelines (highlighted with a red arrow), Process of Harmonisation, MedDRA, CTD, Electronic Standards, Consideration Documents, Public Consultations, and GCP Renovation. Below the navigation bar, the main content area is titled "ICH Guidelines" and features four large, stylized letters (Q, S, E, M) representing different guideline categories: Quality, Safety Guidelines, Efficacy Guidelines, and Multidisciplinary Guidelines. Each category has a brief description of its focus.

ICH Guidelines
The ICH topics are divided into four categories, which are assigned according to these categories.

Q Quality
Harmonisation in the Quality area includes the conduct of studies, thresholds for safety, flexible approaches based on Good Manufacturing Practice (GMP) risk management.

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

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

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

ICH Regional Public Meeting: Overview of ICH Quality Topics

Ashley B. Boam, MSBE
Director

Office of Policy for Pharmaceutical Quality
CDER/OPQ

Current Quality and Related Activities

- Q3C – Guideline for Residual Solvents
- Q3D – Guideline on Elemental Impurities
- Q11 – Q&As: Selection and Justification for Starting Materials for the Manufacture of Drug Substances
- Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- M9 - Biopharmaceutics Classification System-based Biowaivers
- M10 – Bioanalytical Method Validation

ICH Q3C - Residual Solvents

Q3C Objectives

- To recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient.
- Guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Q3C Maintenance Procedure

- The Maintenance Procedure for Q3C is followed when there is a proposal of a "permitted daily exposure" (PDE) for a new solvent or a revised PDE for an already classified solvent.
- The procedure is similar to the Formal ICH Procedure in that it follows the 5 ICH steps.

ICH Q3C – Current Activities

- EWG is following formal Maintenance procedures to address proposals to add five additional residual solvents.
- Background information is being generated and EWG will be solicited for input on the appropriateness of inclusion of each compound.
- Once a final decision is made on the inclusion of solvents (goal is May 2017), the EWG will work via email and teleconference to draft monographs and develop Permissible Daily Exposure levels for each solvent.

ICH Q3D – Elemental Impurities

Q3D Objectives

- To develop global policy for limiting elemental impurities in drug products
 - Harmonised, safety-based limits for elemental impurities, especially those of highest toxicological concern
 - Selection of elements to control
 - Methodology for establishing safety-based limits
 - Permitted daily exposures for specific elements
 - Appropriate risk-based approach to ensure control for elements likely to be present in drug products and ingredients.

Permitted Daily Exposures (PDEs) for 24 Elements by 3 Routes of Administration

PERIODIC TABLE OF ELEMENTS

1 H Hydrogen 1.01 G 2.2																	2 He Helium 4 G				
3 Li Lithium 6.94 S 1.0	4 Be Beryllium 9.01 S 1.5	<div style="display: flex; flex-direction: column; align-items: center; justify-content: center;"> <div style="width: 100px; height: 20px; background-color: #e9967a; margin-bottom: 5px;"></div> <div style="width: 100px; height: 20px; background-color: #a6c9ec; margin-bottom: 5px;"></div> <div style="width: 100px; height: 20px; background-color: #00b0f0; margin-bottom: 5px;"></div> <div style="width: 100px; height: 20px; background-color: #6aa84f; margin-bottom: 5px;"></div> </div>														5 B Boron 10.81 S 2.0	6 C Carbon 12.01 S 2.6	7 N Nitrogen 14.01 G 3.1	8 O Oxygen 15.99 G 3.5	9 F Fluorine 19 G 4.0	10 Ne Neon 20.18 G
11 Na Sodium 22.99 S 0.9	12 Mg Magnesium 24.31 S 1.2															13 Al Aluminum 26.98 S 1.5	14 Si Silicon 28.09 S 1.9	15 P Phosphorus 30.97 S 2.2	16 S Sulfur 32.07 S 2.6	17 Cl Chlorine 35.45 G 3.2	18 Ar Argon 39.95 G
19 K Potassium 39.1 S 0.8	20 Ca Calcium 40.08 S 1.0	21 Sc Scandium 44.96 S	22 Ti Titanium 47.88 S	23 V Vanadium 50.94 S	24 Cr Chromium 52 S	25 Mn Manganese 54.94 S	26 Fe Iron 55.85 S	27 Co Cobalt 58.93 S	28 Ni Nickel 58.69 S	29 Cu Copper 63.55 S	30 Zn Zinc 65.39 S	31 Ga Gallium 69.72 S 1.6	32 Ge Germanium 72.61 S 1.9	33 As Arsenic 74.92 S 2.0	34 Se Selenium 78.96 S 2.5	35 Br Bromine 79.9 L 2.9	36 Kr Krypton 83.8 G				
37 Rb Rubidium 85.47 S 1.0	38 Sr Strontium 87.62 S 1.0	39 Y Yttrium 88.91 S	40 Zr Zirconium 91.22 S	41 Nb Niobium 92.91 S	42 Mo Molybdenum 95.94 S	43 Tc Technetium [99] S	44 Ru Ruthenium 101.07 S	45 Rh Rhodium 102.91 S	46 Pd Palladium 106.42 S	47 Ag Silver 107.87 S	48 Cd Cadmium 112.41 L	49 In Indium 114.82 S 1.7	50 Sn Tin 118.71 S 1.8	51 Sb Antimony 121.75 S 2.1	52 Te Tellurium 127.6 S 2.3	53 I Iodine 126.9 S 2.6	54 Xe Xenon 131.29 G				
55 Cs Cesium 132.91 S 0.7	56 Ba Barium 137.33 S 0.9	57 La Lanthanum 138.91 S	72 Hf Hafnium 178.49 S	73 Ta Tantalum 180.95 S	74 W Tungsten 183.85 S	75 Re Rhenium 186.21 S	76 Os Osmium 190.2 S	77 Ir Iridium 192.22 S	78 Pt Platinum 195.08 S	79 Au Gold 196.97 S	80 Hg Mercury 200.59 L	81 Tl Thallium 204.38 S 1.8	82 Pb Lead 207.2 S 1.8	83 Bi Bismuth 208.98 S 1.9	84 Po Polonium [209] S 2.0	85 At Astatine [210] S 2.2	86 Rn Radon [222] G				
87 Fr Francium [223] S 0.7	88 Ra Radium [226] S 0.9	89 Ac Actinium [227] S	104 Rf Rutherfordium [261] Sv	105 Db Dubnium [262] Sv	106 Sg Seaborgium [263] Sv	107 Bh Bohrium [262] Sv	108 Hs Hassium [265] Sv	109 Mt Meitnerium [266] Sv	110 [269]	111 [272]	112 [277]	113	114	115	116	117	118				

