Overview of International Conference on Harmonisation of technical requirements for the registration of pharmaceuticals for human use

May 15, 2015
ICH Background

• Started in 1990, as a unique harmonisation project involving the regulators and research-based Industries of US, EU and Japan

• 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
The Original ICH World

EU

EMA/EC

EFPIA

Japan

MHLW/PMDA

JPMA

United States

FDA

PhRMA

Observers: WHO, Canada, EFTA
ICH and Health Canada

• Became Steering Committee (SC) members in June 2014
• Expected to become standing members following reform
• Cathy Parker and Supriya Sharma are SC members
• Celia Lourenco is the coordinator
• Internal committees and structures in place to oversee ICH activities within HC
• Deliverable under RCC workplan
The ICH Steering Committee

Governs the ICH

Determines ICH policies and procedures

Decides on the adoption of ICH projects
  • Selects topics for harmonisation
  • Endorses the creation of ICH Working Groups

Monitors and facilitates the progress of ICH Working Groups

Signs off ICH documents
Steps of ICH Harmonization

STEP 1--Building Scientific Consensus

STEP 2--Agreeing on Draft Text
>SC SIGN OFF<

STEP 3--Consulting with Regional Regulatory Agencies—Comment Period

STEP 4--Adopting Harmonized Guidelines
>SC SIGN OFF<

STEP 5--Implementing Guidelines in ICH Regions
Health Canada’s Approach to ICH

• Policy Statement: even as observer, Health Canada was committed to adoption and implementation of all ICH guidelines

• Now ICH guidelines are adopted ‘as is’
  -> become Health Canada guidelines
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
ICH Keys to Success

- Involvement of both regulators and industry
- Science-based, consensus driven
- Well managed
- Limited number of players with comparable regulatory and technical capability (*NB - this is now changing with ICH Reform…*)
- Commitment of regulators to implement products of harmonization
- A common *global* platform and tools
Thank you/Merci!
For more information:
www.ich.org
www.fda.gov
www.hs-sc.gc.ca
Update on ICH Reforms

Theresa M Mullin, PhD
Director, Office of Strategic Programs
FDA Center for Drug Evaluation and Research
May 15, 2015
Goals

Goals for Future of ICH -- to be achieved through the proposed changes to ICH membership and governance

**Goal 1:** Focus global pharmaceutical regulatory harmonization work in one venue

**Goal 2:** Create a venue that allows all key pharmaceutical regulatory authorities and industry stakeholders the opportunity to be more actively involved in pharmaceutical harmonization work

**Goal 3:** Maintain efficient and well-managed operations and harmonization work processes
Focus

The focus of the reform has been on the following 4 areas:

**Governance and transparency:** focus the role of regulators in ICH and improve transparency and openness of ICH and its processes

**International outreach:** increase the involvement of other regulators as well as those global industry sectors that are affected by ICH guidelines

**Funding:** identify an alternative funding model that would make ICH less dependent in the future of the current form of industry funding

**Legal entity:** set up ICH as a legal entity as continuing activities in the current informal setting will be difficult in the changed environment e.g. with more members
Agreement on new procedures for the adoption of guidelines

The enhanced role of regulators has been introduced through the following measures:

- Decisions to open a new topic or re-opening an existing guideline are taken by regulators only in case of absence of consensus with industry.
- Regulatory chairs, in addition to the rapporteur, are appointed in working groups to ensure the integrity of the whole process.
- The guideline development process is divided into 2 well-distinguished parts: (a) development of a technical document (involving industry and regulatory experts) in Step 2a, and (b) development and adoption of the guideline (under the responsibility of the regulators) in Step 2b.
Steps in the ICH Process

- **Step 1**: Consensus Building – Technical Document
- **Step 2a**: Confirmation of ICH Party Consensus on Technical Document
- **Step 2b**: Adoption of draft Guideline by ICH Regulatory Parties
- **Step 3**: Regulatory Consultation and Discussion
- **Step 4**: Adoption of an ICH Harmonised Guideline
- **Step 5**: Implementation
Major improvements regarding transparency of ICH have been achieved by making more information available to the public regarding on-going ICH activities. Notably the following is published on the ICH website:

- Agendas and minutes of the Steering Committee meetings
- Work plans of the active expert working groups
- ICH procedures and a summary of their key elements

http://www.ich.org/home.html
Governance under new legal entity

1. Structure (non-profit Association under Swiss law) comprising e.g. the following bodies:
   - Assembly -- The Members will convene as the ICH Assembly
   - Management Committee -- A Management Committee will be in charge of administrative matters

2. Membership
   - Assembly
     - Members -- 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
   - Management Committee -- to include initially Permanent Members and subsequently also Elected Members.
Remit of the Assembly vs. the Management Committee

Assembly:
- The overarching body of the Association that makes a number of important decisions, e.g. on amendments of the Articles of Association, admission of new Members and adoption of ICH guidelines

