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

May 6, 2016

Agenda

- ICH Process and ICH Reforms
- MedDRA and MedDRA Points to Consider
- Efficacy Topics
- Safety Topics
- Quality Topics
- Electronic Standards Topics
- Public Presentations

Health Canada Santé Canada

Canada

Overview and Reform of International Council for Harmonisation

of technical requirements for pharmaceuticals for human use

May 6, 2016

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Objective

- Provide an overview of ICH
- Highlight the key aspects of Reform

ICH – a harmonisation initiative across regions

- Started in 1990
  - Regulators and industry

- Canada an observer from the beginning
  - Became a Steering Committee (SC) member in June 2014
  - Now a Standing Member through the reform along with Swiss Medic

- With well-defined objectives:
  - To improve efficiency of new drug development and registration process
  - To promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness

- **Accomplished through the development and implementation of harmonised guidelines and standards**

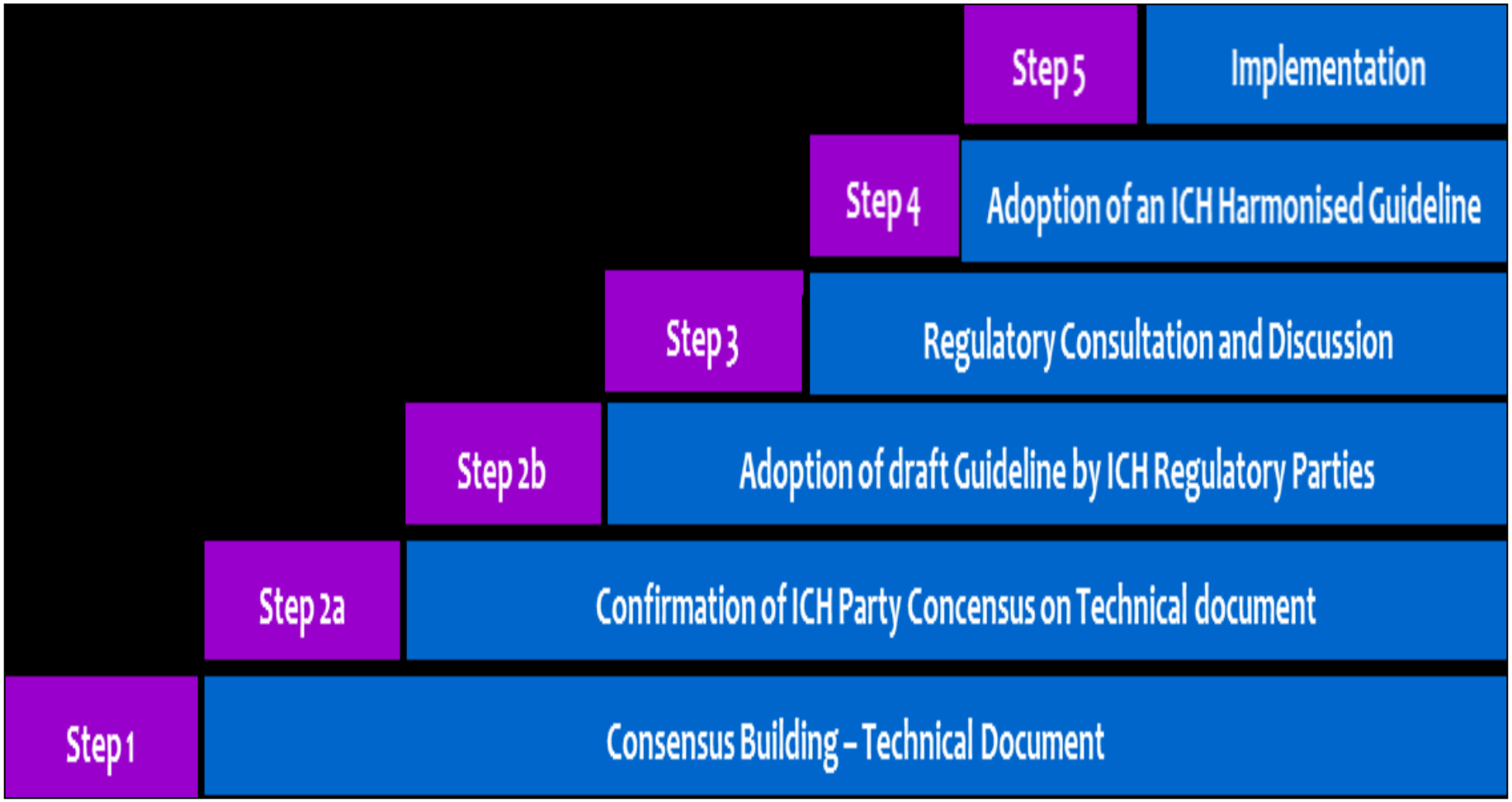
Benefits of Regulatory Harmonisation are Clear and Tangible