58 Ce Cerium 140.12 S	59 Pr Praseodymium 140.91 S	60 Nd Neodymium 144.24 S	61 Pm Promethium [147] Sv	62 Sm Samarium 150.36 S	63 Eu Europium 151.97 S	64 Gd Gadolinium 157.25 S	65 Tb Terbium 158.93 S	66 Dy Dysprosium 162.5 S	67 Ho Holmium 164.93 S	68 Er Erbium 167.26 S	69 Tm Thulium 168.93 S	70 Yb Ytterbium 173.04 S	71 Lu Lutetium 174.97 S
90 Th Thorium [232] S	91 Pa Protactinium [231] S	92 U Uranium [238] S	93 Np Neptunium [237] Sv	94 Pu Plutonium [244] Sv	95 Am Americium [243] Sv	96 Cm Curium [247] Sv	97 Bk Berkelium [247] Sv	98 Cf Californium [251] Sv	99 Es Einsteinium [252] Sv	100 Fm Fermium [257] Sv	101 Md Mendelevium [258] Sv	102 No Nobelium [259] Sv	103 Lr Lawrencium [260] Sv

ICH Q3D – Current Activities

- End of 2016 – approval for the EWG to convene in order to develop PDEs for the 24 Elemental Impurities addressed in Q3D when administered by the Cutaneous and Transdermal Route
- In 2017 the EWG has worked on addressing questions submitted to ICH regarding the finalized Q3D guideline.
- Moving forward, the EWG will meet via teleconference to initiate:
 - discussions on which elemental impurities will need to have a safety-based PDE, and then
 - development of PDEs where appropriate using methodologies described in Q3D
- EWG is tentatively planning to meet in November 2017 continue this work.



ICH Q11 Q&As: Selection and Justification of Starting Materials for Manufacturing of Drug Substances

Q11 Q&As Objectives

- To provide further clarity of the principles described in the original Q11 guideline, in order to improve the likelihood that industry proposals for starting materials will be acceptable to regulators
 - Clarify existing principles and not re-open ICH Q11 parent guidelines
 - Provide further information on a number of the terms mentioned in the guideline as well as points that should be considered when proposing a starting material in applications for marketing authorization and/or Master Files

ICH Q11 Q&As – Current Activities

- Step 2 document containing 16 Q&As was published on the ICH website in Nov 2016, and subsequently published by regulatory members of the IWG
 - Two earlier drafts were shared within the ICH Parties prior to posting for Step 2 consultation
- US Docket closed March 23; 39 comments were received via the Federal Register
 - Comment periods have also closed for EMA, Swissmedic, MHLW/PMDA, Health Canada, ANVISA (Brazil), and MFDS (S. Korea)
- Regional sub-teams (e.g., Americas, Europe, Japan) will have meetings/teleconferences over next month to draft proposed edits based on comments received by the region
- Full IWG will edit the Q&A document at the Montreal ICH meeting, using the regional recommendations to focus the discussion
- Goal is publication as a final Step 4 document in Nov/Dec 2017

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

Q12 Objectives:

- To provide 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 that can work with ICH Q8 - 11
- Optimization of industry and regulatory resources
- Support innovation and continual improvement and help to assure reliable drug product supply

ICH Q12 – Current Activities

- At November 2016 meeting in Osaka, EWG agreed to share version 7.0 within the EWG members' constituencies to identify major comments and concerns
- EWG agreed to hold an interim face-to-face meeting in April 2017 to address any major concerns from EWG members or their constituencies to increase the likelihood of reaching step 1/2a by the end of the May/June 2017 meeting
- Interim meeting held April 4-7 in Washington, DC
 - Significant progress made to address major comments - multiple chapters revised
- Agreed on a detailed workplan to generate Q12 version 8 and to reach step 1/2a in Montreal