Management Committee:
- The body that will oversee operational aspects on behalf of all members of the Association and has responsibility primarily for administrative and financial matters
- Its financial responsibilities include, initially, to ensure the continued funding of ICH operations (budget...) and oversight of the organization and preparation of the ICH Assembly meetings.
Membership in the Assembly—Eligibility criteria for Regulators

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 certain number of WGs

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
Membership in the Assembly—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 certain number of WGs

Impact of ICH Guidelines
• The Association and/or its members must be regulated or affected by ICH guidelines
Summary of the rights/duties of Regulatory Members

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
Summary of the rights/duties of Industry Members

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:
  - Observers have the right to attend ICH Assembly meetings but no right to vote and no automatic right to appoint experts in Working Groups
  - The current observers in the Steering Committee (WHO and IFPMA) will be 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: as soon as the legal entity has been established, any party eligible as member 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 to include as Permanent Members the current members of the Steering Committee 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.
Next steps

- 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 initially be ensured by the Permanent Members of the Management Committee. This ensures continuation of ICH operations and contributes to a smooth transition to the new structure. In the future, however, the ICH is expected to be funded through membership fees which are to be approved by the Assembly, on the basis of a proposal from the Management Committee.
- The **Articles of Association** are now being finalized. They will be complemented by **Rules of Procedures**. The aim is to set up the legal entity by June 2015.
- The **target date** for the completion of the reform is January 2016.
Thank you!
Background/ Introduction

- The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- Launched nearly 25 years ago
- Brings together regulatory authorities from United States, Europe, Japan, Canada, and Switzerland, along with representative industry trade associations from three ICH regions

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* 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
Evolving Focus for ICH

• 70+ scientific guidelines produced (1990 – 2013)

• PhRMA member company scientific and regulatory leaders agree that ICH provides value
  – More than three-fourths believe existing ICH guidelines address intended challenges
  – Over 80% believe ICH is well-positioned for future regulatory harmonization efforts

• Significant efforts underway to reform ICH
  – ICH Membership and Governance
  – 5-year Strategic Plan
Looking forward

- Much progress over 25 years - Many advancements upon which to build...... now seeking directional focus for the future

- Opportunities to:
  - Revisit: Improve implementation (facilitate)
  - Reinvigorate: Decrease divergences (focus on exceptions)
  - Redirect: Sponsor new topics (foster forward considerations)

<table>
<thead>
<tr>
<th>“E” topics</th>
<th>“S” topics</th>
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<tr>
<td>Pediatric Drug</td>
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<tr>
<td>Development</td>
<td>Reprotoxicity (revision of ICH S5)</td>
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<td>Benefit/Risk</td>
<td>ICH S9 Q&amp;A (implementation issues)</td>
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<td>Assessment</td>
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<td>Multi-regional</td>
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<td>Management</td>
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<tr>
<td>API for starting</td>
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<tr>
<td>materials</td>
</tr>
</tbody>
</table>
Why promote harmonization?

- Faster access to medicines
- Reduced duplication
- Training and Capacity Building
- Better use of limited resources
- Sharing of experience and knowledge
- Fewer clinical trials needed
ICH MedDRA
MedDRA Management Board (MMB)
M1 Points to Consider Working Group (M1PtC)

ICH Public Meeting
May 15, 2015
MedDRA

“Medical Dictionary for Regulatory Activities”

What is it?

• An international terminology for coding of medical information throughout the regulatory cycle (clinical trials phases 1-3, and post-marketing)

• Enables standardized communication of coded safety data between regulators and manufacturers/sponsors
  – Terminology can be exchanged between parties using terms or corresponding 8-digit numbers

• Enables medical accuracy and transparency in coding of verbatim terms with extensive, specific MedDRA preferred terms

• International in scope - translated into ten other languages (Spanish, French, German, Japanese, and more)

• Governed by the ICH MedDRA Management Board (MMB) and maintained by the MedDRA Maintenance and Support Services Organization (MSSO)
MedDRA Management Board (MMB)

Selected MMB Activities for Fukuoka

- Review MSSO proposal for translations development and maintenance
- Review MSSO proposal for MedDRA subset mapping to other terminologies
- Conduct activities to address interest by regulators beyond ICH regions
- Assess feedback on new MedDRA web-based browser launched on December 1, 2014
- Conduct briefings on:
  - MSSO operations status
  - Progress in implementation of a 27th SOC in March 2016
  - MSSO engagement with relevant PV initiatives
  - SMQ development
M1 Points to Consider Group (M1PtC)

- Authors and maintains Points to Consider (PtC) documents for harmonized use of MedDRA terminology
  - Term Selection
  - Data Retrieval and Presentation
- Updates PtC documents with each MedDRA version
- Provides guidance on ICH MedDRA initiatives
Recent Activities of The M1PtC

• MedDRA Web-Based Browser
  - Testing for launch

• November 2014 Working Group meeting
  - Provided updates to the PtC documents for MedDRA Version 18.0, including the addition of options for coding maternal exposures and medication errors without clinical consequences in the MedDRA Term Selection: Points to Consider document
  - Provided consultation to the EU on its “Good Practice Guide for Recording, Coding, Reporting and Assessment of Medication Errors” and provided input on sections that reference the PtC documents.