- *Standardization of requirements* and format, content of regulatory documentation
- *Reduction of cost and time* for both regulators and industry
- *Improve the capacity of regulators* through more efficient and collaborative use of resources
- *Bring new therapies to patients faster* and at lower cost to all stakeholders
- *Downward pressure on the price of medicines* by enabling greater economies of scale and a leveled regulatory playing field

Guidelines & standards in four disciplines

- Expert working group formed with representatives from each region
- Rapporteur assigned to chair and lead
- Regulatory chair to ensure scope and monitor progress

Steps in the ICH process



Over 80 ICH Guidelines

- Efficacy - 9 topics/ 20 guidelines
- Safety - 9 topics/18 guidelines
- Quality - 10 topics/41 guidelines
- Multidisciplinary
  - Medical Terminology - MedDRA
  - Electronic Standards for the Transfer of Regulatory Information – ESTRI
  - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals- M3 (R2)
  - The Common Technical Document – CTD
  - Data Elements and Standards for Drug Dictionaries - M5

Ongoing topics

Efficacy – E6, E9, E11, E14, E17, E18

Safety – S1, S5, S9, S11

Quality – Q3C, Q3D, Q11, Q12

Multidisciplinary – M2, M4Q/E, M7, M8

www.ich.org

Goals of ICH Reform

- Focus global pharmaceutical regulatory harmonization work in one venue
- Create a venue that allows all key pharmaceutical regulatory authorities and industry stakeholders the opportunity to be more actively involved in pharmaceutical harmonization work
- Maintain efficient and well-managed operations and harmonization work processes

Focus of the reform

ICH = international *council* on harmonisation

•Governance and transparency: improve transparency and openness of ICH and its processes

•International outreach: increase participation of other regulators and affected global industry sectors

•Funding: alternative funding model with less dependence on industry funding

•Legal entity: set up ICH as a legal entity (Association) under Swiss law

Membership under new legal entity

- Permanent members

Founding members:

- US FDA, EU, PMDA/MHLW, PhRMA, EFPIA, JPMA

Standing members:

- Health Canada, Swiss Medic

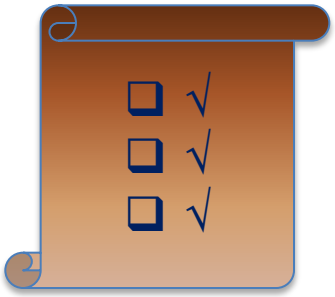
- Other

Standing observers

- WHO, IFPMA

Future members and observers

Governance under new legal entity



Structure:

- ICH Assembly – overarching body
- Management Committee -- Will be in charge of administrative matters

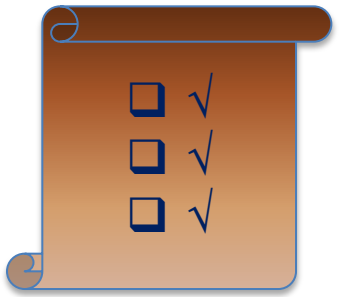
Membership:

- Assembly -- to include drug regulatory authorities and international pharmaceutical industry associations, who apply to become an ICH Member and meet the eligibility criteria, subject to admission by the Assembly
- Observers – to include authorities and organizations that are not (or not yet) eligible for or interested in becoming ICH Members

http://www.ich.org/about/membership-application.html

Management Committee -- to include initially Permanent Members and subsequently also Elected Members.

Eligibility criteria for regulatory bodies



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 2 or more Working Groups

Application of ICH Guidelines:

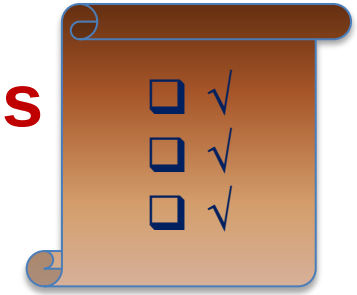
- Having implemented at least the following ICH guidelines upon application for membership:

Q1: Stability Testing guidelines

Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

E6: Good Clinical Practice guideline

Eligibility criteria for industry associations



Type of organization:

- Be a global pharmaceutical industry association representing a global constituency

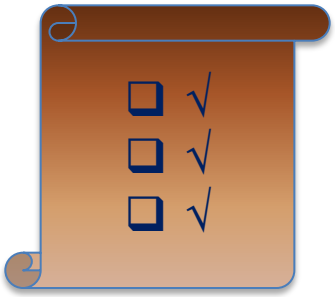
Engagement in the ICH Process:

- Past regular attendance (as interested party or observer) in at least 3 ICH meetings (Global Cooperation sessions and/or Working Groups) during the previous 2 consecutive years
- Past appointment of experts in at least 2 Working Groups

Impact of ICH Guidelines:

- The organization and/or its members must be regulated or affected by ICH guidelines

Regulatory member rights and duties



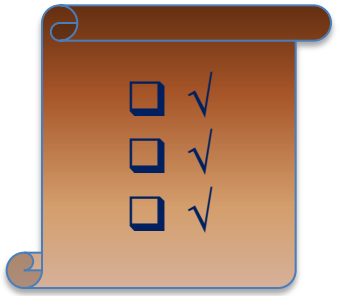
Rights of Regulatory Members:

