ASSEMBLY

AGENDA PAPERS

9 – 10 November 2016

Osaka, Japan
ICH2016/18
ICH ASSEMBLY MEETING
DRAFT AGENDA
November 9 - 10, 2016
Osaka, Japan

Opening of the ICH Assembly Meeting
Welcoming remarks from the ICH Assembly Chair and Vice-Chair.
The Assembly will note the Member representatives and Observer delegates appointed to the Assembly and participating in the Osaka meeting.

Adoption of the Agenda
➢ The Assembly is invited to adopt the agenda and timetable for the ICH Assembly meeting.

1. Procedural Matters

   Articles of Association
   The Chair/Vice-Chair will inform the Assembly on several minor amendments proposed to the Articles of Association which were approved by the Founding Members at the Inaugural Assembly meeting in October 2015.
   ➢ The Assembly is invited to take a decision to adopt the revised Articles of Association.

   Assembly Rules of Procedure
   The Chair/Vice-Chair will inform the Assembly on the amendments proposed to the Assembly Rules of Procedure (RoP) which were last updated and approved by the Assembly in June 2016. These amendments concern e.g. introducing an annex on an ICH Donation Policy.
   ➢ The Assembly is invited to take a decision to adopt the revised Rules of Procedure.

   Standard Operating Procedures for EWGs/IWGs
   The Chair/Vice-Chair will present to the Assembly the Standard Operating Procedures for Expert Working Groups (EWGs) / Implementation Working Groups (IWGs) approved by the ICH MC.

   MedDRA MC Rules of Procedure
   An update will be provided by the MedDRA MC Chair or Chair’s delegate on the status of the development of the MedDRA MC’s RoP.

2. Membership and Observership

   The ICH Management Committee (MC) will present to the Assembly its recommendation regarding Membership and Observership applications processed since the Lisbon meeting in June 2016.
   ➢ The Assembly is invited to take a decision regarding the applications for ICH Membership/Observership recommended by the MC.
3. **Financial Matters**

The ICH MC will provide an update on ICH financial matters including: preparation of the 2017 ICH Budget; reflections regarding the level of the annual fee for new Members; development of a proposal for a participation fee for non-membership fee paying ICH meeting participants; development of a Donation Policy and recommendation of an auditing firm for appointment as ICH Auditors.

The MedDRA MC Chair or Chair’s delegate will provide an update on the preparation of the 2017 MedDRA Budget, including the 2017 subscription fees.

- The Assembly is requested to take a decision to approve the 2017 ICH Budget;
- The Assembly is invited to take a decision to approve the annual fee for new Members for publication on the ICH website and confirm agreement to a 2018 implementation;
- The Assembly is invited to approve the publication of the Donation Policy (if adopted as part of the RoP, referred to under agenda item 1) on the ICH website;
- The Assembly is requested to take a decision to appoint an auditing firm as the ICH Auditors for an initial period of two years to audit the annual financial statements of the Association;
- The Assembly is requested to take a decision to approve the 2017 MedDRA Budget.

4. **Strategic Discussions**

- The Assembly is invited to hold a strategic discussion focusing notably on the following potential topics proposed by the MC:
  - Good Clinical Practice (GCP)
  - Compliance of Reliability for Electronic Data
- The Assembly is invited to discuss follow-up actions from this discussion.

5. **New ICH Topics**

The MC will highlight the overall status of ICH harmonisation activities on current ICH topics and the process agreed in Lisbon in June 2016 for the selection of new ICH topics.

The MC will provide the Assembly with an update on its considerations since the Lisbon meeting in June 2016 of the new proposals on Safety Data Collection and Adaptive Clinical Trials.

- The Assembly will be invited to provide its views and consider approval of any new topics for ICH Guidelines recommended by the MC.

6. **Communication**

*Communication Activities*

The MC will provide an update on current communication activities including development of: a general slide deck on ICH; a transparency policy; and stakeholder engagement plan.

The Assembly will also note recent updates to the ICH website.

- The Assembly will be invited to share its views.

*ICH Regional Public Meetings*

- The Assembly will be invited to share information on any ICH Regional Public Meetings in their respective regions prior to/following the ICH meeting in Osaka in November 2016.

7. **Training**

The MC will present to the Assembly on the development of an ICH Training Strategy.

- The Assembly will be invited to share its views.

8. **Update on MedDRA**

The MedDRA MC Chair or Chair’s delegate will provide a report on current MedDRA activities.

- The Assembly will be invited to share its views on the report.
9. **Annual Work Plan and Multi-Annual Strategic Plan of the Association**

The ICH MC will present to the Assembly the 2017 ICH Work Plan and Multi-annual Strategic Plan.
- The Assembly is requested to take a decision to approve the 2017 ICH Work Plan and Multi-annual Strategic Plan.

The MedDRA MC Chair or Chair’s delegate will present to the Assembly the 2017 MedDRA MC Work Plan.
- The Assembly is requested to take a decision to approve the 2017 MedDRA MC Work Plan.

10. **Implementation of ICH Guidelines**

- The Regulatory Members of the Assembly will be invited to share information on the status of implementation of the ICH Guidelines in their respective countries or regions.

11. **Reports on Current Topics**

11. **Status Report on Topics**

The Assembly will note the current status of draft Guidelines and predictions for progress towards Step 2 and Step 4.

12. **S5(R3) EWG: Revision on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility**

The Acting Rapporteur will report on the outcome of the S5(R3) EWG meeting held on November 6 – 10, 2016 and progress made towards revising the ICH S5(R2) Guideline on *Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility*.
- The Assembly will be invited to provide its views on the report;
- The Assembly will be invited to approve the new Rapporteur for the S5(R3) EWG.

*Step 1 sign-off and Step 2a/b endorsements are expected by Q3 2017.*


The Rapporteur will report on the outcome of the S11 EWG meeting held on November 7 – 10, 2016 and progress made towards collecting data on juvenile animal studies and to develop the draft S11 Technical document on *Nonclinical Safety Testing in Support of Development of Paediatric Medicines*.
- The Assembly will be invited to provide its views on the report.

*Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.*

14. **Q12 EWG: ICH Guideline on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**

The Rapporteur will report on the outcome of the Q12 EWG meeting held on November 6 – 10, 2016 and progress made towards developing the draft Q12 Technical document on *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*.
- The Assembly will be invited to provide its views on the report.

*Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.*
15. **E2B(R3) IWG: Revision of the Electronic Submission of Individual Case Safety Reports**

The Rapporteur will report on the outcome of the E2B(R3) IWG meeting held on November 7 – 10, 2016 and progress made towards the completion of a document on how to use the EDQM routes of Administration; progress towards an editorial update to the Implementation Guide to reflect the Q&A document; and progress towards the determination of any conflicts in ICSR messages based upon review of regional Implementation Guides.

- The Assembly will be invited to provide its views on the report;
- If *Step 3* of the editorial changes made to the Implementation Guide to reflect the Q&A document is reached in Osaka, the E2B(R3) Regulatory experts will be invited to sign-off; and the Regulatory Members of the Assembly will be invited to adopt as final under *Step 4* this document; The Assembly will note the temporary change in the Rapporteurship of the E2B(R3) IWG.

*Step 3 sign-off and Step 4 adoption are expected by November 2016.*

16. **E9(R1) EWG: Addendum to Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses**

The Rapporteur will report on the outcome of the E9(R1) EWG meeting held on November 4 – 8, 2016 and progress made towards developing the draft E9 Addendum on *Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses*.

- The Assembly will be invited to provide its views on the report, and if *Step 1* of the Addendum is signed-off by the E9(R1) EWG, the Assembly will be invited to endorse *Step 2a* of the E11 Addendum, following which the Regulatory Members of the Assembly will be invited to endorse *Step 2b* of the E11 Addendum.