• PtC documents:
  - March 2015 – released updates for MedDRA v18.0 via MedDRA and JMO websites
Overview of Current Quality Topics

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Director (Acting), Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality
CDER

Christopher Joneckis, Ph.D.
Associate Director for Review Management
Office of the Director
CBER

ICH Regional Public Meeting

May 15, 2015
ICH “Q” Activities

• Q3C – Guideline for Residual Solvents
• Q3D – Guideline on Elemental Impurities
• Q7 – GMPs for Active Pharmaceutical Ingredients: Q&A
• 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

• 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)

• The EWG will not be meeting in Fukuoka but has been communicating via email & teleconference
ICH Q3C - Residual Solvents

- The EWG has been drafting and revising an assessment of MIBK and TEA
- A teleconference was held April 1 and subsequent email communications occurred to discuss the current draft document.
- General agreement on the current draft has been expressed by EWG members.
- The goal for a Step 2 document is May 2015.
ICH Q3D – Elemental Impurities

• Objectives
  – 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

<table>
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<th>Element</th>
<th>Class</th>
<th>Mass (G)</th>
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<tbody>
<tr>
<td>Li (Lithium)</td>
<td>Class 1</td>
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</tr>
<tr>
<td>Be (Beryllium)</td>
<td>Class 1</td>
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<td>Na ( Sodium)</td>
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<td>[233]</td>
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<td>Cu (Copper)</td>
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<td>Pu (Plutonium)</td>
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<td>Am (Americium)</td>
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<td>Cm (Curium)</td>
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<tr>
<td>No (Nobelpium)</td>
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<td>Lr (Lawrencium)</td>
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ICH Q3D – Elemental Impurities

• 2010, ICH convened Q3D
• June 2013, ICH Q3D reached step 2
  – Public comments addressed at June 2014 Meeting of the ICH EWG in Minneapolis, MN USA
• September 2014, ICH Q3D reached step 4
  – Approved by the ICH Steering Committee in November, 2014
  – Published on the ICH Website on 16 December, 2014
• Implementation timelines
  – Application of Q3D to new drug products
    • EMA Committee on Medical Products for Human Use has announced that Q3D will apply to new drug application in the EU as of June 2016.
  – Application of Q3D to existing products is not expected prior to 16 December 2017 (36 months after publication of the guideline by ICH). (This timeline is established in the Q3D Guideline.)
ICH Q3D Implementation Working Group

• Q3E Implementation Working Group (IWG) formed in December 2014

• Objectives
  – 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
  – Facilitate an aligned interpretation and harmonized implementation of Q3D

• Nine (9) modules will be prepared
  – Expected to be completed in Summer of 2015
ICH Q7 – GMPs for Active Pharmaceutical Ingredients: Q&A

• Nov. 2012 - First Meeting of Q7 IWG
  – Q7 IWG convened in San Diego to produce Q&A document to aid and update interpretation of Q7
  – Additional meetings 6/2013 (Brussels) & 11/2013 (Osaka).

• June 2014 – Minneapolis meeting
  – Reviewed/revised/edited Q&As which had been worked on by the regional teams
  – 14 Q&As completed

• November 9-13, 2014 – Lisbon meeting
  – Completed 41 Q&As remaining from Minneapolis (total of 55 Q&As) for final review
ICH Q7 Q&A
Update - After Lisbon

• Dec. 2014 - 55 final draft Q&As sent for review/concurrence by constituencies.
• Feb. 20, 2015 – IWG T-con #1: Consensus reached on 53 of 55 Q&As. Decided no additional face-to-face meetings were needed to complete work.
• March 5, 2015 - IWG T-con #2: Consensus on all 55 Q&As.
• April 13, 2015 - Q&As completed informal clearance through FDA for submission to ICH Secretariat.
• April 20, 2015: Final IWG T-con:
  – IWG voted to accept the Version 5.0 of the 55 Q&A document as final.
ICH Q7 Q&A
Current/Pending Issues

• May 6, 2015: ICH began clearance of the document by requesting IWG Experts to sign Step 3 – due May 14

• May 8, 2015: Considering keeping “unused” Q&As (those collected during development but that did not meet criteria to be included in final Q&As) for future reference, should ICH Steering Committee decide to reopen the topic in the future.
  – IWG constituent responses on this issue due by May 22.
  – IWG consensus to be transmitted to ICH Secretariat
ICH Q11 Q&As: Selection and Justification of Starting Materials for Manufacturing of Drug Substances