- Attend the ICH Assembly meetings
- Appoint experts in Working Groups
- Vote in the Assembly

Main duty of Regulatory Members:

- Commit to implement ICH guidelines

Industry member rights and duties



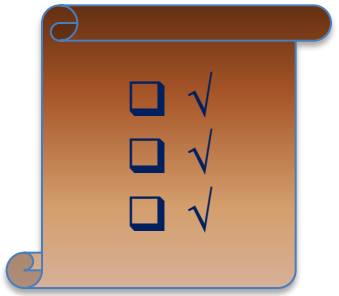
Rights of Industry Members:

- Attend the ICH Assembly meetings
- Appoint experts in Working Groups developing ICH Guidelines which will affect that Member
- Vote in the Assembly with some exceptions, e.g. adoption of ICH guidelines

Main duty of Industry Members:

- Actively support the compliance with ICH guidelines

Observers



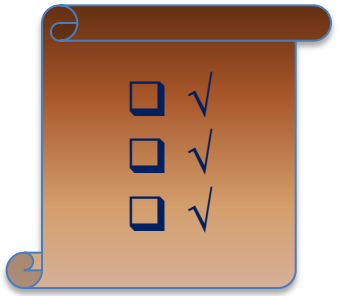
- Very limited eligibility criteria for new Observers

- Rights of Observers:
  - attend ICH Assembly meetings
  - no right to vote and no automatic right to appoint experts in Working Groups
  - WHO and IFPMA, who were observers under the previous structure are now Standing Observers in the Assembly, maintaining their right to appoint experts in WGs

- No duties are imposed on Observers

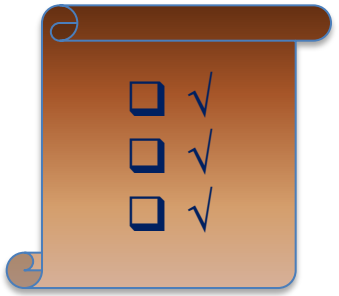
- Most of the Regional Harmonization Initiatives (RHIs) will remain observers as they are unlikely to meet the eligibility criteria for regulatory members

Functioning of the Assembly



- Opening up of membership:
  - Following the establishment of the legal entity, any party eligible can apply for membership
  - Decisions on membership admission by the Assembly become effective on the date of the decision
- Decision-making is on consensus basis
- Voting only in exceptional cases where consensus cannot be reached
- Each member has one vote

The Management Committee



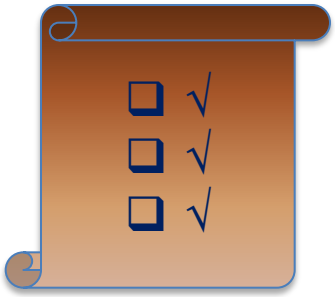
Membership: Initially includes as Permanent Members the current members of the SC and as Permanent Observers the current observers in the SC.

Timing: After two years, and in addition to the Permanent Members, to include Elected Members to be elected by the Assembly from amongst its members.

Eligibility criteria: Similar but somewhat higher than those for Assembly members.

Subcommittees

- Rules of Procedure
- Financial
- Membership
- Communication
- Secretariat Liaison



Additional Elements of the Reform

- ICH Members and Observers commit to self-financed attendance in future ICH meetings with an expectation of continuity and stable participation

- The funding of ICH operations (secretariat, meetings etc.)
  - will be funded through membership fees approved by the Assembly
  - modest participation fees for non-members attending ICH meetings may be introduced.

- The Articles of Association are now finalized and a virtual inauguration took place on October 23rd, 2015.
- They will be complemented by Rules of Procedures, which have also been finalized.
  - 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
  - http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Organisational_changes/Final_Assembly_RoPs_Approved_by_Assembly_10Dec2015.pdf

- The first in-person meeting of the Assembly took place in Jacksonville Florida, Dec. 5-10, 2015.

- The next meeting of the Assembly will take place in Lisbon, Portugal, June 11-16, 2016.

Conclusions

- A global legal entity for development of harmonised technical guidelines
- Collaborative, involving both regulators and industry
- Science-based, consensus driven
- Well managed, further improved with reform
- A common *global* platform and tools, increasing predictability for industry, increase efficiencies, reduce costs
- Benefits to regulators, industry, and patients

Thank you/Merci!

For more information:

www.ich.org

www.fda.gov

www.hc-sc.gc.ca

Overview of MedDRA and MedDRA Points to Consider

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

06 MAY 2016

ICH M1 Points to Consider Group

- *This Working Group is charged with the continuing development and maintenance of the MedDRA Points to Consider (PtC) documents. As new areas of MedDRA are developed, refinements to the PtC documents are necessary. In addition, the documents are routinely updated in line with MedDRA version releases twice a year. This WG also provides guidance on ICH MedDRA initiatives.*
- **Regulatory Chair:** Sonja Brajovic, FDA
- **Rapporteur:** Hilary Vass, Biogen
- **Editor:** Judy Harrison, MSSO
- **Last Face-to-Face Meeting:** 10-12 November 2014, London
  - The changes agreed in London were released on 1st March 2015 with MedDRA Version 18.0 as part of the usual scheduled updates.