*Step 1 sign-off and Step 2a/b endorsements are expected by November 2016.*

17. **E17 EWG: ICH Guideline on Multi-Regional Clinical Trials**

The Rapporteur will report on the outcome of the E17 EWG meeting held on November 7 – 10, 2016 and progress made towards updating the draft E17 Guideline on *Multi-Regional Clinical Trials* with comments received during the consultation period in the ICH regions.

- The Assembly will be invited to provide its views on the report.

*Step 3 sign-off and Step 4 adoption are expected by June 2017.*

18. **E18 EWG: ICH Guideline on Genomic Sampling and Management of Genomic Data**

The Rapporteur will report on the outcome of the E18 EWG meeting held on November 7 – 10, 2016 and progress made towards updating the draft E18 Guideline on *Genomic Sampling and Management of Genomic Data* with comments received during the consultation period in the ICH regions.

- The Assembly will be invited to provide its views on the report.

*Step 3 sign-off and Step 4 adoption are expected by June 2017.*

The Rapporteur will report on the outcome of the M8 EWG/IWG meeting held on November 7 – 10, 2016 and progress made on the current activities of the M8 EWG/IWG including: updating the Implementation Package and Specification Change Request document; developing the v4.0 Q&A v1.0; and communication with vendors.

- If **Step 3** of the eCTD v4.0 Implementation Package v1.2 and the eCTD v4.0 Q&As and Specification Change Request Document v1.0 are reached in Osaka, the M8 Regulatory experts will be invited to sign-off; and the Regulatory Members of the Assembly will be invited to adopt as final under **Step 4** these 2 documents.

**Step 3 and Step 4 of the eCTD v4.0 Implementation Package v1.2 are expected in November 2016.**

**Step 3 and Step 4 of the eCTD v4.0 Questions and Answers and Specification Change Request Document v1.0 are expected in November 2016.**

20. **M9 EWG: Biopharmaceutics Classification System-based Biowaivers**

The Rapporteur will report on the outcome of the first meeting of the M9 EWG held on November 7 – 10, 2016 and progress made towards developing the draft guideline on *Biopharmaceutics Classification System-based Biowaivers*.

- The Assembly will be invited to provide its views on the report.

**Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.**

21. **M10 EWG: Bioanalytical Method Validation**

The Rapporteur will report on the outcome of the first meeting of the M10 EWG held on November 7 – 10, 2016 and progress made towards developing the draft guideline on *Bioanalytical Method Validation*.

- The Assembly will be invited to provide its views on the report.

**Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.**

22. **EWGs/IWGs/Discussion Groups Not Meeting in Osaka**

- **S1 EWG: Revision of the Rodent Carcinogenicity Studies for Human Pharmaceuticals Guideline**

The Assembly will be updated on the current activities of the S1 EWG including the progress made towards the collection and review of confidential submissions of Carcinogenicity Assessment Documents (CADs) and summary report submissions by sponsors to DRAs within each region and considerations regarding the timeframe for drafting the S1 Technical document.

**Step 1 sign-off and Step 2a/b endorsements are expected by June/November 2019.**

- **S3A IWG: Q&As on Note for Guidance on Toxicokinetics**

The Assembly will be updated on the current activities of the S3A IWG and the progress made by the group to collect comments on the draft S3A Q&As in the respective ICH regions.

**Step 3 sign-off and Step 4 adoption are expected by June 2017.**

- **S9 IWG: Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals**

The Assembly will be updated on the current activities of the S9 IWG and the progress made by the group to collect comments on the draft S9 Q&As in the respective ICH regions.

**Step 3 postal sign-off is expected by December 2016.**

**Step 4 is expected in June 2017 at the subsequent Assembly meeting.**
Q3C(R6) Maintenance EWG: Maintenance of the Guideline for Residual Solvents
The Assembly will be updated on the current activities of the Q3C(R6) EWG including: the progress made towards reaching Step 3 and Step 4.
The Assembly will note that a new Q3C Rapporteur will be nominated for the period 2017-2018 in line with the Q3C maintenance procedure.

- If Step 3 is reached ahead of Osaka, the Regulatory Members of the Assembly will be invited to adopt Step 4 of the Q3C(R6) Guideline.

Step 3 postal sign-off is expected in Q3/Q4 2016.
Step 4 is expected in November 2016.

Q3D(R1) Maintenance EWG: Guideline for Elemental Impurities
The Assembly will be updated on the current activities of the Q3D EWG including the finalisation of the Q3D training package, the outcome of the regional Q3D workshops held in the different ICH regions in 2016 and the initiation of its new activity regarding the development of permitted daily exposures for all 24 elements included in the Q3D Guideline for the cutaneous and transdermal route of administration.

Q11 IWG: Q&As on API Starting Materials
The Assembly will be updated on the current activities of the Q11 IWG including progress made towards reaching Step 2a/b for the Q11 Q&A document on API Starting Materials.

- If Step 1 of the Q&A document is signed-off by the Q11 IWG, the Assembly will be invited to endorse Step 2a of the Q11 Q&A document, following which the Regulatory Members of the Assembly will be invited to endorse Step 2b of the Q11 Q&A document;
- The Assembly will be invited to endorse the nomination of a new Regulatory Rapporteur for Q11 IWG, recommended by the MC.

Step 1 postal sign-off is expected in October 2016.
Step 2a/b endorsements are expected in November 2016.

E6(R2) EWG: Integrated Addendum to Good Clinical Practice (GCP)
The Assembly will be updated on the status of the finalisation of the draft E6 Integrated Addendum on Good Clinical Practice.

- The Regulatory Members of the Assembly will be invited to adopt as final the E6(R2) Integrated Addendum.

Step 4 is expected in November 2016.

E11(R1) EWG: Addendum to Paediatric Drug Development
The Assembly will be updated on the current activities of the E11(R1) EWG including progress made towards collecting comments on the draft E11 Addendum on Paediatric Drug Development which was endorsed by the Regulatory Members of the Assembly under Step 2b of the ICH process in September 2016.

Step 3 postal sign-off is expected in May 2017.
Step 4 is expected in June 2017.

E14/S7B Discussion Group (DG): The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
The Assembly will be updated on the current activities of the E14/S7B DG to review advances in science and methods related to the clinical assessment of QT prolongation and to monitor the progress of the discussion of the Comprehensive In vitro Proarythmia Assessment Initiative.

E14/S7B DG recommendation on whether to reopen the E14 Guideline for a complete revision is expected by December 2017.
**M1 PtC WG: MedDRA Points to Consider**
The Assembly will be updated on the current activities of the M1 PtC WG with respect to the updating with each MedDRA release of the two PtC documents on *Term Selection* and *Data Retrieval and Presentation*; and the development of a proposal for a new area of work.

**M2 EWG: Electronic Standards for the Transfer of Regulatory Information**
The Assembly will be updated on the outcome of MC discussions in Osaka regarding M2 activities.

**M4Q(R1) (CTD-Quality) IWG: Addressing CTD-Q-Related Questions**
The MC will provide its recommendation to the Assembly on whether the group should be disbanded or continue its work depending on whether questions have been received following the implementation of the M4 Granularity Document.

**M7(R1) EWG: Addendum to Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**
The Assembly will be updated on the current activities of the M7(R1) EWG including the progress made towards finalising the M7(R1) Addendum on *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

*Step 3 sign-off is expected by December 2016.*

*Step 4 is expected in June 2017.*

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**DATES/LOCATION OF NEXT MEETINGS FOR 2017/2018**
- The Assembly will receive an update on the organisation of next ICH meetings for 2017/2018 including selected dates and locations.