• Objective
  – To provide clarification on what information about the selection & justification of starting materials should be provided in marketing authorisation applications
    • Clarify existing principles and not re-open ICH Q11
    • Focus on chemical entity drug substances
    • Operate mainly by tcon and email
    • Perhaps hold interim face-to-face meeting in September if approved by ICH Steering Committee
ICH Q11 Q&As

• Project Status
  – Targeting initial draft by end of July
  – Focusing current efforts on four areas:
    • General principles and terminology
    • Impurities and controls
    • Selection of starting materials
    • Lifecycle
ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

• 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 – Lifecycle Management

Objectives

• Develop a guideline on lifecycle and change management:
  – intended to work with existing ICH Q8 – Q11 guidelines
  – provide a framework to facilitate the management of post-approval CMC changes in a more transparent and efficient manner across the product lifecycle

• Adoption of this guideline should
  – promote innovation and continual improvement,
  – strengthen quality assurance and reliable supply of product
  – allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in, a firm’s pharmaceutical quality system (PQS) for management of post-approval CMC changes
ICH Q12 – Lifecycle Management

• First EWG meeting held in Lisbon, November 2014
• After Lisbon, 3 sub-teams created to identify key elements, alignment challenges, and areas of agreement on 3 main areas of proposed guideline:
  – Pharmaceutical Quality System (PQS)
  – Regulatory Dossier & “Regulatory Commitments”
  – Post-Approval Change Management Plans and Protocols
• Sub-teams made proposals to the EWG on key elements and high-level outline. All met at least twice and shared their reports with the EWG.
• Inter-regional drafting teams were created at the February 2015 EWG meeting to develop “bullet points” content for the guideline in March & April.
ICH Q12 – Lifecycle Management

• As of early May, initial text developed for 3 main areas; bullet points for remaining content
• Discussion of draft text and bullet points in EWG phone call May 13
• Plan to have an initial working draft of the guideline for discussion at the F2F June 2015 meeting in Fukuoka.
• Plan to finalize a Step 2a doc at the June 2016 meeting.
ICH M4Q – Addressing CTD-Q Related Questions/Change Requests Raised by eCTD

Questions from M8
• “Control Strategy” placement in CTD-Q
• Granularity: should files (“leaf elements”) be permitted at:
  – In the Module 2 “Quality Overall Summary”
    • 2.3.P.x (i.e. subordinate to P.2 Pharm Development)
    • 2.3.A.x (i.e. subordinate to Appendices)
  – In Module 3
    • 3.2.P.2.x (i.e. subordinate to P.2 Pharm Development)
• How to handle future M8 questions
• Revision to existing XML Attributes/Keywords
<table>
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<th>Attributes/Keywords</th>
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</table>
Thank you!
Overview of Current Safety Topics

Joseph DeGeorge
PhRMA (Merck)
Disclaimer

- These are personal views and do not represent the views of Merck or PhRMA.
ICH Processes

- Highly valuable
- Allows for one global approach for non-clinical development
- Harmonizes philosophies across industry and agencies
- Minimizes differences in interpretation and implementation through further guidance clarification
- Fosters streamlined non-clinical development while reducing animal use and improving assessment of safety
EWG for S1A-S1C – Carcinogenicity Studies

Background:

- Based on PhRMA Carcinogenicity Database Analysis Project (published Feb 2011) - evaluated datasets that identified key determinants that may anticipate the outcome of the 2-year rat carcinogenicity study.

**Conclusions:**

- NO histologic risk factors for neoplasia in a 6-month rat study + NO genetic toxicology + NO hormonal perturbation signals = **NO value added from conducting a 2-yr rat carco study.**
- 91% overall test sensitivity with no human relevant misses among the 14 false negatives in the 266 chemical database.

**Goals of potential revision of guidance:**

- Providing a more holistic and integrated approach to understand the human carcinogenicity risk of a small molecule
- Understanding when conducting a 2-year assay provides value to the overall carcinogenicity risk assessment
ICH EWG has developed a prospective data gathering approach and pharmacology assessment (Regulatory Notice Document published Aug 2013)

- Will allow for unbiased prospective evaluation as to how well WOE (Weight of Evidence) elements predict the 2-yr rat carcinogenicity outcome
- Creates CAD (carcinogenicity assessment document) to be used to document WOE elements and prediction and to determine feasibility of implementing evaluation process

Current PhRMA, EFPIA, JPMA surveys suggest the target number of 50 CAD submissions will be reached in 2016 with study results to assess predictions available between 2015-2018.