Milestones

Completion Date	Deliverable
1 March 2015	*Release of "MedDRA Term Selection: Points to Consider"(MTS:PtC) and "MedDRA Data Retrieval and Presentation: Points to Consider"(DRP:PtC) documents, including updates for MedDRA v18.0 via MedDRA and JMO websites.*
14 April 2015	*Publication for public consultation of Draft EU Good practice guide on recording, coding, reporting and assessment of medication errors (note: this is not a WG deliverable, but the WG has consulted on the document)*
1 September 2015	*Release of "MedDRA Term Selection: Points to Consider" and "MedDRA Data Retrieval and Presentation: Points to Consider" documents, including updates for MedDRA v 18.1 via MedDRA and JMO websites.*
November 2015	*Publication of Final EU Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors*
1 March 2016	*Release of "MedDRA Term Selection: Points to Consider" and "MedDRA Data Retrieval and Presentation: Points to Consider" documents, including updates for MedDRA v 19.0 via MedDRA and JMO websites.*

Work Plan ICH 2016 Meeting

- Review drafts of condensed version PTC documents with a view to developing condensed documents that can be translated into all 11 MedDRA languages.
- Develop/review concept descriptions for Medication Errors arising from
  - EMA Good Practice Guide
  - Input from MedDRA Expert Panel
  - Revision of the EU's Good Pharmacovigilance Practice (GVP) Module VI
- Develop/review concepts for new SOC-Product Issues based on input from MedDRA Expert Panel
- Update PtC documents for MedDRA Version 19.1 (September 2016) based on user feedback and requests

ICH Regional Public Meeting: Overview of Current ICH Efficacy Topics

Jocelyn Ulrich, MPH
Assistant Vice President
Science and Regulatory Advocacy
PhRMA

May 5, 2016

Current Active ICH Efficacy Working Groups

- E6(R2) – Integrated Addendum: Good Clinical Practice
- 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
- M4E(R2) – Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH

Efficacy Topics meeting at the June 2016 ICH Meeting

- E6(R2) – Integrated Addendum: Good Clinical Practice
- E9(R1) – Addendum: Statistical Principles for Clinical Trials
- E11(R1) – Addendum: Clinical Investigations of Medicinal Products in the Pediatric Population
- M4E(R2) – Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH

Current Open Public Consultations

- E18 - New Guideline on Genomic Sampling Methodologies for Future Use

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

E6(R2) INTEGRATED ADDENDUM: GOOD CLINICAL PRACTICE

E6(R2) Integrated Addendum: Good Clinical Practice

- Goal
  - To facilitate innovative approaches to good clinical practice (GCP) to better ensure human subject protection and clinical data quality

- Discussion topics within the E6(R2) Expert Working Group
  - Quality risk management
  - Quality by design processes
  - Emphasizing upfront assessment of risks specific to a study design and protocol
  - Risk-based monitoring, focusing on critical study elements
  - Use of technological tools to ensure robust conduct, oversight, and reporting

E6(R2) Integrated Addendum: Good Clinical Practice

- Format
  - In this "Integrated" Addendum, changes were integrated directly into several sections of the parental Guideline, as opposed to a consolidated addendum at the end.

- Current Activities
  - The E6(R2) Integrated Addendum reached *Step 2* of the ICH process in June 2015.
  - E6(R2) is completing the public consultation as part of *Step 3* of the ICH process.
  - The E6(R2) EWG will meet at the next ICH Meeting in Lisbon to reach consensus on the final guideline.
  - Step 4 is anticipated in November 2016.

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 describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data.

- Goal
  - Focus on planning clinical trials better by looking at:
    - How treatment benefit will be quantified (Estimand)
    - How will data be used at end of a trial (Estimator)
    - How will problems like missing data be dealt with (Sensitivity analyses)

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

- Current Activities & Plans for June 2016 ICH Meeting
  - Continue discussion of methodological issues identified at the ICH meeting in December 2015.
  - Continue writing sections of the Step 1 Technical Document and the technical appendix.
  - Prepare document(s) to support communication to the clinical community, including case studies, and organize regional discussions both with statisticians and non-statisticians.
  - Continue review of the ICH E9 parent guideline in relation with concepts to be developed in the ICH E9 Addendum, and further propose annotations or modifications.
  - Continue review of other affected ICH 'E' guidelines.
  - Step 1 is anticipated by December 2016.