**Summary of Decisions in Osaka, Japan on November 9 - 10, 2016**

**PRESS RELEASE**
- The Assembly will be informed of the development and publication of the ICH Press Release for the Osaka meeting.

**ANY OTHER BUSINESS**
ICH2016/18

ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 1

1. Procedural Matters

*Articles of Association*
The Chair/Vice-Chair will inform the Assembly on several minor amendments proposed to the Articles of Association which were approved by the Founding Members at the Inaugural Assembly meeting in October 2015.

*Action:*
- The Assembly is invited to take a decision to adopt the revised Articles of Association.

*Assembly Rules of Procedure*
The Chair/Vice-Chair will inform the Assembly on the amendments proposed to the Assembly Rules of Procedure (RoP) which were last updated and approved by the Assembly in June 2016. These amendments concern e.g. introducing an annex on an ICH Donation Policy.

*Action:*
- The Assembly is invited to take a decision to adopt the revised Rules of Procedure.

*Standard Operating Procedures for EWGs/IWGs*
The Chair/Vice-Chair will present to the Assembly the Standard Operating Procedures for Expert Working Groups (EWGs) / Implementation Working Groups (IWGs) approved by the ICH MC.

*MedDRA MC Rules of Procedure*
An update will be provided by the MedDRA MC Chair or Chair’s delegate on the status of the development of the MedDRA MC’s RoP.
Background Document:


*Chronicle:*

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The ICH Secretariat presented to the Assembly several minor proposed amendments to the existing version of the Assembly Rules of Procedure (RoP) dated December 10, 2015.

The Assembly received presentations on the outcome of the Regional Harmonisation Initiatives (RHIs) and Drug Regulatory Authorities/Department of Health (DRAs/DoH) pre-meetings which were held on June 14, 2016 and where participants (currently Observers) discussed the impact of the ICH Reforms, the Articles of the Association and the Assembly RoP.

The Assembly was also updated on the finalisation of the MC RoP, the development of the RoP for the MedDRA MC as well as the Standard Operating Procedures (SOPs) for Working Groups (WGs).

The Assembly also noted the role of IFPMA (representing the Global Biopharmaceutical Industry) in ICH, and the provision of a platform to national industry organisations that are interested in engaging with ICH as their national authorities become new Regulatory Members.

**Decisions/Actions:**

- The Assembly approved the proposed changes to the Assembly RoP;
- The Revised Assembly RoP will be published on the ICH website;
- The MC RoP, the MedDRA MC RoP as well as the SOPs for WGs once finalised, will be made available on the ICH website.
The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Standard Operating Procedures of the ICH Working Groups
ICH EWG/IWG SOP
Document History

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<thead>
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<th>Circular (MC Report)</th>
<th>Date</th>
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<td>June 2016</td>
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<tr>
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<td>The ICH Management Committee endorsed Version 1.0 of the EWG/IWG Standard Operating Procedure.</td>
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Glossary

5-year strategic plan: A 5-year planning tool for the ICH Association to assess current ICH Topics and their anticipated time for completion and assess when new harmonization activities should begin.

Business Plan: Outlines the costs and benefits of harmonising a topic that was previously proposed by a Concept Paper and focuses on regulatory feasibility (See Annex 10)

Concept Paper: Describes the perceived problem and the issues to be resolved by a harmonization project (see Annex 9)

Deputy Topic Leader: Co-participant of a Working Group who represents the views of their Member during any ICH interactions and supports the work of the Topic Leader.

Expert Working Group (EWG): An EWG is charged with developing a harmonised guideline that meets the objectives in the Concept Paper and Business Plan. ICH Members nominate representatives and, unless otherwise specified by the Management Committee, the official membership is limited to two representatives per ICH Member per working group and one representative per ICH Observer, if nominated.

Federal Register: A daily publication of the US federal government that issues proposed and final administrative regulations of US federal agencies.

Founding Industry Member: An Industry Member who was an original member of the former ICH Association, known as the International Conference on Harmonisation, and founded the new ICH Association established on October 23, 2015.

Founding Regulatory Member: A Regulatory Member who was an original member of the former ICH Association, known as the International Conference on Harmonisation, and founded the new ICH Association established on October 23, 2015.

ICH Assembly: Overarching body of the ICH Association that consists of all Members of the Association and adopts decisions related to the harmonisation of Guidelines.

ICH Coordinator: Nominated by ICH Members to assist in the efficient operation of ICH harmonization activities. A Coordinator acts as the central point of contact with the ICH Secretariat and facilitates conversation between the ICH Management Committee and Working Groups as needed.

ICH Management Committee: Oversees operational aspects of the ICH Association on behalf of all Members of the Association.

ICH Member: A legislative or administrative authority or international organization who meets all qualifications for membership according the ICH Articles of Association article (11) & (12) and has applied and been accepted to join the ICH as a voting Member of the Assembly. ICH Members actively support the compliance with ICH Guidelines, appoint experts in Working Groups, and support the aims of the ICH Association.
**ICH Observer:** Attendees of ICH Assembly meeting who may provide input on ICH harmonisation activities but who do not have voting rights.

**ICH Secretariat:** The staff responsible for the day-to-day management of ICH, including preparations for and documentation of meetings of the ICH Assembly and its Working Groups.

**ICH Standing Observer:** The World Health Organization and the International Federation of Pharmaceutical Manufacturers & Associations who attend meetings of the Assembly and Management Committee but do not have any voting rights. ICH Standing Observers may appoint experts to Working Groups.

**ICH Standing Regulatory Member:** A legislative or administrative authority that has the responsibility of the regulation of pharmaceutical products for human use and has been a Member of the Steering Committee of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use immediately prior to the establishment of the new ICH Association.

**Implementation Working Group (IWG):** A Working Group established for the purposes of developing a Q&A document following the implementation of a Guideline.

**Informal Working Group:** A working group established for the purposes of developing a Concept Paper and Business Plan for a harmonisation activity.

**Informal Working Group Leader:** An expert from an informal Working Group that is designated to lead the efforts of the informal Working Group.

**New Topic Proposal:** A Proposal for a new ICH harmonisation activity.

**Quorum:** The minimum number of Members of the Assembly that must be present at any of its meetings to make the proceedings of that meeting valid.

**Rapporteur:** Is a representative of one of the ICH Members, who is designated by the Assembly when a new topic is formally adopted. The Rapporteur is responsible for leading a working group (EWG/IWG) and ensuring that the group keeps an up-to-date action plan and timetable, with clear deliverables and deadlines. The Rapporteur shall regularly present reports to the Assembly, focusing in particular on the timelines and milestones.

**Regulatory Chair:** Is a representative of one of the ICH Regulatory Members, who is designated by the Regulatory Members when a new topic is formally adopted. The Regulatory Chair provides regulatory oversight throughout the ICH 5-step process ensuring its timely execution and adherence to the Concept Paper and Business Plan, including scope and timelines. The Regulatory Chair works in close collaboration with the Rapporteur.

**Standards Developing Organisation (SDO):** An organization whose primary activities are developing technical standards.

**Step Process:** The formal ICH process that consists of 5 Steps: Step 1: Consensus Building, Step 2a: Confirmation of Member Consensus, Step 2b: Adoption of Draft Guideline by Regulatory Members, Step 3: Regulatory Consultation and Discussion, Step 4: Adoption of an ICH Harmonised Guideline, and Step 5: Implementation.
**Technical Coordinator:** Support their respective ICH Coordinators and facilitate actions of the ICH Management Committee by applying their scientific knowledge.

**Topic Leader:** Co-participant of a Working Group who leads in the representation of the views of their Member during any ICH interactions with support of the Deputy Topic Leader.