Benefits may include:
- Elimination of some 2 year rat carcinogenicity studies where Drug Regulatory Agencies and Sponsors agree that a particular molecule presents a low risk or a likely risk of human carcinogenicity
  - Reduction in animal use
  - Shorter development timelines (when 6-month Tg mouse study is conducted in place of 2 year assay)
  - More science-based cancer risk assessment process for pharmaceuticals

EWG awaiting more CADs prior to meeting, Face to face, potentially in November 2015
S5 - Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

**Rationale for Updating**

- ICH S5 is over 20 years old; originally finalized for Step 4 in 1993
- Needs to be aligned with newer ICH guidances
  - ICH M3 (R), ICH S6 (R1), ICH S9
- Needs to inform on human risk assessment strategies
  - Current focus is primarily on study designs
- Should include other currently used testing paradigms
  - Opportunities to reduce animal use
  - May enable newer scientific approaches to be used in regulatory settings
IWG met twice previously, first EWG meeting in June

Potential topics that will likely be considered include:

- Appropriate exposure multiples to set high dose in reproductive tox studies
- Combining specific reproductive tox studies (when appropriate).
- Guidance on in vitro assays
- Integrated reproductive risk assessment
ICH S9 was finalized as Step 4 in November 2009.

Rationale for Q & A document includes:

- While S9 is viewed as a highly valuable guidance, a number of differences in interpretation have arisen during implementation.
- Opportunity to harmonize and clarify intent, and minimize differences in interpretation and implementation.
A few questions that will likely be considered:

- Guidance covers severe and life-threatening malignancies, but...
  - What about extended survival periods? At what point would a full battery of non-clinical studies be needed?
  - Should carcinogenicity studies ever be considered?
- When should recovery groups be added to studies?
  - How many species? Which studies?
- Evaluation of impurities
- No face to face meetings planned at this time; work executed by TC and WebX
Nonclinical Safety Testing in Support of Development of Pediatric Medicines

- New Safety Topic for Guidance was endorsed by ICH Steering Committee in November 2014.
- Rationale includes:
  - Multiple guidances (FDA, EMA, ICH M3(R2)) currently exist, don’t align, are more than a decade old, and not informed by extensive experience gained since implementation
  - Specific recommendations from regulatory bodies frequently conflict in the need for and design of juvenile non-clinical studies in support of pediatric clinical development
  - Significant differences in designs proposed and executed by sponsors in the absence of harmonized guidance
  - Opportunity to evaluate study utility and provide unified study design recommendations
- First meeting of EWG in June
M7 Addendum: Planned Step2b May 2015

Application Of The Principles Of The ICH M7 Guideline To Calculation Of Compound-Specific Acceptable Intakes

- ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Step4 June 2014
  - Use staged TTC for mutagens of unknown carcinogenic potency
  - Develop compound-specific limits when carcinogenicity data available
- Addendum to ICH M7 (EWG meets by WebX)
  - Acceptable intakes (AIs) derived for a set of chemicals that are mutagens and carcinogens, selected because are common in pharmaceutical manufacturing, or Illustrate the principles from M7
  - Likely mutagenic mode of action; “default approach” from ICH M7 of linear extrapolation from the calculated cancer potency estimate
  - Compounds which highlight alternative principles to deriving compound-specific intake (various examples)
Conclusion

- Safety topics are active and critical to development approaches that will facilitate the modernization of non-clinical testing strategies.

Questions?
Updates from ICH ‘E’ Working Groups

Lisa M. LaVange, PhD
Office of Biostatistics
OTS/CDER/FDA

ICH Co-Efficacy Lead for FDA

ICH Regional Public Meeting
FDA White Oak Campus

May 15, 2015
E Working Groups

- E6 – Good Clinical Practice (GCP)
- E9 (R1) – Estimands and sensitivity analysis
- E11 – Clinical investigations in pediatric populations
- E14 – Pro-arrhythmic potential of new drugs
- E17 – Multi-regional clinical trials (MRCTs)
- E18 Genomic sampling methodologies for future use
- M4E CTD Section 2.5.6: Benefits and risks conclusions
E6 GOOD CLINICAL PRACTICE (GCP)
Addendum to ICH E6: Good Clinical Practice Consolidated Guideline

- To facilitate innovative approaches to good clinical practice (GCP) to better ensure human subject protection and data quality
- ICH expert working group (EWG) discussion topics
  - Quality risk management
  - Quality by design processes
  - Emphasize 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

Source- Concept paper, ICH E6, [www.ICH.org](http://www.ICH.org)
E9 (R1) ESTIMANDS AND SENSITIVITY ANALYSIS
ICH E9 (R1): Estimands and Sensitivity Analysis

• Planning clinical trials better by:
  – How treatment benefit will be quantified
    ......Estimand
  – How you will use your data at end of trial
    ......Estimator
  – How you will deal with problems:
    ...Missing data & other aspects: Sensitivity analyses
Survey of Industry Practices: Developed by Working Group

- American Statistical Association provided help
- On-line survey to be accessible to ICH regions
- Assess current practices
- Results will inform the writing of the document
- Hope to have summary in time for Japan
- Also organizing sessions for various professional and scientific meetings to solicit input
Other Plans for June ICH Meeting