ICH M9 - Biopharmaceutics Classification System-based Biowaivers

- Topic endorsed by ICH Management Committee in October 2016
- Challenge
 - Biopharmaceutics Classification System (BCS)-based biowaivers may be applicable to BCS Class I and III drugs; however, BCS-based biowaivers for these two classes are not recognized worldwide
- M9 Objectives:
 - Provide recommendations to support the biopharmaceutics classification of medicinal products
 - Provide recommendations to support the waiver of bioequivalence studies
 - Resulting in the harmonisation of current regional guidelines/guidance and supporting streamlined global drug development

ICH M9 – Current Activities

- First meeting of EWG in Osaka, November 2016
- Since Osaka, EWG has expanded to include additional members/observers including regulatory agencies and trade associations from South Korea, Chinese Taipei, and Brazil; Paul Seo (FDA) joined as Regulatory Chair
- In Osaka, EWG identified areas of overall agreement as well as areas where further work was needed to work towards agreement. Several subgroups formed to work on individual areas where additional work is needed.
- Teleconferences and emails amongst EWG members are ongoing for debate and exchange of views
- EWG plans to meet in Montreal (May/June 2017)

ICH M10 – Bioanalytical Method Validation

- Topic endorsed by the ICH Management Committee in October 2016
- Challenge
 - Reliable data derived through validated bioanalytical methods are key for the review of marketing authorisation applications
- M10 Objectives:
 - Will apply to the validation of bioanalytical methods and study sample analyses in non-clinical and clinical studies
 - Provide recommendations on the scientific regulatory requirements for bioanalysis conducted during the development of drugs of both chemical and biological origins
 - Address issues on method validation by considering the characteristics of the analytical methods used in bioanalysis, e.g., chromatographic assay and ligand binding assay.

ICH M10 – Current Activities

- First meeting of EWG in Osaka, November 2016
- In Osaka, EWG developed an outline for the document and discussed key issues.
- Since Osaka, EWG has expanded to include additional members/observers including regulatory agencies and trade associations from South Korea, Chinese Taipei, and Brazil
- Regulatory agencies have written draft v 1 for consideration by the EWG
- EWG has convened two teleconferences since November, and will hold one more before Montreal
- EWG plans to meet in Montreal (May/June 2017)



THANK YOU



International Council for Harmonization Regional Public Consultation US FDA and Health Canada

April 24th, 2017



YOUR HEALTH AND SAFETY... OUR PRIORITY.

Overview of Current ICH Efficacy Topics

Ariel E. Arias MD, PhD, FISPE

Senior Advisor,

Centre for Biologics Evaluation (CBE)

Biologics & Genetic Therapies Directorate (BGTD)

Current Active ICH Efficacy Working Groups

- E9(R1) – Addendum: Statistical Principles for Clinical Trials
- E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population
- E17 – New Guideline on General Principles on planning/designing Multi-Regional Clinical Trials
- E18 – New Guideline on Genomic Sampling and Management of Genomic Data

Efficacy Working Groups at the ICH May 2017 Meeting

- E9(R1) – Addendum: Statistical Principles for Clinical Trials
- E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population
- E17 – New Guideline on General Principles on planning/designing Multi-Regional Clinical Trials

Open Public Consultations

- None currently

Please refer to the ICH website for more details (www.ich.org).

E9(R1) – Addendum: Statistical Principles for Clinical Trials

ICH E9 (R1) Addendum: Statistical Principles for 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: Statistical Principles for Clinical Trials

- Current Activities & Plans for May 2017 ICH Meeting
 - Progress towards Step 1 and Step 2a.
 - Working to finalise the Step 1 Technical Document. Draft circulated to EWG April 2017 for review and comment.
 - Continue discussions of methodological issues to support drafting of the Addendum.
 - Prepare training materials including communication to the clinical community; organise regional discussions both with statisticians and non-statisticians.
 - Depending on comments and further discussion, Step 1 might be achieved at the May 2017 meeting.

E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population

E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population

Background

- Pediatric medical product development has advanced since the current ICH E11 guideline was adopted in 2000.
- United States (US) and the European Union (EU) now have permanent legislation that mandates plans for pediatric medical product development.

E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population

Goal

- Address gaps in the current E11 guidance due to advancements that have not had parallel development of harmonized guidance in the following areas:
 - Targeted scientific and technical issues relevant to pediatric populations
 - Regulatory requirements for pediatric development plans, and
 - Infrastructure for undertaking complex trials in pediatric patient populations has been considerably advanced in the last decade, without a parallel development of harmonized guidance in these areas

E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population

Current Activities

- Approved by the ICH Assembly under Step 2 and released for public consultation October 2016.
- Currently working on addressing comments from the public consultation period for step 3 sign off.
- The EWG will meet face to face at the May 2017 ICH Meeting in Montreal, Canada.

E17 – New Guideline on General Principles on Planning/Designing Multi-Regional Clinical Trials

E17 – New Guideline on General Principles on Planning/Designing Multi-Regional Clinical Trials

Background

- Drug development has become increasingly global.
- While MRCTs for regulatory submission have widely been conducted in ICH regions and beyond, regulatory agencies are currently facing challenges in evaluating data from MRCTs for drug approval.