**Work Plan:** A work plan is developed by a Working Group and is used to establish milestones and develop a timeline for completion of activities. Additionally, a Work Plan will include an agenda for any face-to-face meetings.
Introduction

This Standard Operating Procedure (SOP) is intended to provide an overview of the standard processes for the harmonization activities that take place under the ICH Association and to provide guidance for the Working Groups that carry out these activities. The ICH harmonization activities fall into six categories outlined in Table 1 below. These activities include 1) the formal ICH procedure, 2) Q&A procedure, 3) revision procedure, 4) the maintenance procedure, 5) error correction, and 6) Guideline withdrawal. This SOP begins with an overview of the activities that need to occur prior to initiating a harmonization activity followed by a detailed overview of each harmonization process.

Table 1 Summary of ICH Harmonization Processes

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<th>Type of Harmonization Procedure</th>
<th>Technical Discussion Group</th>
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<td>Formal ICH Procedure</td>
<td>EWG</td>
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<td>Q&amp;A Procedure</td>
<td>IWG</td>
<td>Creation of Q&amp;As to assist in the implementation of existing Guidelines</td>
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<td>Revision Procedure</td>
<td>EWG</td>
<td>Revision/modification of existing Guidelines through amendments to content or a Guideline or addition of Addenda or Annexes</td>
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<tr>
<td>Maintenance Procedure</td>
<td>EWG</td>
<td>Updating existing Guidelines; adding standards to existing Guidelines and/or recommendations</td>
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<tr>
<td>Error Correction</td>
<td>EWG/IWG and/or ICH Secretariat</td>
<td>Correction of errors in ICH documents</td>
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<td>Guideline Withdrawal</td>
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The ICH Management Committee is responsible for oversight of the ICH Working Group process and operations (Article 35 (2)(a)) and is therefore, responsible for developing this SOP and approving any revisions. When it becomes apparent that a revision is necessary to the EWG/IWG SOP, it is recommended that the ICH Coordinators from the respective regions work together to develop a recommendation for the ICH MC. Once the MC provides its endorsement for any revisions to this document, the ICH Assembly should be informed of the approved revisions.
1. ICH Harmonization Activities before Step 1

1.1. Selection of New Topics

1.1.1. Topic Nomination and Review
A topic proposal can be submitted by any ICH Member or Observer. New topic proposals should be submitted to the Management Committee (MC) by completing all sections of the New Topic Proposal Template (see Annex 8). The MC will review any topic proposals received, and prioritize proposals that are recommended for endorsement. The MC will then provide a recommendation to the Assembly to endorse any recommended topics and their prioritization. The Assembly will make a decision at the next face to face meeting to either endorse or reject a topic proposal. If the Assembly chooses to endorse the topic that is being proposed for harmonization, an informal Working Group will be established to develop a Concept Paper and a Business Plan, if requested.

In principle, the agreement of all ICH Members of the Assembly is necessary for initiating any ICH harmonisation activities. However, in exceptional cases when Assembly consensus cannot be achieved, the Assembly will proceed to voting where a decision to endorse a new topic proposal will be adopted by majority. Please refer to the ICH Rules of Procedure of the Assembly Section 3.6 and 3.6.1 for a more detailed discussion of the Assembly decision making process and decisions on selection of ICH topics.

1.1.2. Scheduling and Timing for Planning Approach
At minimum, new ICH Guideline topic proposals will be considered in the context of the work plan at least once per year. The MC will review new topic proposals ahead of each biannual ICH Assembly meeting. Topics must be submitted within three months prior to the upcoming Assembly meeting to be considered at the next face to face meeting. Any topic proposals received after the three month deadline will be put into a queue to be considered at the meeting subsequent to the next Assembly meeting. The Assembly will be provided with a copy of the topic proposals that will be considered at the next Assembly meeting no later than one month prior to the meeting. The MC will provide its recommendation to the Assembly during the Assembly meeting.

The Assembly should discuss the necessity to develop a new ICH Guideline, to revise an existing ICH Guideline, or to develop a Q&A document. Any changes to the content of an existing ICH Guideline are considered as a revision of the Guideline. This includes an addendum of a new paragraph and/or partial replacement of the sentence but does not
mean adding an identified list of standards (i.e. level of residual solvents) and/or correction of a typographical error.

1.2. Establishment of an informal Working Group

An informal Working Group is formed prior to an official ICH harmonisation activity with the objectives of developing and finalizing a Concept Paper, as well as developing a Business Plan if the Concept Paper is endorsed. In general, the Management Committee (MC) oversees all operations of an informal Working Group. If an ICH Member proposed a selected topic, that Member will be provided the opportunity to lead the informal Working Group. Otherwise, the MC will designate a Member to lead the informal Working Group. As a principle, informal Working Groups should work by e-mail and tele/web conference and should not need to meet face-to-face. In exceptional cases, an informal Working Group may be allowed to meet face-to-face with the approval of the MC.

1.2.1. Informal Working Group Membership

ICH Members nominate representatives to informal Working Groups. Unless otherwise specified by the Assembly, the official membership of an informal Working Group shall be limited to two representatives per ICH Member per Working Group (one expert shall be designated as Topic Leader and the other as Deputy Topic Leader), and one representative per ICH Observer if requested. At a minimum, every Founding Member should nominate at least one expert to each informal Working Group. Any experts nominated to the informal Working Group should have expertise relevant to the subject matter. The MC reserves the right to allow additional members to join or limit the size of an informal Working Group; however, to support the efficiency and effectiveness of working group operations it is recommended that as a general rule a Working Group should not exceed 25 participants.

The Topic Leaders/Deputy Topic Leaders will participate in the informal Working Group discussions and be the point of contact for any consultation carried out between meetings by correspondence, fax, e-mail etc. It is the responsibility of the Topic Leader/Deputy Topic Leader to officially represent a consolidated view from their Member during any ICH interactions (e-mails and tele/web conferences). An expert from the Member responsible for originally proposing the topic shall be nominated Group Leader and will lead the efforts of the informal Working Group.

To support the work of the informal Working Group, each Member may appoint additional support staff to assist with the preparation of that Member organization’s contributions to the Working Group. Their names would be submitted to the ICH
Secretariat for inclusion on emails for the informal Working Group. These additional staff would generally work outside of the ICH Working Group sessions in their support of ongoing operations of the informal WG and no upper limit of support staff is set per Member. However, a Member’s position should be presented solely by the Experts nominated to the Working Group; additional staff should not opine on technical aspects of the Working Group discussions.

The entire membership of an informal Working Group shall be copied on e-mails and invited to participate in tele/web conferences.

The presence of at least one expert from each Founding Regulatory Member and if nominated, one expert from each Founding Industry Member and Standing Regulatory Member nominated to the informal Working Group, is required to constitute a quorum. Each Regulatory Member and Industry Member appointed to the informal Work Group is expected to actively participate in and contribute to the work of the informal Working Group on a continuous and regular basis until the work is completed to ensure continuity. The absence of an Observer from an informal Working Group meeting will not prevent the meeting from taking place.

1.3. Developing a Concept Paper for a Selected Topic

A Concept Paper is developed by an informal Working Group after a topic proposal has been selected to go forward in the harmonisation process. The Concept Paper provides further context surrounding a proposal and should be completed in accordance with the Concept Paper Template (see Annex 9).

The Concept paper should be a maximum of two pages. If necessary, further documentation and reports may be annexed to the Concept Paper. The Concept Paper should be completed within two months (60 days) following the endorsement of the topic proposal by the Assembly.