- Improve accessibility of statistical concepts:
  - Provide case studies to outline principles
  - Develop a framework for the case studies
- Develop a glossary to augment ICH E9
- Prepare a non-technical document plus introduction:
  - Draft to be developed before meeting in Japan
E11 PEDIATRIC TRIALS
E11: 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

- Regulatory information sharing among ICH
E11 Background (cont’d)

• There are clear gaps in the current guidance due to advancement without a parallel development of harmonized guidance in these 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 Activities

• 2014 Expert working group formed
  – Regulatory, Industry and Academic members

• Format of revision process resolved
  – No editing of existing text of E11 *Clinical Investigation of Medicinal Products in the Pediatric Population*, December 2000
  – Addition of an Annex I with Introduction, reference to existing E11 and new/updated sub-sections
E11 Activities (cont’d)

- Proposed addendum to 2000 document topics:
  - Commonality of Content
  - Age definitions
  - Extrapolation of data
  - Ethical Considerations
  - Clinical Study Methodology
  - Pediatric Formulations
  - Model-Informed Drug Discovery Development (MID3)
E11 Timeline

- Jan-Oct 2014
  - Concept paper finalized
  - Full expert working group (EWG) and Topic Leaders assigned
- November, 2014- ICH meeting (Lisbon, Portugal)
  - Consensus Building for Step 1 Technical Document
  - Consensus achieved on principal approach for all 7 topic areas,
- December, 2014
  - Obtain consensus from absent parties (Swiss-medic, WHO)
  - Updated Work Plan for 2015
E11 Timeline (cont’d)

• January-May, 2015
  − Continue Step 1 Technical Document in 7 topic areas by WG through conference calls and email
• June, 2015- ICH meeting (Fukuoka, Japan)
  − Discussion and active authoring of the addendum which will constitute the Step 1 Technical Document
  − Consensus building on regulatory implications and resolution of critical issues
  − Assembly and editing of expanded topics
E14 PROARRHYTHMIC POTENTIAL OF NON-ANTIAARRHYTHMIC DRUGS
History as prelude

• E14 “Finalised” June 2005
• 17 revisions through Q&A document (clarity, technical improvements)
  – June 2008 (n=8)
  – April 2012 (n=5)
  – March 2014 (n=4)
• Became “E14/S7B Discussion group” to monitor several ongoing development efforts
Fukuoka Agenda

• Is it time to revise core document, rolling up all the Q&As? If so, deliverable is *plan*.

• Are we ready to accept exposure-response analysis as a substitute for classical TQT? If so, start drafting new Q&A or revision to E14).

• Update on progress to replace clinical testing for proarrhythmia with non-clinical assay. Initiate discussion regarding validation package.
Exposure-response

- Supported by anecdotal retrospective analyses → prospective study → standardized retrospective analyses of 30 sequential TQT studies
- Leads to conclusion that TQT-quality data can be obtained from early phase SAD/MAD studies (sooner and cheaper)
- E-R is not expected to be controversial.
- However, there is currently no satisfactory substitute for the TQT study’s positive control.
In vitro proarrhythmia assay

- QT is not the right biomarker
- False positives → bad labeling/missed opportunities
- Basis for TdP-like arrhythmias fully understood
- Mechanistic assay based on drug effects on cloned human cardiac ion channels
- Large multifaceted effort (academics, pharma, regulatory) → couple of years from fruition
- Needs timely input on a “validation” strategy.
E17 MRCT
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
Table of Contents

• Introduction
  – Objectives, background, scope, and general principles

• General recommendations
  – Strategy-related points (value of MRCTs, basic requirements, regulatory interactions)
  – Clinical trial design and protocol-related topics
    • Pre-consideration of regional variability on efficacy/safety
    • Subject selection
    • Dose selection
    • Choice of endpoints
    • Estimation of sample size and allocation to regions
    • Collecting and handling efficacy/safety data
    • Statistical analysis planning
    • Selection of comparator
    • Handling concomitant medications
  – Glossary
Recent Activities

• June – Nov, 2014: Working group prepared and agreed upon the final outline and primary topic areas
• Nov 2014: Working group met in Lisbon, created three writing teams, and developed a rough draft of most sections during the meeting
• Nov 2014 – May 2015: Remaining sections drafted by writing teams, detailed comments circulated via email, and teleconference held in Feb to discuss draft document; additional statistician from EU joined the group
• June 2015: Working group will meet in Japan to complete the consensus draft (Step 1) followed by submission to the ICH SC for adoption under Step 2
E18 GENOMIC SAMPLING
E18: Genomic Sampling Methodologies for Future Use

- Concept endorsed June 2014
- Issues:
  - FDA, EMA, PMDA have regional guidances on DNA sampling
  - Genomic information is increasingly included in drug labels, but sample collection rates remain low\(^1\)
  - Storage of genomic samples and data in clinical studies may be subject to national laws and regulations
- Purpose:
  - Clarify technical aspects relating to collection, handling and storage of genomic samples for future use
Draft Table of Contents