Goal

- Development of a harmonized ICH guideline to promote appropriate conduct of MRCTs, focusing on scientific issues in planning/designing MRCTs.
- This new Guideline will complement the guidance on MRCTs provided in ICH E5(R1) Guideline and facilitate MRCT data acceptance by multiple regulatory agencies.

E17 – New Guideline on General Principles on Planning/Designing Multi-Regional Clinical Trials

Objectives

- Provide general principles for planning and designing MRCTs
- Promote use of MRCTs in regulatory submissions spanning multiple regions
- Minimize conflicting submission requirements from regulatory agencies

E17 – New Guideline on General Principles on Planning/Designing Multi-Regional Clinical Trials

Current Activities

- The E17 Expert Working Group met face to face at the November 2016 ICH Meeting in Osaka, Japan.
- Currently, discussing how to address comments from public consultation period and creating a revised guideline.
- Step 4 is anticipated in 4Q 2017

E18 – New Guideline on Genomic Sampling and Management of Genomic Data

E18 – New Guideline on Genomic Sampling and Management of Genomic Data

Background

- Genomic research is increasingly employed
- No harmonized ICH guideline
- Harmonization would facilitate genomic research

E18 – New Guideline on Genomic Sampling and Management of Genomic Data

Goal

- To provide harmonized principles of genomic sampling and management of genomic data in clinical studies;
- To facilitate the implementation of genomic studies by enabling a common understanding of critical parameters;
- To increase awareness and provide considerations regarding subject privacy, data protection, informed consent and transparency of findings;
- To foster interactions amongst stakeholders, including drug developers, investigators and regulators.

E18 – New Guideline on Genomic Sampling and Management of Genomic Data

Current Activities

- The E18 Expert Working Group met face to face at the November 2016 ICH Meeting in Osaka, Japan, and continued working towards step 3 of the ICH process.
- Currently, continue working on addressing comments from public consultation period and create a consensus guideline for step 3 sign off.
- Step 4 is anticipated by June 2017.

THANK YOU

Overview of Current Safety Topics

Karen Davis-Bruno PhD
FDA/CDER/OND

US FDA/Health Canada Regional ICH Public Consultation
April 24, 2017

Outline of Safety Topic Updates

1. ICHS₁A-1C Rodent Carcinogenicity
2. ICHM₇ Addendum Assessment & Control of Mutagenic Impurities
3. ICHS₉ Nonclinical oncology Q & A
4. ICHS₃A Q & A Note on Toxicokinetics: microdosing
5. ICHE₁₄/S₇B Discussion Group
6. ICHS₅(R₃) Reprotox
7. ICHS₁₁ Nonclinical Safety for Pediatrics

EWG for ICHS1A-S1C –Rodent Carcinogenicity Studies for Human Pharmaceuticals

- EWG in prospective data gathering & assessment mode (Regulatory Notice Document Aug 2013)
 - Goal is to address feasibility of a WOE approach to carcinogenicity assessment of small molecule pharmaceuticals
 - Conducting an unbiased, prospective evaluation of WOE elements to predict 2yr rat study outcomes and value
- 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
 - Shorter development time when 6-month Tg mouse is used

ICH S1A-S1C Continued

- Carcinogenicity Assessment Documents (CADs) with WOE elements and outcome predictions accepted until Dec 2017
 - Alignment around CAD predictions and study outcomes that support rat carcinogenicity waivers most important for establishing conditions of a WOE option
 - Target is ≥ 20 CADs with study outcomes supporting rat carcinogenicity waiver to assess feasibility of approach (~Nov 2019)
 - Publication of Status Report to [www.ICH.org](http://www.ich.org) March 2016

EWG ICHM7(R1) Addendum Assessment & Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

- This Addendum to M7 provides Acceptable Intake (AI) or Permissible Daily Exposure (PDE) values for 15 mutagenic/carcinogenic chemicals selected based on their common use in pharmaceutical manufacturing.
- Defined criteria were applied in selecting the studies used to calculate these limits.
- Initial draft was released for public comment & EWG reviewed the submitted comments & revised the document.
- The Addendum will be finalized Q2 2017 & updated under a Maintenance procedure when info becomes available for relevant chemicals.

IWG ICHS9 Q&A Nonclinical Evaluation for Anti-Cancer Pharmaceuticals

- Rationale for Q & A includes:
 - Harmonization of differences in interpretation which arose during implementation (2009)
 - Scope of the guidance includes life-threatening malignancies but what about...
 - Cancer, but slightly less advanced?
 - Extended survival periods?
 - What nonclinical studies are needed?
 - When should recovery groups be added?
 - Step 2B

IWG ICHS3A Q&A Note on Toxicokinetics: Assessment of Systemic Exposure; Microsampling

- The IWG was endorsed by the ICH Steering Committee in 2014.
- The Q&A is intended to incorporate microsampling techniques in main study animals
- Collated public comments, Step 4 December 2017

E14/S7B Discussion Group (DG)

- The DG includes experts in clinical (E14) and non-clinical drug development (S7B)
- The DC was created to discuss advances in the science and methods related to the clinical assessment of QT prolongation and to continue its discussion of the Comprehensive in vitro Proarrhythmia Assessment (CIPA)

CiPA Initiative

- The goal of the CiPA initiative is to develop a new in vitro paradigm for cardiac safety evaluations of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential.
- The Assessment seeks to 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.