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

E11(R1): Clinical Investigation 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): Clinical Investigation 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 study 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): Clinical Investigation of Medicinal Products in the Pediatric Population

- Current Activities
  - The EWG has been working virtually via teleconference and email since June 2015.
  - Current activities include finalization of all remaining subsections of the E11 Technical Document that continue to be refined by the topic groups, including collecting input from each represented party of the E11 EWG on the final wording of the technical document.
  - Remaining subsections include Extrapolation, Model Informed Drug Discovery and Development (MID3), and Novel methodologies in clinical trial design.
  - The EWG will meet at the next face to face ICH Meeting in Lisbon.
  - Step 1 is anticipated at this meeting.

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

PhRMA
RESEARCH • PROGRESS • HOPE

Background

- Drug development has become increasingly global.
- While MRCTs for regulatory submission has 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 December 2015 ICH meeting to make progress toward completing the *Step 1* document.
- Since December, the EWG has worked via teleconference and email to review final ICH constituent comments, and review and integrate all sections for final content and editorial changes.
- The EWG is anticipated to reach Step 1 and Step 2 prior to the next ICH Meeting in Lisbon, and thus will not convene during this meeting.

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

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

Background

- Genomic information is increasingly included in drug labels, but sample collection rates remain low.
- Storage of genomic samples and data in clinical studies may be subject to national laws and regulations.

Goal of the new E18 Guideline

- Address regional differences across FDA, EMA, PMDA on DNA sampling.
- Clarify technical aspects relating to collection, handling and storage of genomic samples for future use.

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

Current Activities

- The E18 Expert Working Group met face to face at the December 2015 ICH Meeting, and completed the Step 1 and 2 of the ICH Process.
- Public consultation among all ICH regions in anticipated to be completed by the end of 2016.
- Step 4 is anticipated by June 2017.

M4E(R2) – REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH (CTD SECTION 2.5.6)

M4E(R2) – Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH

PhRMA
RESEARCH • PROGRESS • HOPE

Background

- Current ICH guideline is limited in detail and lacks a recommended structure for benefit-risk (B-R) assessments.
- Regulators observe significant variability in how applicants describe their benefit-risk assessment in regulatory submissions.

Goal

- Revise Section 2.5.6 “Benefits and Risks Conclusions” of ICH M4E guideline to standardize the format and content of benefit-risk information.
- Standardization should increase efficiency in communication of the benefit-risk assessment between industry and regulators.
- Out of scope: specifying a recommended methodology in conducting benefit-risk assessments.

M4E(R2) – Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH

<u>Current Activities</u>

- M4E(R2) reached *Step 2* of the ICH process in August 2015.
- Underwent public consultation as part of *Step 3* of the ICH process.
- The EWG will meet during the face to face ICH meeting in Lisbon to reach consensus on the Step 3 Experts Draft Guideline.
- Step 4 is anticipated to be reached as this meeting.

Sources

www.ICH.org

- Concept Papers
- Business Plans
- Work Plans

Thank you!

Overview of Current Safety Topics

Karen Davis-Bruno PhD
FDA/CDER/OND

US FDA/Health Canada Regional ICH Public Consultation
May 6, 2016

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 Nonclincal 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

ICHS1A-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 carci waivers most important for establishing conditions of a WOE option
  - Target is ≥20 CADs with study outcomes supporting rat carci waiver to assess feasibility of approach (~Nov 2019)
  - Publication of Status Report to www.ICH.org March 2016

EWG ICHM7(R1) Addendum Assessment & Control of DNA Reactive (mutagenic) Impurities in Pharmaceutics 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 is currently reviewing & revising the document.
- The list will be updated with more chemicals when information becomes available for such compounds.

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?

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
- Reached step 2a in February 2016, currently seeking public comments

E14/S7B Discussion Group (DG)

- The DG includes experts in clinical (E14) and non-clinical drug development (S7B)
- The DG 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

Guidance finalized 1993 needs updating-focus is on study designs

Revised guidance 1st meeting June 2015

- Alignment with ICHM3, ICHS6, ICHS9
- Opportunity to reduce animal use, consider other scientific approaches to testing

Potential topics in revised guidance:

- High dose selection in reproductive toxicity studies using an exposure multiple where appropriate instead of a MTD
- 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

ICH Regional Public Meeting: Overview of Current ICH Quality Topics

Moheb Nasr, PhD
Vice President, CMC Strategy
GlaxoSmithKline

May 5, 2016

Current ICH "Q" 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
- M4Q – Addressing CTD-Q Related Questions/Change Requests Raised by eCTD

ICH Q3C - Residual Solvents

- Q3C Objectives
  - The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient.
  - The 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.