The informal Working Group may consult the MC as needed to resolve any issues that may arise during development of the Concept Paper. The MC will work with the informal Working Group to ensure that a Concept Paper is developed in line with the topic proposal endorsed by the Assembly. The Concept Paper should identify any considerations for special subpopulations (e.g. pediatrics) and how the proposed Guideline may need to be tailored to meet the needs of a particular population. The final Concept Paper will be submitted to the MC and Assembly. The MC will provide a recommendation to the Assembly on the decision to endorse the Concept Paper at the next face to face meeting.
When complete consensus cannot be achieved on the Concept Paper within the agreed time frame, the informal Working Group will make a report to the MC indicating the extent of agreement reached and highlighting the points on which differences between the Members remain. Experts from all ICH Members represented on the informal Working Group will have the opportunity to explain their position to the MC. The MC may then:

- Allow an extension of the time frame, if the Working Group can give assurances that consensus could be reached within a short, specified period;
- Provide a recommendation to the Assembly to suspend or abandon the harmonisation project and disband the informal Working Group; or
- Elevate the decision on how to proceed to the Assembly

1.4. Development of a Business Plan

A Business Plan should be developed in alignment with the Business Plan Template (see Annex 10). It is highly encouraged that the Business Plan be developed in parallel with the Concept Paper. The Business Plan will be submitted by the informal Working Group for review and approval by the MC no later than 30 days following endorsement of the Concept Paper by the Assembly, or if needed, a longer time period that is requested by the Working Group and approved by the MC. The informal Working Group will work through e-mail, tele/web conference and, exceptionally, face-to-face meetings to develop a Business Plan.

The Business Plan submitted to the MC will be reviewed for either feedback to/revision by the WG, or approval by the MC. This review will be handled by the MC through tele/web conference, at the next face to face meeting, or by email. The MC will report the decision to approve the Business Plan to the Assembly and following that, an Expert Working Group or Implementation Working Group will be established to initiate harmonization activities.

If in working to develop the Business Plan, consensus among the informal WG cannot be achieved on the Business Plan within the agreed time frame, the informal working group should consult the MC indicating the extent of agreement reached and highlighting the points on which differences between the Members remain. Experts from all ICH Members represented on the informal Working Group will have the opportunity to explain their position to the MC. The MC may then:

- Allow an extension of the time frame, if the EWG can give assurances that consensus could be reached within a short, specified period;
- Provide guidance to the Working Group on how to proceed; or
• Provide a recommendation to the Assembly to modify the scope of the harmonization project or to suspend or abandon the harmonization project and disband the informal Working Group.

1.5. Development of Work Plan by EWG/IWG

An Implementation Working Group (IWG) or Expert Working Group (EWG) is responsible for developing a detailed Work Plan prior to initiation of any work activity. The development of a Work Plan is led by the EWG or IWG Rapporteur with input from the entire Working Group. The Work Plan should follow the template provided in Annex 11 and include anticipated milestones, a timeline for the completion of activities, a summary of any issues, and a justification for a face to face meeting, if requested. The details of a Work Plan should focus on the process steps that will be required to carry out any identified tasks, it is not necessary to provide substantive technical information in the context of the Work Plan. The Work Plan should be updated as needed. This should be done prior to the biannual face-to-face meeting and other key teleconference such as the Coordinators teleconference that takes place approximately 3 months prior to each biannual meeting. The Work Plan for each Working Group will be posted on the ICH Public Website and an updated Work Plan will be shared with the Assembly ahead of each biannual meeting.

1.6. Establishment of the EWG/IWG

Following the Assembly’s endorsement of a Concept Paper and MC’s approval of a Business Plan an Expert Working Group (EWG) or Implementation Working Group (IWG) will be established depending on the type of work to be undertaken. An EWG will be established for the development or revision of new or existing Guidelines and an IWG will be established for the development of a Q&A document. In general, the Management Committee (MC) oversees all operations of a Working Group (WG). The timing of the establishment of the EWG or IWG should align with the priorities of the ICH in accordance with the 5-year strategic plan. If a harmonization project is abandoned at any time the EWG or IWG should be dissolved.

1.6.1. EWG/IWG Membership

The ICH Members nominate representatives to EWGs and IWGs. The Founding Regulatory Members are required to appoint an expert to all EWGs and IWGs. Founding Industry Members, Standing Regulatory Members and other Assembly Members are not required to appoint technical experts in all EWGs/IWGs. Unless otherwise specified by the Assembly, the Membership of an EWG/IWG shall be limited to two representatives per ICH Member per Working Group (one expert shall be designated as Topic Leader and the other as Deputy Topic Leader), and one representative per ICH Observer.
Any ICH Observers who would like to participate in an EWG or IWG should submit a request in writing to the MC with an explanation of their anticipated contribution to the Working Group (WG) (see Annex 12). The ICH Observers may nominate an alternate member to the WG, who shall be added to the email list, which may replace the representative for the Observer if he or she is unable to participate. Any experts nominated to an EWG or IWG should have expertise relevant to the subject matter. The MC reserves the right to allow additional members to join a WG or limit the size of the WG. However, as a general rule, to support the efficiency and effectiveness of working group operations, a WG should not exceed 25 participants.

The Topic Leaders/Deputy Topic Leaders will participate in the EWG discussions and be the point of contact for any consultation carried out between meetings by correspondence, e-mail etc. It is the responsibility of the Topic Leader/Deputy Topic Leader to officially represent a consolidated view from their Member, during any ICH interactions (e-mails, tele/web conferences and face-to-face meetings).

To support the efficiency and effectiveness of Working Group (WG) operations, an expert should not be appointed to work in more than one Working Group at a time. However, in exceptional cases the MC can decide that an expert may serve on more than one WG and the merits outweigh the adverse impacts on the work process for the other experts on the WG. Additionally, it is encouraged for an expert on a given WG to serve as a liaison across WGs when appropriate due to similarities in the scope of technical issues and to ensure complementarity across topics (e.g. liaison for M2 and E2B).

Where appropriate, additional experts may contribute to the discussion but the official voice of each delegation rests with the Topic Leader and his Deputy. ICH Regulatory Members may nominate additional personnel (e.g. "MHLW Officials" for MHLW/PMDA) to the EWG mailing list for information only.

As a general principle, new Members and Observers to the ICH Association can nominate an expert to a Working Group at any time during the step process within the first year of their membership. However, in exceptional cases the MC may designate that new Members can only join an already in-progress Working Group after a specified milestone has been achieved. Additionally, the MC may limit a new Member’s participation in a Working Group if the size of the Working Group would exceed a reasonable number.
Additional Experts: If an EWG/IWG Member wishes to include an additional expert to serve in a consulting capacity to address (and limited to) a specific technical issue or set of issues within the scope of the Assembly endorsed Concept Paper, the Member will need to communicate this to the EWG/IWG Rapporteur and Regulatory Chair and notify their respective coordinator. Additionally, the member should submit the expert’s name to the ICH Secretariat so the Secretariat can notify the coordinators from the other regions. To ensure the continued smooth operation of the EWG/IWG and adhere to the limits on the number of each Member’s representatives the involvement of additional experts should be managed, firstly by the Member’s Topic Leader and Deputy Topic Leader for that WG and also by the active management of the Rapporteur and Regulatory Chair as needed. As noted above, where appropriate, additional experts may contribute to the discussion but the official voice of each delegation rests with their Topic Leader and Deputy Topic Leader and they are not expected to participate outside the scope of their agreed-upon role.

An editor should be identified during the formation of an EWG or IWG. It is the responsibility of the editor to ensure that Guidelines, Q&As, and Technical Documents are formatted according to the ICH style guide. Ideally, the editor should be nominated from one of the already existing experts however, in exceptional cases the MC reserves the right to decide if an additional expert should be nominated to the Working Group for the sole responsibility of editing any documents.