1. INTRODUCTION
   • 1.1 Objective(s) of the Guideline
   • 1.2 Background
   • 1.3 Scope of the Guideline
   • 1.4 General Principles

2. GUIDELINES
   • 2.1 Rationale for genomic sampling
   • 2.2 Genomic sampling
     2.2.1 Collection and Processing of sample
     2.2.2 Transport, Storage and Disposition of sample
   • 2.3 Genomic data
     2.3.1 Type of genomic data
     2.3.2 Generation of genomic data
     2.3.3 Handling and storage of genomic data
   • 2.4 Privacy and confidentiality
     2.4.1 Coding
     2.4.2 Access to the genomic data
   • 2.5 Emerging topics
E18: Progress and Plans

• E18 Concept endorsed, June 2014
• First F2F meeting in Lisbon, Portugal, Nov 2014
  – Agreement on content & workplan; TOC accepted by steering committee
• First Draft, Mar 2015
  – Created by three workstreams; group teleconferences
• Second F2F meeting in Fukuoka, Japan, Jun 2015
  – Line by line revision of the draft E18 guideline
  – Goal: Step 1 document sign off
• Third F2F meeting in Jacksonville, US, Dec 2015
  – Goal: Step 2 document sign off
M4E CTD SECTION 2.5.6
Revision of CTD Section 2.5.6
M4E Expert Working Group

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

• EWG Charge—
  – Revise Section 2.5.6 “Benefits and Risks Conclusions” of ICH M4E guideline to standardize the format and content of B-R information
  – Such standardization should increase efficiency in communication of the B-R assessment between industry and regulators
  – Specifying a recommended methodology in conducting B-R assessments is out of scope
  – Topic endorsed by ICH in June 2014
M4E Activities and Plans for June 2015 ICH Meeting

• First Face-to-Face Meeting in November 2014
  – Reviewed internal guidance used by regulators and applicants in conducting B-R assessments
  – Summary examples of Section 2.5.6 showed that additional and varied substructure is often created by applicants in Section 2.5.6
  – Common elements of B-R assessment became evident; consensus reached on a new sub-section structure for Section 2.5.6
  – First rough draft of guideline revision produced

• Monthly teleconferences beginning in December 2014

• June 2015 ICH Meeting—Complete a consensus draft revision (Step 1) followed by submission to the ICH SC for adoption under Step 2.
Overview of Current Electronic Standards Topics
Developments and Future Direction

ICH Regional Public Meeting
Canada – U.S. Regulatory Cooperation Council
May 15th, 2015
Agenda

Electronic Data Standards – The Vision
ICH – Data Standards of Interest
M2
E2B
M8
Next Steps
• Receiving data electronically in a standardized format can:
  ➢ Enhance the efficiency and effectiveness of the safety review process
  ➢ Support inter-operability in a regional and international context
  ➢ Benefit both industry and regulators by streamlining the flow of data from collection through submission, and facilitate data interchange
  ➢ Support inter-agency efforts to develop international repositories and information sharing
  ➢ Standards are really a specification for interoperability – regionally and within a global context
  ➢ Support automated all electronic submission environments for review of regulated products over the entire product life-cycle.
Electronic Data Standards - The Vision

Agency A
- Medicinal Product Info
- eCTD (M8)

Agency B
- Medicinal Product Info
- ICSR (E2B)

Registration Authority
- Pharmaceutical Product Info
- Substances
- Dose Forms, Representation, Routes of Adm., Packaging
- Units

Sponsor A
- Medicinal Product Marketing Authorisation Application
- eCTD (M8)

Sponsor B
- ICSR (E2B)

Data comparison and data exchange

Collaboration platform
- Shared data

Information Request and Response

Requesting and Issuing Codes

Mandatory Reporting

Distribution
ICH Data Standards of Interest

- ICH recently committed to developing future standards through the use of SDOs
  - ICH defines the requirements
  - SDO (in this case HL7) develops the technical standard
  - ICH tests the standard and confirms that it meets requirements

- **Safety of Consumer Products**
  - E2B
    - Individual Case Safety Reports (ICSR) ICH/HL7/ISO
  - M1
    - Medical Dictionary of Regulatory Activities (MedDRA) ICH/HL7/ISO

- **Regulatory Submissions**
  - M8
    - Regulatory Product Submission (RPS) HL7
    - electronic Common Technical Document (eCTD) ICH
M2 Electronic Standards

• Electronic Standards for the transfer of Regulatory Information
  - Its key role is to provide a service to ICH that supports the information technology requirements of projects being undertaken within ICH. M2 is not directly involved in the development of the technical solution itself, this is the responsibility of the EWG concerned. M2 provides the framework for the efficient and effective development of the technical solutions by these groups.