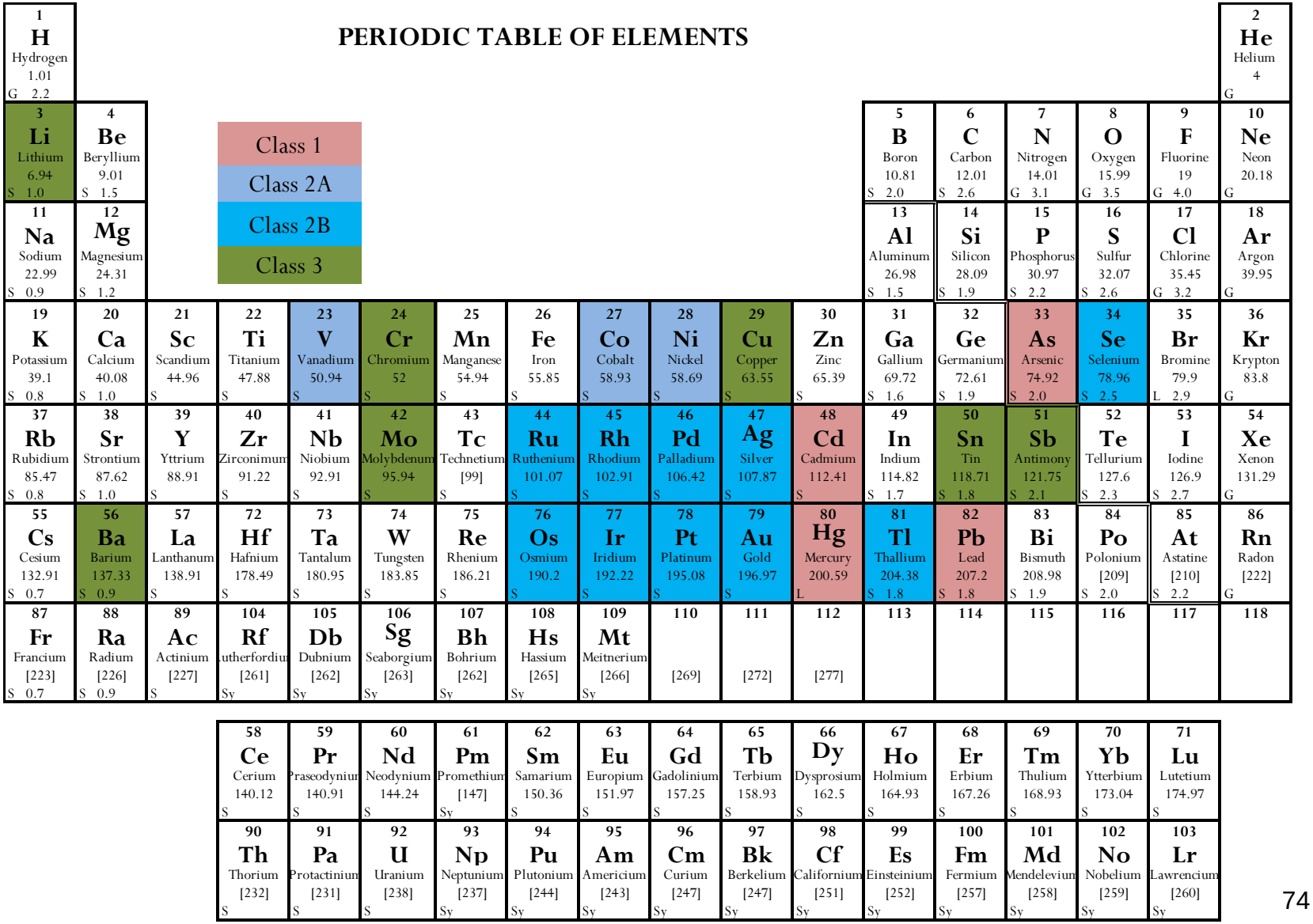
ICH Q3C - Residual Solvents

- Current Activities
  - ICH Q3C is undergoing maintenance to include:
    - Revision of Permissible Daily Exposure (PDE) for methylisobutylketone (MIBK) based on data from new 2-year carcinogenicity studies
    - Inclusion of new residual solvent triethylamine (TEA)
  - Since February 2016, the EWG has been reviewing and resolving comments of an assessment of MIBK and TEA after internal and external consultation in ICH regions
  - The EWG will not be meeting in at the next ICH Meeting in Lisbon but has been communicating via email & teleconference
  - The goal for a Step 4 document is June 2016.

ICH Q3D – Elemental Impurities

- Q3D Objectives
  - The objective of the Q3D guideline is 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



ICH Q3D – Elemental Impurities

- Current Activities
  - Q3D Implementation Working Group (IWG) formed in December 2014
  - Q3D IWG Objectives
    - Prepare a comprehensive training program and associated materials to facilitate an aligned interpretation and harmonized implementation of ICH Q3D in the ICH and non-ICH regions.
    - Provide examples of the application of Q3D to situations that are described, but not illustrated, in the Guideline.
      - Training material must not expand the scope of the final guideline
  - Nine (9) training modules will be prepared to close out the IWG's workplan
    - Training workshops will be held in 2016 in US, Europe, and Japan.
  - The Q3D IWG will not meet at the next ICH Meeting in Lisbon