E14/S7B DG Current Activities

- The DG continues to discuss the progress of the CiPA initiative, review data as it emerges, and provide guidance on developing a path towards using these assays for regulatory decision making
- When the CiPA initiative is ready for widespread implementation, the DG will assess the scope of the effort required to re-open ICH E14 and S7B for complete revision and make a recommendation

EWG ICHS5(R3)-Detection of Reproductive Toxicity for Medicinal Products & Toxicity to Male Fertility

A rough draft has been assembled

Testing strategies, study designs retained in Appendix

Potential topics in revised guidance:

- High dose selection in reproductive toxicity studies, >25-fold exposure multiple where appropriate instead of a MTD
- Use of existing data (pharmacodynamics, human genetics) in planning evaluations
- Deferral or waiving of studies in certain circumstances
- Focus on teratogenicity and embryofetal lethality (TEFL), variations are of minimal concern
- New study design: “streamlined EFD”
- Use of surrogates (highly selective and non-highly selective pharmaceuticals)
- Combining specific reproductive toxicity studies where appropriate
- Use of DRF studies for risk assessment
- Concepts around use of disease and genetic models
- Study choices to support biologics
- Considerations in species selection and study type
- Guidance on in vitro assays: requirement of use & possible integration in risk assessment
- Integrated reproductive assessment

EWG ICHS11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines

- 1st meeting June 2015
- Rationale to recommend harmonized nonclinical standards to support safety for pediatric drug development
 - Opportunity to evaluate utility and provide a unified study design recommendations
 - Data collection across regions is ongoing

Summary Safety Topics

- Active area
- Provide some global consistency in adequate nonclinical approaches
 - Harmonizes philosophies across agencies and industry
 - Minimizes interpretation & implementation through guidance clarification
- Critical to development of approaches that will facilitate the optimization of nonclinical testing strategies

Overview of MedDRA and MedDRA Points to Consider Group

Christopher D. Breder, MD PhD
Medical Officer FDA/CDER/OND
FDA Topic Leader ICH M1 PTC Group

ICH Public Meeting 24 APR 2017

MedDRA: Medical Dictionary for Regulatory Activities



- Standardised medical terminology developed by ICH to facilitate sharing of regulatory information
 - Used for registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale
- Under the governance of the ICH MedDRA Management Board, MedDRA is continuously enhanced to meet the evolving needs of regulators and industry around the world.
 - ICH M1 Points to consider group – Document maintenance and initiative development
- The MSSO (Maintenance and Support Services Organization), contracted by ICH with technical and financial oversight by the MedDRA Management Board, is tasked to maintain, develop and distribute MedDRA.

MedDRA News and Updates



MMB Osaka Meeting 5-6 November 2016

- **Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA, 2nd ed.**
 - The Council for International Organizations of Medical Sciences (CIOMS)
- **Unqualified Test Name Term List is now available to improve data quality**
 - Terms not meant for use in other data fields capturing information such as adverse events/adverse reactions, medical history, or indications
- **2017 MSSO subscription rates for MedDRA have been reduced at least 9-10% for all subscription levels**
 - Due in part to wider subscription base
 - Expanding list of interested nations
- **Five New Standardised MedDRA Queries (SMQs) go into production in March 2017 for MedDRA Version 20.0.**

ICH M1 Points to Consider Group

- The current ICH M1 Points to Consider Working Group develops and maintains two documents on the use of MedDRA for data entry (coding) and data retrieval/analysis. The latter includes guidance on the use of SMQs, Standardised MedDRA Queries, as powerful tools for assisting with safety signal detection. Both documents are updated twice a year, with every MedDRA release.
- **Rapporteur:** Christine Winters, EFPIA
 - Recent Retirement of Hilary Vass, EFPIA
- **Regulatory Chair:** Sonja Brajovic, FDA
- **Editor:** Judy Harrison, MSSO

Plans for Meeting

- MedDRA Management Board
 - Plan to meet in Montreal and Geneva
 - Budget and Business Plans
- Points to Consider Group
 - Plan to meet in Geneva
 - Work on Companion documents and Maintenance activity

ICH Electronic Standards Overview and Update of Activities

Mary Ann Slack

FDA/CDER Office of Strategic Programs

April 24, 2017

Topics

- **E2B (R3) – ICH next-gen Individual Case Safety Report**
- **M8 eCTD v4.0 – ICH next-gen electronic Common Technical Document**
- **M2 overview & Current Activities**
- **ESTRI – The source for ICH electronic standards**

Electronic Standards Under Implementation

E2B(R3) – The next-generation Individual Case Safety Report

- E2B(R3) is the ICH implementation of ICSR – a normative ISO/CEN/HL7 exchange standard for adverse event information
- Currently in Step 4 – ready for implementation
- Implementation activities in regions