1.6.2. Appointment of the Regulatory Chair and Rapporteur

The ICH Regulatory MC Members officially designate a Regulatory Chair from the Regulatory Members and the Assembly officially designates a Rapporteur among the Topic Leaders designated by the ICH Members when a new ICH topic is formally adopted. In general, the Regulatory Chair and the Rapporteur should be from different regions. In addition, in order to effectively perform the role of Regulatory Chair, the appointed individual should not be nominated as an expert to more than one active WG and by the same token should not serve as Regulatory Chair on more than one WG.

In exceptional cases, both a Rapporteur and a Co-Rapporteur may be appointed. Whenever possible, Co-Rapporteurs should be from different regions and should not both be from a Regulatory or Industry Member. If an Industry Member is appointed to be the Rapporteur for a Working Group, a Regulatory Member will need to replace the Industry Member following completion of Step 2b; however, the Industry Member will still be invited to participate in the Working Group discussions going forward.
Members who have nominated experts as either a Regulatory Chair or Rapporteur may nominate one additional representative to the WG. Additionally, it is encouraged that a Member serving as either the Regulatory Chair or Rapporteur nominate someone to serve as a project manager to assist in the going operations of the Working Group such as note taking and scheduling of meetings.

In the case that external expertise may be helpful, and subject to Assembly approval in consultation with the MC, a WG may also consider inviting one or two liaisons from an entity outside of ICH to participate in the WG as an ad hoc Observer to provide additional technical expertise. The level of participation would be decided by the Assembly (e.g., tele/web conference, emails, and face-to-face meetings).

1.6.2.1. **Roles and Responsibilities of the Regulatory Chair**

The role of the Regulatory Chair is to ensure timely execution of the ICH process and adherence to the Concept Paper and Business Plan, including scope and timelines. The Regulatory Chair shall work in close collaboration with the Rapporteur.

Responsibilities of the Regulatory Chair include:

1. Ensuring timeframes are met and work is within the scope of the EWG/IWG mandate.
2. Collaborating with the Rapporteur in developing a work plan that is consistent with the scope and time frame of the Assembly-approved Concept Paper and MC-approved Business Plan.
3. Regularly reporting to the MC on progress of the EWG/IWG regarding timeliness, adherence to scope and conflicting views if they arise and ensuring that all expert perspectives are reflected in the documents presented to the MC and Assembly.
4. If conflict arises, working with the Rapporteur to achieve consensus within the EWG/IWG by reconciling divergent views. If the Regulatory Chair and the Rapporteur fail to achieve consensus, the Regulatory Chair will elevate the issue to the MC for resolution as early as possible.
5. Addressing the behavior of any expert within the EWG/IWG that is disruptive or is not constructive, in consultation with the Regulatory Chair’s Coordinator. (see Annex 2—Ground Rules for Good Practices of ICH Working Groups)
6. Deciding when it is necessary to document significant differences of position or conflicting views among members of the EWG/IWG and will work on this task with the assistance of the Rapporteur.
In exceptional circumstances, the MC reserves the right to replace a Regulatory Chair when it is considered necessary for a WG to progress according to plan.

1.6.2.2. Roles and Responsibilities of the Rapporteur

When a new ICH Topic is formally adopted, the Assembly appoints the Topic Rapporteur among the Topic Leaders designated by the ICH Members. In exceptional cases, a Co-Rapporteur may also be appointed to assist the Rapporteur. Whenever possible, Co-Rapporteurs should be from different regions and should not both be from a Regulatory or Industry Member. If the Rapporteur is a representative from one of the Industry Members, the Rapporteur role will then have to be transferred to a Regulatory Member after Step 2b is reached. In general, to ensure the independence and efficiency of the two key leadership roles of a WG, the role of the Rapporteur and Regulatory Chair should be assumed by two different Members. In general, a single Regulatory Member should not assume the role of both the Regulatory Chair and Rapporteur except in exceptional cases and with explicit agreement of the Assembly.

The role of the Rapporteur is to serve as the scientific co-chair, to facilitate and manage scientific and technical activities of the EWG/IWG, reconciling scientific differences of opinion, in order to produce an ICH document with the scientific and technical content that is in accordance with Assembly decisions/expectations. The Rapporteur shall work in close collaboration with the Regulatory Chair.

Responsibilities of the Rapporteur include:
1. Develop a detailed work plan in collaboration with the Regulatory Chair that will achieve the technical objectives outlined in the ICH Assembly-approved Concept Paper and MC-approved Business Plan and contains clear technical deliverables and associated deadlines; the updated work plan, approved by the whole EWG, shall be provided ahead of Coordinator/MC web conference for MC consideration.
2. Maintaining a record of participation of the ICH Members nominated to the Working Group.
3. Responsible for day-to-day management including setting deadlines, assigning work to the members of the EWG/IWG and assuring all ICH Members’ views are incorporated into documents and presentations as appropriate.
4. The Rapporteur shall seek to reconcile scientific and technical differences among EWG/IWG members.
5. The Rapporteur shall make sure that the views of the different Members are reflected in an appropriate and fair manner in any outcomes of the EWG/IWG work.

6. The Rapporteur shall regularly present reports to the Assembly, on the technical and scientific aspects of the document under development.

7. Upon reaching Step 4, the Rapporteur shall ensure the development of a presentation for review by EWG/IWG members, and provision to the ICH Secretariat to be included in a library of presentations and implementation materials made available on the ICH public website.

In exceptional circumstances, the MC may provide a recommendation to the Assembly to replace a Rapporteur when it is considered necessary for a WG to progress according to the plan.

1.6.3. Meetings of the EWG/IWG
Any face-to-face meetings of a WG will be subject to decision by the MC. WGs shall not systematically meet in conjunction with every Assembly meeting if not justified. In order to minimize organizational and logistical costs of the ICH Process, WGs should meet face-to-face only when necessary and justified and when sufficient discussion materials are available. Interim face-to-face meetings (i.e., WG meetings outside the regular ICH Assembly meetings) should be exceptional, and only when there is an absolute necessity in order for the topic to meet its assigned objectives in time. ICH WGs are encouraged to communicate through e-mail to progress draft Guidelines between face-to-face meetings and tele/web conferences.

ICH does not cover the cost of travel or accommodation for WG participants. Participation is at the expense of the Member or Observer concerned.

For logistical purposes, it is essential that in preparation for any official biannual face-to-face meeting, each ICH Member communicate the names of its representatives to the ICH Secretariat, and that the host organisation is informed of each Member delegation well in advance of the meetings. The ICH Secretariat shall keep a record of experts’ nominations.

1.6.4. Meeting Attendance
A quorum, consisting of representatives of those Members who are required to appoint an expert to all EWGs and IWGs, is required at minimum in order for an ICH EWG/IWG meeting to occur. The presence of at least one expert representative from each Founding Regulatory Member and if nominated, one expert from each Founding
Industry Member and, if nominated, one expert from each Standing Regulatory Member is required to constitute a quorum. However, all Regulatory Members and Industry Members who have appointed expert representatives to the WG are expected to actively participate in and contribute to the work of the WG on a continuous and regular basis until the work is completed to ensure continuity. Section 4.3.7 of the ICH Rules of Procedure of the Assembly also outlines the criteria and expectations for participation of Observer experts appointed to a WG. It should be noted that the absence of an Observer from a WG meeting will not prevent the meeting from taking place.

The requirement for continuous and regular participation is intended to ensure both the benefit of continued contribution of the Member representative’s expertise, and to minimize the harm or disservice to the WG’s already-challenging process from disruptions or lost time for the other experts due to needed repetition and revisiting of the same issues, discussions, or decisions for the benefit of the expert who was repeatedly absent. If a Member’s expert representative is absent from a WG meeting where a decision was made, that member shall not request that the WG revisit decisions made in that Member’s expert’s absence. If an appointed expert is absent from two consecutive meetings of a Working Group (either face to face or through teleconference) and it appears that expert will continue to be absent, the ICH Member should appoint another qualified expert.