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

- Q11 Q&As Objective
  - To provide clarification on what information about the selection & justification of starting materials should be provided in marketing authorization applications
    - Clarify existing principles and not re-open ICH Q11 parent guidelines
    - Focus on chemical entity drug substances in four areas:
      - General principles and terminology
      - Impurities and controls
      - Selection of starting materials
      - Lifecycle

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

- Current Activities
  - In September 2015, the Q11 IWG held an interim face-to-face meeting in Ottawa, Canada to progress drafting of the Q&As
  - In particular, the IWG is considering proposals for a Q&A relating to considerations to assure that enough of the drug substance manufacturing process is provided in the application, aspects of the pharmaceutical quality system to support selection and justification of starting materials, and approaches to post-approval change management.
  - The Q11 IWG will meet at the next ICH Meeting in Lisbon to F2F meeting to further develop and understand the new concepts proposed and their practical implementation within regional regulatory frameworks.
  - The timeframe for reaching Step 2 will be determined at this meeting.

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 - 10
  - Optimization of industry and regulatory resources
  - Support innovation and continual improvement and help to assure reliable drug product supply

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

- Q12 Origin
  - Proposed by the Informal Quality Discussion Group (IQDG) and accepted by the ICH Steering Committee in Minneapolis, June 2014

- Perceived problems to be addressed
  - Lack of alignment regarding necessary information and level of detail in the regulatory dossier (application)
    - Impact on change management and regulatory reporting
  - Desire for more post-approval 'operational flexibility' regarding change management
    - Inconsistent acceptance and use of tools such as "post-approval change management plans" and "comparability protocols"

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

- Current Activities
  - Since December 2015, there have been at least four EWG teleconference meetings to assess progress on major issues and revise current draft Q12 Technical Document
  - An interim informal 2-day meeting of the Established Conditions sub-team was held in London, UK, April 6-8, 2016 to prepare proposed text for discussion at the June face-to-face ICH Meeting meeting in Lisbon, Portugal
  - The goal of the face-to-face meeting will be to review the next version of the Q12 Technical Document and address disagreements and concerns
  - Step 1 is expected by June 2017

ICH M4Q – Addressing CTD-Q Related Questions/Change Requests Raised by eCTD

- M4Q Objective
  - Revise ICH M4Q to remove inconsistencies with eCTD v4 (ICH M8)

- Current Activities
  - eCTD placement of “Control Strategy” - COMPLETED
  - Address questions related to the Granularity – COMPLETED
  - XML Attributes/keywords – COMPLETED
  - Procedures to handle future M8 questions – *Proposal submitted for consideration to the ICH Association*
  - M4Q will not meet at the next ICH Meeting in Lisbon

Sources

www.ICH.org

- Concept Papers
- Business Plans
- Work Plans

Thank you!

Overview of Current ICH Electronic Standards Topics

Mark Gray
Sr. Program Manager
FDA/CBER/OCD
May 6, 2016

Overview

- E2B(R3) Implementation: Electronic Transmission of Individual Case Safety Reports
- M8 Electronic Common Technical Document (eCTD)
- M2 Electronic Standards

E2B - Individual Case Safety Report (ICSR)

- Adverse drug reaction reports (ICSRs) supplied in E2B format can be loaded directly into the regulator's adverse event database (e.g., Eudra Vigilance) with minimal user interaction
- ICH E2B (R2) ICSR adopted by EU, FDA, TGA, Japan, WHO, etc.:
  - ICH E2B (R2) was implemented by EU ; applicants (MAH & Sponsors) have been making regulatory submissions since May 2003
- The ISO/HL7 27953-2 specification supports the E2B (R3) ICSR:
  - Harmonized content (data elements and MedDRA coding) for human pharmaceuticals reporting
  - Harmonized HL7 Version 3 XML Messaging
  - Facilitates consistent EU adoption based upon the ISO/CEN Vienna Agreement for joint standards recognition

E2B - Individual Case Safety Report (ICSR)

- ICH E2B (R3) offers new functionality to support pharmacovigilance and harmonize with other healthcare exchanges using ISO and HL7 standards:
  - ISO Identification of Medicinal Products (IDMP) terms and identifiers used in the ICSR Drug Information Section G.K.
  - HL7 Common Product Model and Structured Product Labeling (SPL)
- E2B IWG formed to help facilitate adoption and implementation across ICH regions:
  - Published Question and Answers (Q&A) Document January 2015
  - Evaluating candidate ISO IDMP controlled terminology for Routes of Administration and Dosage Forms

E2B – Individual Case Safety Report (ICSR)

E2B (R3) Adoption Activities

- Japan initiated a pilot in 2013 and is ongoing
  - ✓ Levering pilot experience to finalized their regional implementation
- US initiated a pilot in 2012 which included alpha/beta testing with EU
  - ✓ Published draft regional technical specifications to support pre-production pilot for vaccines: May 2014