E2B (R3) Implementation Activities

- **EU**
 - Published regional technical specifications.
 - Implementation target date is estimated in Nov 2017
- **Japan**
 - Implemented in April 2016 with a three year migration period
- **US**
 - Production submissions implemented for vaccines in June 2015.
 - Drug and biologics regional technical specifications document release in June 2016.
 - Drug and biologics implementation estimated in Q2 2019

E2B(r3) Work Plan Now to Summer

- **Conduct cross-regional pilot**
 - Plans finalized, pilot to be conducted shortly
 - Assess findings and address issues
- **Develop information paper on use of external terminology standards**
 - Develop information paper for EDQM
 - Develop information paper for UCUM
- **Work with M2 on process for change management when using externally maintained terminologies**

Electronic Standards Under Implementation

M8 – The next-generation eCTD (eCTD v4.0)

- eCTD v4 is the ICH implementation of HL7's RPS – a normative HL7 exchange standard for adverse event information
- Currently in Step 4 – ready for implementation
- FDA anticipates implementation late 2019 to early 2020
- Other regions anticipate implementation in 2020-2021

M8 - November 2016 Change Requests

- **eCTD v3.2.2**
 - Processed 1 change request
 - Addition of 3 human factors study valid values
 - HF validation protocol / HF validation report / HF other
 - Also required an update to the eCTD v4.0 document type controlled vocabulary

- **eCTD v4.0**
 - Processed 48 change requests/questions
 - All from eCTD tool vendors to clarify technical details

M8 Work Plan

- **eCTD v3.2.2**
 - Continue Q&A process until current ICH M8 regulators transition completely to v4.0.
- **eCTD v4.0**
 - Continue v4.0 Q&A process with additional communication channel that delivers informal answers to implementation-related technical questions.

M2 Overview

- **Coordination of ICH Activities with Information Technology Requirements**
 - Technical support for WGs
 - Evaluating existing ICH topics for technical impacts and opportunities; “connecting the dots” across topics
- **Assessment and Recommendation of Technology and Information Standards**
 - Always starts with a business problem
- **Execution of ICH technical harmonization projects**
 - Starts with a MC approved project opportunity proposal

How Does M2 Operate?

- **M2 is not considered a traditional EWG or IWG with specific tasks and timeline that follow the ICH Step process, although specific projects may.**
- **Governed by a small Steering Group that consists of three Co-Rapporteurs (currently from EU, FDA & MHLW) and a Regulatory Chair (HC).**
- **Projects are generally conducted by subgroups within M2, with consensus agreement of final product.**

M2 Work Plan Now Thru Summer

- **ICH Project Opportunities Proposals**
 - 1-2 potential technological project opportunity proposals will be provided to the MC for their review and discussion.
- **Evaluation of existing ICH topics for technical opportunities**
 - M2 members talk with their experts around Step 1 to better understand the topic and be able to support potential technological questions.
 - M2 review EWG guidelines at Step 3 or 4 to discuss technological opportunities or concerns with the EWGs.

M2 Work Plan Now Thru Summer

- **Finalized Information Paper on Redaction**
 - This paper will present the capabilities and constraints when redacting specific ICH recommended submission file standards such as PDF and JPEG.
- **Finalized PDF Specification update**
 - Collaborate with M8 to investigate further harmonization of PDF requirements across the regions.
- **Maintenance Process for External Terminologies**
 - Defining a process for terminology change requests and appeals to external maintenance organizations (ex: EDQM, Regenstrief).

ESTRI (M2, E2B, M8)

The International Conference on Harmonisation (ICH) Multi-disciplinary Group 2 (M2) Expert Working Group (EWG) was established during the 1994 ICH Meeting in Brussels to facilitate international electronic communication by evaluating and recommending open and non-proprietary - to the extent possible - Electronic Standards for the Transfer of Regulatory Information (ESTRI) that will meet the requirements of the pharmaceutical companies and regulatory authorities.

Due to the information technology (IT) nature of the topic, some of the activities of the M2 EWG result in Recommendations. These Recommendations do not undergo the formal ICH step process in order to allow flexible change as both science and technologies evolve. They are agreed in the EWG, signed by all parties of the EWG, and are approved and signed off by the ICH Steering Committee within the M2 Recommendation Notebook. The Recommendations page was last updated August, 2016.

[Recommendations](#)

The first Specification developed by the M2 EWG to follow the Step process was the Individual Case Safety Report (ICSR), created as the electronic message for the ICH E2B(R2)M step 4 document version 4.4, Data Elements for Transmission of Individual Case Safety Reports. The Message Specification for E2B(R2) ICSR page was last updated on October 25, 2005. A revised specification was provided for public awareness on June 26, 2009. It was open for comment until 22 July 2009. A further revision to the specification was provided for feasibility testing

[Message Specification for E2B\(R2\)](#)

ESTRI Web Pages Hold Technical Standards and Recommendations



M2 Recommendations & Technical References

ESTRI Home

The M2 EWG has provided valuable functionality to the diverse international information exchange needs identified by the members of the ICH regions and observers. The M2 EWG Recommendations provide a well-defined approach for the evaluation and recommendation of standards. The M2 tasks have led to the recommendation of various open international standards that allow for the international transmission of information regardless of the technical infrastructure.