If the ICH Member's expert has been absent from two consecutive meetings, and if no other qualified expert from that Member participates in the subsequent meeting of the Working Group, the Regulatory Chair and Rapporteur should provide a report to the MC. The Regulatory Chair and Rapporteur should report on the impact of that expert’s absence from the working group and may provide a recommendation on how to proceed to the MC. The MC will make a decision on how to proceed; however, in principle that Member will lose its right to appoint an expert to that working group after two subsequent absences. Refer to the ICH Rules of Procedure of the Assembly Section 4.3 for a more detailed discussion of the expectations for expert participation in working groups and the consequences of failure to maintain participation on a continuous and regular basis.
2. ICH Process for Each Harmonization Activity

This section provides an overview of the process for each harmonization activity including the formal ICH procedure, the Q&A procedure, and the procedures for revision, maintenance, and error correction of ICH documents.

2.1. Formal ICH Procedure by EWG

The Formal ICH Procedure is a step-wise procedure that is used to develop a harmonised Guideline for implementation within each Member’s region and consists of 5 steps. This procedure is used for new Guidelines and is initiated following the endorsement of a Concept Paper by the Assembly.

Each Member is responsible for following any internal processes that are required for that Member to provide their endorsement for, or adoption of, an ICH product. For example, the review of a final Guideline by a Member’s legal counsel may need to occur before that Member can endorse the Guideline in the Assembly. To facilitate this process, a Working Group should aim to have a draft document prepared for internal review one month in advance of a face to face meeting. In the event that significant changes are made to a document during a biannual face-to-face meeting and the working group is requesting endorsement or adoption by the Assembly, a Member’s internal approval procedure should be considered, and sufficient time be allowed for these processes. However, each Member should work to complete any additional internal approval during the course of the face to face meeting so as not to delay the decision of the Assembly, particularly in instances where adoption of a final guideline is being requested.

2.1.1. Step 1: Consensus Building – Technical Document

In step 1 of the Formal ICH Procedure, the EWG works together to prepare a consensus draft of the technical document based on the objectives set out in the Concept Paper. The Rapporteur prepares an initial draft of the technical document in consultation with the experts appointed to the EWG. The initial draft and successive revisions are discussed among the EWG and circulated with comments. Each Member with experts appointed to the EWG is responsible for providing any comments within the allotted timeframe.

To the extent possible, the EWG will work by e-mail and teleconferences. Face-to-face meetings of the EWG will normally only take place at the time and venue of the biannual Assembly meetings. Additionally, face-to-face meetings of the ICH EWG need to be agreed, in advance, by the Management Committee (MC).
The EWG should consult the MC if any issues arise during Step 1 that could delay the timeline, or if there are any issues that may make it difficult for the EWG to reach consensus.

The EWG Regulatory Chair and Rapporteur will provide an interim report at each meeting of the Assembly.

2.1.1.1. **Step 1 Experts Sign-Off**

When the EWG reaches consensus on the technical document, the experts of the EWG will sign the Step 1 Experts Sign-off sheet (see Annex 13). The consensus text approved by the ICH Members’ experts in the EWG is signed-off by those experts as *Step 1 Technical Document*. Once the EWG signs off on the technical document, the *Step 1 Technical Document* with expert signatures is submitted to the Assembly to request endorsement under Step 2a of the ICH process. After Step 1 has been reached, the Working Group should provide, to the MC, an estimate of the length of time for the public consultation period in each region.

In exceptional circumstances where the EWG cannot come to full consensus on all aspects of the technical document, the Regulatory Chair with support of the Rapporteur will provide a report to the MC indicating the extent of agreement reached and highlight points where there are differences among Members. Experts from all ICH Members represented on the EWG will have the opportunity to explain their position to the MC.

The Regulatory Chair with support of the Rapporteur will propose a potential resolution to the MC (such as preparing a technical document that includes the different alternatives which are supported by the experts or minority opinions).

The MC may then:

- Allow an extension of the timetable, on the basis that the EWG can give assurances that consensus could be reached within a short, specified period;
- Request the EWG to develop a technical document, intended to inform further MC discussion and decision making, that identifies and analyzes different alternatives reflecting those positions which are supported by a minority as well as those supported by the majority of EWG experts;
- Provide guidance to the EWG/IWG to proceed with a certain course of action or elevate the decision to the Assembly;
- Decide to recommend to the Assembly to suspend or abandon the harmonisation project and disband the EWG/IWG.
If consensus is reached following work under the extended timetable or further analysis of alternatives, then the EWG will sign the *Step 1 Experts Sign-off sheet*. In the event that an EWG reaches consensus between an ICH biannual meeting, the ICH Secretariat will organize a postal (electronic) sign-off at the expert level.

2.1.2. **Step 2a: Confirmation of consensus on the Technical Document**

In Step 2a, the MC will provide a recommendation to the Assembly on the decision to endorse the final Technical Document, based on the report of the EWG that there is sufficient scientific consensus on the technical issues for the Technical Document and recommendation to proceed to the next stage of regulatory consultation.

The consensus text is endorsed by the Assembly as a *Step 2a Final Technical Document* either during a face to face meeting or through an electronic approval procedure that is organized by the ICH Secretariat. Ideally, an EWG would provide the technical document one month in advance of a face-to-face meeting where endorsement will be requested, however, a revised version may be submitted closer to the meeting, or during the meeting, if necessary.

Irrespective of whether or not an Assembly Member has appointed technical experts in a Working Group, all Members will be invited to endorse the Step 2a as ICH Members.

In the unlikely situation where consensus cannot be reached, the Assembly will proceed to voting where a decision to endorse the Step 2a Final Technical Document will be adopted by majority. If the majority votes to endorse Step 2a then the Assembly’s endorsement will be captured in the Assembly Meeting Report. Please refer to the *ICH Rules of Procedure of the Assembly* Section 3.6 for a more detailed discussion of the Assembly decision making process.

2.1.3. **Step 2 for Testing (Optional)**

*Step 2 for Testing* is an optional step where the proposed implementation guide, standard, or specification is tested by an ICH Member against the ICH requirements (e.g. business, technical, system and functional requirements) to confirm technical adequacy. An Observer may also participate in the testing; however, this is not required. The ICH Secretariat will publish a consensus document on the ICH website for review of the proposed implementation guide, standard, or specification by the public. The document will be published in English only and it will not be required to be translated by ICH into other languages. Testing is intended to be conducted by the ICH regions, however, comments will be considered from external parties. *Step 2 for Testing* may be repeated if considered necessary. The duration of *Step 2 for Testing* is
flexible and may be set based upon the timescale allowed by the project of concern (e.g. Standards Development Organisation (SDO) ballot timelines or target for ICH Step 2).

*Step 2* for Testing is particularly relevant to an EWG that develops an ICH Implementation Guide as part of an SDO project where the ICH step process is aligned with SDO processes. *Step 2* for Testing is conducted to assess technical feasibility of proposed SDO solutions prior to ICH *Step 2* because there is a greater ability to influence the degree of modification of technical solutions at this stage of development rather than at later stages.

*Step 2* for Testing is distinguished from general feasibility testing in the sense that feasibility testing can be conducted at any time during the development of a technical standard in an informal way.

### 2.1.4. *Step 2b: Adoption of the Draft Guideline*

On the basis of the Final Technical Document, the ICH Regulatory Members will take the actions they deem necessary to develop the “draft Guideline”. The consensus text of the draft Guideline is endorsed by the Regulatory Members of the ICH Assembly as *Step 2b Draft Guideline* either during a face to face meeting or through an electronic approval procedure that is organized by the ICH Secretariat.