E2B (R3) Implementation Activities

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

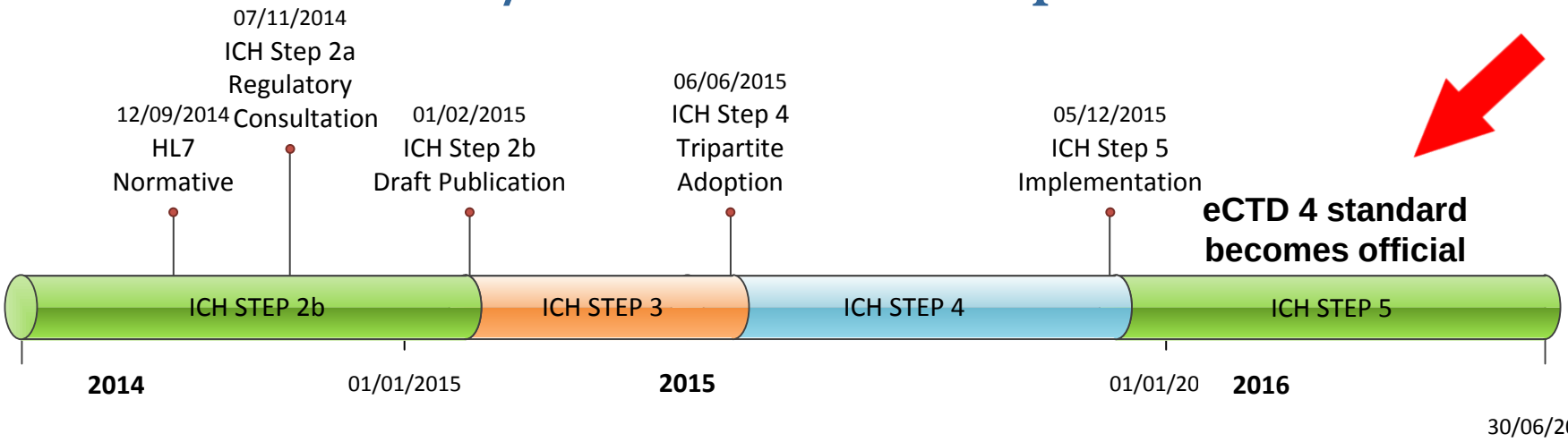
M8 - Electronic Common Technical Document (eCTD)

- Electronic Common Technical Document (eCTD)
  - In November 2010, the ICH Steering Committee endorsed the establishment of an Expert Working Group (EWG) / Implementation Working Group (IWG) for the eCTD and assigned the topic code "M8".
- Purpose
  - Support of the progression of the eCTD through the Standards Development Organisation (SDO) process to develop the eCTD as an International Standard. This is in accordance with the 2008 Steering Committee decision that the next major version of the eCTD be developed in collaboration with SDOs, with development first as a Health Level Seven (HL7) standard, and then as an International Organization for Standardization (ISO) standard.
  - The M2 EWG provides a service to ICH that supports the information technology requirements of projects being undertaken within ICH, and provides the framework and oversight for the efficient and effective development of the solutions by these groups.

M8 - Benefits of eCTD 4 / RPS

- 130 Requirements defined by ICH as of November 2010(1)
- Core enhancements to eCTD 3.2.2 include
  - Enhanced Dossier Management
    - Improved electronic message standardization
    - Simple reuse of previously submitted documents across dossiers
    - Support for multiple application submissions
    - Enhanced document life cycle capabilities
    - Support for file grouping through the use of a new keyword
    - Improved document ordering capabilities
    - Identification of documents for additional processing
- Greater flexibility
  - Designed to provide flexibility for future changes (e.g., heading/section modifications, new keywords).
- Support for Two-Way Communications

M8 - eCTD 4.0 / RPS 3 Next Steps



- Started in 2010 preliminary work at Health Level 7 completed in 2014 allowing for eCTD approval for comment (Step 3) as of February 2015.
- ICH approved the eCTD standard to proceed to step 4 in June 2015 (Fukuoka, Japan)
- Step 4 (adoption) of the was reached in December 2015 (Jacksonville, Florida) and M8 is currently in the implementation phase
- The ICH implementation package was posted the beginning of April
  - FDA – posted M1 implementation package on March 31
- All regions working towards implementation, earliest acceptance of eCTD 4 messages will likely in 2018

M2 Electronic Standards for the Transfer of Regulatory Information

- The M2 Expert Working Group was established in 1994 with the objective of facilitating electronic communication by evaluating and recommending, open and non-proprietary Electronic Standards for the Transfer of Regulatory Information (ESTRI)
- M2 has the responsibility for the evaluation and recommendation of standards, and also has the responsibility for SDO relationship management
- M2 also provides consultative support to the ICH Working Groups that require technical specifications

M2 Current Activities

- Technology Watch Reporting – An assessment will be conducted to identify opportunities for ICH that may impact existing guidance and/or specifications and current or future work of ICH. Additionally, key regulatory trends will be presented for further technology investigation.
- M8 SDO Project survey results – M2 will conduct a survey based on the ICH SDO projects evaluation criteria

Questions

Public Presentations and Comment Period

Thank you!