The recommendations have been endorsed by the ICH Steering Committee at their different meetings. The Recommendations are categorized as follows:

- General
- File Format
- Information Transfer
- File Integrity

Current M2 Recommendations **UPDATED**

Category	Title	Version	Date Endorsed	Implemented				
				EU	JP	US	CA	CH
General	Procedure	3.0	June, 2015	Yes	Yes	Yes	Yes	Yes
General	ESTRI Gateway	3.0	June, 2015	Yes	Yes	Yes	Yes	Yes
File Format	PDF	2.0	April, 2011	Yes	Yes	Yes	Yes	Yes
File Format	XML	1.0	November, 2005	Yes	Yes	Yes	Yes	Yes
File Format	PDF/A	1.0	June, 2014	Yes	Pending	Yes	Yes	Yes
File Format	DOCX	1.0	June, 2015	Yes **	Pending	Yes **	Yes **	Pending
Information Transfer	Genericode	1.0	June, 2015	Yes	Pending	Yes	Pending	Pending
Information Transfer	EDIINT AS1/AS2	2.2	June, 2010	Yes	Yes	Yes	Yes	Yes
File Integrity	MD5	1.0	June, 2010	Yes	Yes	Yes	Yes	Yes
File Integrity	SHA-256	1.0	June, 2015	Pending	Pending	Yes	Pending	Pending

**** Check with regulator for specifics**

Notes

- Technical terms in the above Recommendations are defined in the [Glossary](#)
- The previous categories "Physical Media" and "Network" have now been retired

Thank You!
Any Questions?





The Value and Benefits of ICH to Industry

Jerry Stewart, JD, MS, RPh

Deputy Vice President, Scientific & Regulatory Advocacy

PhRMA

PhRMA
RESEARCH • PROGRESS • HOPE

Background / Introduction

- The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- Launched nearly 27 years ago
- Founded by regulatory authorities from United States, Europe, and Japan, along with respective regional industry trade associations

ICH's mission is to achieve greater harmonization in the guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.

Benefits of Regulatory Harmonization are Clear and Tangible

- Standardization of requirements, format, and content of regulatory documentation
- Better use of limited resources across regulators and industry
- Improve the capacity of regulators through more efficient and collaborative use of resources
- Bring new therapies to patients faster
- Increase value across the medical product lifecycle by enabling greater economies of scale and a leveled regulatory playing field

Impact of ICH Guidelines

In 2016, PhRMA conducted a survey of key stakeholders within our member companies on the value and benefits of ICH.

- 93% of survey respondents agree that existing ICH guidelines provide value in addressing intended challenges
- 87% of respondents rate the consistency of guideline implementation across regions as satisfactory, good or excellent
- Over 80% believe ICH is well-positioned for future regulatory harmonization efforts

Key Guidelines Recently Completed or Under Development

Efficacy	Safety	Quality	Multidisciplinary
<ul style="list-style-type: none">• Pediatric Drug Development• Multi-regional clinical trials• Good Clinical Practice• Benefit/Risk Assessment	<ul style="list-style-type: none">• Nonclinical safety studies for pediatric drugs• Reprotoxicity• Nonclinical Evaluation of Anticancer Pharmaceuticals	<ul style="list-style-type: none">• Lifecycle Change Management• API Starting Materials	<ul style="list-style-type: none">• BCS-Biowaivers• Bioanalytical Method Validation

Looking Forward

- Much progress over 27 years, and many advances upon which to build
- Recent ICH reform and expansion will help to further the ICH mission
- Opportunities to:
 - Improve implementation of existing ICH guidelines
 - Further decrease regulatory divergences in high-impact areas of regulatory science
 - Sponsor forward-looking, strategic themes (including innovative areas of regulatory science) and topics for harmonization aligned across the drug development spectrum

Connecting the Dots: Designing Training & Capacity Building Initiatives for ICH Guidelines

- Opportunity to strategically connect the ICH infrastructure that develops harmonized guidelines to other regulatory training and capacity initiatives around the world
- ICH Training Subcommittee - ICH training pilots with trusted training providers on prioritized ICH guidelines (per survey of members & observers)
- APEC Regulatory Harmonization Steering Committee Activities
 - Center of Excellence (CoE) training model and associated roadmaps for 6 priority work areas
 - Multi-regional clinical trials and Good Clinical Practice
 - Pharmacovigilance and Device-vigilance
 - Supply Chain Integrity
 - Biotherapeutics
 - Good Regulatory Management
 - Cell Therapies

Why promote harmonization?