• Roles and Responsibilities
  - Coordination of ICH Projects with Information Technology Requirements
    - Inventory of ICH Projects with Defined Technical Components
    - Technological Assessment of ICH Concept Papers
    - Review of Technical Proposals from EWGs
    - Development of Maintenance Practices
    - Standards Development Organisations (SDO) Relationship Management
    - Inventory of SDO Projects With Potential Relevance to ICH
    - Review of SDO Activities in Context of ICH Scope and Activities
M2 - Electronic Standards

• M2 Roles and Responsibilities – continued

  ➢ Assessment and Recommendation of Technology and Information Standards (previously performed by a subgroup of M2 known as SENTRI)
    • Overview of Evolving Technology and Information Standards
    • Propose New Technical Recommendations for ICH Adoption

  ➢ Recently added
    • Establish and Maintain an Information Source for EWGs (e.g. working practices, guidance documents and templates)
    • Deliver Consultative Support to EWGs Requiring Technical Specifications
    • Establish and Maintain ICH OIDs
• The process for executing M2 projects remains essentially the same,
• The Portfolio Management approach ensures projects fit with M2’s purpose and enable strategic execution
• Strategic Framework aligns projects, organizing them into logical groupings that more clearly map to the client’s high-level needs
• The Strategic Framework provides a means to make portfolio adjustments to address emerging strategic and a changing technology environment.
M2 Updates

• Strategic
  ➢ Draft Technology Watch Report to SC (finalize in Fukuoka, June 6th – 11th, 2015)

• Projects/ M2 Work Items
  ➢ Redactions
  ➢ ESTRI Recommendations
  ➢ Genericode
    • Draft ESTRI recommendation for Genericode (targeting SC sign-off in Fukuoka, June 6th – 11th, 2015)
  ➢ SHA-256
  ➢ DOCX
    • Gather and evaluate DOCX use cases focused on whether DOCX can be used in a dossier; share information with all parties

• Structured Content Approaches

• M2 Operations
  ➢ OID Information document
  ➢ SDO Monitoring
    • Draft Report to SC on external activities and their potential impact on closed and/or potential ICH topics (finalized in Fukuoka, June 6th – 11th, 2015)
  ➢ Best Practice Update
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., Canada Vigilance) with minimal user interaction

• ICH E2B (R2) ICSR adopted by EU, FDA, TGA, Japan, WHO, etc.:
   ICH E2B (R2) was implemented by Canada Vigilance; trading partners (MAH & Sponsors) have been making regulatory submissions since May 2013

• 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
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 and implementation target date is July 2016
  - Japan: Published regional technical specifications and implementation target is January 2016 with a three year migration period
  - US: Preparing for release of final industry guidance and regional technical specifications to support June 2015 implementation for vaccines. Target date to publish draft drug and biologics regional technical specifications: June 2015
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". Work in relation to the eCTD had previously been undertaken by the M2 EWG.

**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.
• The ICH has developed standardised specifications for the Common Technical Document (CTD) and its electronic version the eCTD.

• The eCTD standard describes a message format for transferring submission documents and processing instructions to an agency system.

• The eCTD standard provides a mechanism to record all interactions from industry to agencies in a way that highlights changes between multiple submissions.

• Strengths (compared to non eCTD (HC), eNDA (FDA), NeeS (EMA))
  • Supports lifecycle
    • Documents can be “replaced” or “deleted”
    • Application lifecycle – amendments / variations
  • Allows for the creation of automated software tools to assemble and view eCTD submissions.

• Validation
  • XML DTD provides absolute rules for validation
  • CTD TOC defined in XML backbone

• Health Canada received its first submission in eCTD format in Dec. of 2004
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
    • Interoperability across product types
    • Simple reuse of previously submitted files across dossiers
    • Improved electronic message standardization
    • Support for multiple application submissions
    • Lifecycle control at the file level
    • File reuse
    • Support for file grouping
    • Improved document ordering capabilities
  
  • Greater flexibility
    • Designed to provide flexibility for future changes (e.g., heading/section modifications, new keywords).

• Support for Two-Way Communications

(1) see estri.ich.org/new-eCTD/
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 (stage 3) as of February 2015.
- Final regulator comment (stage 4) is expected to complete in 2015.
- Final approval (stage 5) is expected in late 2015 or early 2016.
- Review comments on the ICH IG package during the June ICH meeting
  - Sort and evaluate the comments
  - Agree to the actions to the comments
  - Discuss and agree to changes needed to the ICH IG package for Step 4

2014
- Oct 2014 HL7 Normative
- Sep 2014 ICH Step 2a Regulatory Consultation

2015
- Feb 2015 ICH Step 2b Draft Publication
- Jun 2015 ICH Step 4 Tripartite Adoption

2016
- Nov 2015 ICH Step 5 Implementation
- 01/01/20
- eCTD 4 standard becomes official
Looking for your feedback