- Faster access to medicines around the world
- Better use of limited resources
- Reduced duplication
- Sharing experience and knowledge
- Fewer clinical trials needed
- Fewer animals needed for basic research
- Training and capacity building with regulators and industry will be key

ICH Strategic Discussions: Modernization of ICH E8 and Subsequent Renovation of ICH E6

Theresa Mullin, PhD,
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Center for Drug Evaluation and Research

April 24, 2017

ICH Strategic Discussions: Taking “Strategic Portfolio” Approach to New Topics

Features of proposed new approach

- Shift from mostly individual “one-off” topic proposals and planning to one that is more organized by theme
- Develop reflection paper(s) to further describe major revisions or development of guidelines in a specified area, where identified types of expertise are needed, and work would occur through a logical planned sequence of work packages (corresponding to discrete guideline work) over multiple years
- Reflection paper(s) would undergo review and discussion and if favorably received, would then be integrated as a stream of work in the ICH multi-year future work plan
- Per that plan, each discrete work package would later be further developed into a more specific topic proposal, concept paper, etc.
- This approach might eventually account for 70-80% of topic work under way. The remaining 20-30% could be traditional individually proposed topics

Potential Advantages of This Approach

- Enable greater global alignment to more holistically support new drug development and generic drug development—good for patients
- Allow for a more structured and meaningful public stakeholder input where they may have views--on theme areas instead of narrower technical topics
- Support a more strategic and productive discussion and consensus on prioritization within ICH as the Assembly grows larger and more diverse
- Better plan for work on both strategic issues and availability of experts
- Could help “smooth” the number of topics /EWGs in flight and allow for more consistency and predictability in organizing for future meetings

RECENT STRATEGIC DISCUSSION

FOCUS: “RENOVATION OF GCPS”

E6(R2) “Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice”



- Background: Considerations by ICH E6 EWG in 2014:
 - Existing E6 content is relevant and flexible – but need to address:
 - Misplaced emphasis on avoiding all errors (e.g., frequent on-site monitoring)
 - Broader than originally intended application to all types of trials
 - Need to address use of technology (e.g., electronic trial master file)
- E6 (R2) Concept:
 - Keep pace with the scale and complexity of clinical trials and to ensure optimal use of technology
 - Supplement E6 with recommendations on quality risk management, risk-based monitoring, and use of technology will facilitate implementation
 - Draft E6 (R2) guideline developed and reached Step 2b
- Step 3 Regional Consultation on E6(R2) in winter/spring 2015-2016

Current Direction: More Stakeholder Input to Inform Future Work



- Public comments received in response to the E6 (R2) Step 2b draft consultation identified opportunities for further enhancement to address additional issues related to good clinical practice
- Recognizing the importance of:
 - The original focus of E6 on provisions to assure human subject protection and data quality and critical guidance related to training, responsibilities and expectations of investigators, sponsors, IRBs
 - The most recent E6 (R2) has made major steps in this direction clarifying the flexibility; use of a quality management system approach, key responsibilities of investigators versus sponsors, and essential documents
- Stakeholders from clinical research community and others cited further opportunities to modernize ICH GCP-related GLs to be:
 - More explicit attention to quality of study / study design
 - More flexibility to better fit diverse range of studies and data sources

ICH Follow-up to Stakeholder Input: Reflection Paper on GCP Renovation



- Proposal: Update ICH guidelines to both address study quality and provide further flexibility to address the increasing diversity of clinical trial designs and data sources now employed to support regulatory and other health policy decisions
- Modernize *ICH E8 General Considerations for Clinical Trials*
 - Review issues and questions most critical to study quality, e.g., “critical to quality” factors to be considered
 - Provide more comprehensive cross-reference to other ICH GLs with relevant discussions
- Further renovate *ICH E6 Good Clinical Practices* to address a broader range of study types.
 - Create umbrella document of key principles with subsidiary use cases/annexes addressing specific types of studies/ data sources
- ICH posted its Reflection Paper with proposed work and provided 60-day comment period. <http://www.ich.org/products/gcp-renovation.html>

Proposed “GCP Renovation”: Modernization of ICH E8



Proposal to Modernize ICH E8

- ICH E8 was finalized in 1997, when concepts of data quality were procedural in nature.
 - Study quality concepts have evolved, including approaches that embody quality by design.
 - There is a lack of adequate cross-referencing of study-relevant issues across the various ICH E GLs
- Proposal to revise ICH E8 to better address the fundamental issue of study quality to ensure needed data quality and meet its stated study objectives
- Revised ICH E8 would address aspects of trial that are critical to generating reliable data (e.g., relevant critical-to-quality (CTQ) factors) and strategies and actions that could effectively and efficiently support quality in these critical areas.
 - CTQ factors might include considerations related to protocol design, feasibility, patient safety, study conduct, study reporting, third party engagement, and potentially other areas.
- Proposal to revise ICH E8 is included among new topics for Assembly consideration in Montreal in May 2017

ADDITIONAL SLIDES

Examples of Potential Future Theme Areas



1. Continued comprehensive modernization of current ICH guidelines as needed (*e.g., Renovation of GCPs*)
2. Further harmonisation of pharmaceutical quality standards, including new manufacturing technologies and approaches
3. Modern tools to enhance quality and efficiency of new drug development (*e.g., Use of Model-Informed Drug Development ; Use of complex innovative trial designs; addressing rare disease considerations*)
4. Incorporating patient perspective in medical product development and assessment
5. Incorporating new/ nontraditional data sources of evidence in drug development and assessment (through life cycle)
6. Harmonisation of approaches/methods for determining bioequivalence and other topics of particular concern for generic drugs



PUBLIC COMMENT



Health
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U.S. FOOD & DRUG
ADMINISTRATION

ICH Regional Public Consultation

Thank you for your participation!