Each ICH Regulatory Member will be invited to endorse the *Step 2b Guideline* as an ICH Member irrespective of whether or not that Member has appointed technical experts to the Working Group. Ideally, an EWG should provide the draft Guideline one month in advance of a face-to-face meeting where endorsement will be requested, however, a revised version may be submitted closer to the meeting, or during the meeting, if necessary.

In the unlikely situation where consensus cannot be reached, the Regulatory Members of the Assembly will proceed to voting where a decision to endorse the *Step 2b Draft Guideline* will be adopted by majority. If the majority votes to endorse *Step 2b* then the Assembly’s endorsement will be captured in the Assembly Meeting Report. Please refer to the *ICH Rules of Procedure of the Assembly* Section 3.6 for a more detailed discussion of the Assembly decision making process.

The draft Guideline will be made public on the ICH website after Step 2 is reached.
2.1.5. Step 3: Regulatory Consultation and Discussion

Step 3 is divided into three phases including 1) regional consultation, 2) discussion of regional comments, and 3) Step 3 Experts Sign-Off by the regulatory experts.

a) Regional regulatory consultation

At this step, the Step 2b draft Guideline leaves the ICH process and becomes the subject of normal wide-ranging regulatory consultation in each of the Member’s regions. For example, in the EU it is published as a draft CHMP Guideline, in Japan it is translated and issued by MHLW for internal and external consultation and in the USA it is published as draft guidance in the Federal Register with a request for public comment. Swissmedic refers input to the EU consultation and Health Canada solicits its own public comments on draft ICH Guidelines.

Each region’s public consultation period may range from 30 days up to 6 months for more technical Guidelines. Prior to entering Step 2b each Member should report the planned length of their consultation period to the Working Group and the ICH Secretariat.

Following the close of all the regional comment periods, the Regulatory Members review and exchange information on the comments they have received from the public in the various regions, and consider what further revisions to the Step 2b draft Guideline might be needed in order to arrive at a single, harmonised Guideline. There is also an opportunity for Industry Associations and Regulatory Authorities in other regions to comment on the draft consultation documents, which are distributed by the ICH Secretariat via the ICH website.

b) Discussion of regional consultation comments

After obtaining all regulatory consultation results, the EWG that organised the discussion for consensus building will be resumed – including both Industry and Regulatory expert representatives. If the Rapporteur was designated from an industry Member until Step 2b, then a new Rapporteur will be appointed from the regulatory Member, preferably from the same region as the previous Rapporteur. The same procedure described in Step 1 is used to address the consultation results. Although an Industry Member cannot serve as a Rapporteur following step 2b of the Formal ICH Process, Industry Members are expected to continue to participate in the working group until a final harmonised Guideline is developed. The draft document to be generated as a result of the Step 3 phase is called Step 3 Experts Draft Guideline.
c) Finalisation of Step 3 Experts Draft Guideline

If the experts from the ICH Regulatory Members reach consensus on a revised version of the Step 2b Final Draft Guideline after consideration of the consultation results, the *Step 3 Experts Draft Guideline* is signed by the EWG experts of the ICH Regulatory Members. The Step 3 Document with regulatory EWG signatures is submitted to the Assembly to request adoption as Step 4 of the ICH process.

This Step 3 Document with regulatory EWG signatures is named *Step 3 Draft Guideline*, and this sign-off is called the *Step 3 Experts Sign-off*. In the event that an EWG reaches consensus on a revised version of the Step 2b Final Draft Guideline between ICH biannual meetings, the ICH Secretariat will organize a postal (electronic) sign-off at the expert level. For these Working Groups who will not be attending the next biannual face-to-face meeting of the ICH Assembly, the electronic sign-off should be completed at least 2 weeks before an Assembly meeting, to ensure the Guideline can be adopted by the Assembly at the next meeting. If the sign-off is not completed ahead of the Assembly meeting, it may be necessary and likely that the adoption of the Guideline will be delayed until the next meeting of the ICH Assembly.

Where complete consensus has not been achieved within the agreed time frame, the Regulatory Chair in support of the Rapporteur will make a report to the Regulatory Members of the MC indicating the extent of agreement reached and highlighting the points on which differences between the parties remain. Experts from all ICH Parties represented on the EWG will have the opportunity to explain their position to the Regulatory Members of the MC. The Regulatory Members of the MC may then:

- Allow an extension of the time frame, if the EWG can give assurances that consensus could be reached within a short, specified period;
- Decide to recommend to the Regulatory Members of the ICH Assembly to abandon the current draft and resume the discussion from Step 1;
- Decide to recommend to the Regulatory Members of the ICH Assembly to suspend or abandon the harmonisation project and to disband the EWG.

2.1.6. Step 4 – Adoption of an ICH Harmonised Guideline

In Step 4 of the ICH process, the Assembly adopts a harmonised Guideline in consultation with the MC. This adoption is based on a recommendation by the MC and the consensus of the ICH Assembly Regulatory Members affirming that the Guideline is recommended for adoption by the Regulatory Members of the ICH regions. Ideally, the Guideline should be provided to the Assembly one month in advance of a face-to-face meeting where adoption will be requested, however, a revised version may be submitted closer to the meeting, or during the meeting, if necessary. In exceptional
cases when Assembly consensus cannot be achieved, the Assembly will proceed to voting where a decision will be adopted by majority. Please refer to the ICH Rules of Procedure of the Assembly Section 3.6 for a more detailed discussion of the Assembly decision making process.

2.1.7. Step 5 – Implementation
Once step 4 is reached, the harmonised Guideline moves to the final step of the process and is implemented by each of the Regulatory Members in their respective regions. The harmonised Guideline is implemented according to the same national/regional procedures that apply to other regional regulatory Guidelines and requirements, as for example, in the EU, Japan, the USA, Canada, and Switzerland.

Information on the regulatory action taken and implementation dates are reported back to the Assembly and are published by the ICH Secretariat on the ICH website.
2.2. Q&A Procedure by Implementation Working Group

The Q&A Procedure is followed when additional guidance is considered necessary to help with interpretation of a Guideline and ensure consistent implementation in the ICH regions. A need for additional guidance is generally identified when a large number of questions are received during the Step 5 phase (regional implementation) after the Guideline has been finalised by the ICH. The Q&A process is intended to be a mechanism by which questions received from stakeholders are collected, analyzed, reformulated, and ultimately used as model questions for which standard answers are developed and posted on the ICH website. Incoming questions will not be answered individually but will serve to highlight areas that need additional clarification and will be used to develop a model question that will be answered in the Q&A document.

A Q&A document should only be developed following completion of a Guideline; however, in the course of Guideline development it may become apparent to an EWG that a Q&A will be necessary. In that event, an EWG may recommend to the Assembly that a Q&A be developed immediately following finalization of a Guideline.

2.2.1. Process for Q&A Development

The Assembly, in consultation with the MC, will need to endorse all Q&A activities. Proposals for development of a Q&A should be submitted by completing a new topic proposal template and following the process outlined in section 1.1 Topic Nomination and Review of these EWG/IWG Rules of Procedure. The MC will review all Q&A recommendations following the same procedure that is used for the review of new topic proposals and provide a recommendation to the Assembly on the decision to endorse the development of a Q&A document.

Once the Assembly has endorsed the development of a Q&A document, an informal Working Group should be established to develop a Concept Paper. The same process applies for the establishment of an informal Working Group and review of a Concept Paper as in section 1.2 - Establishment of an informal Working Group and section 1.3 - Developing a Concept Paper for a Selected Topic, respectively, of this EWG/IWG SOP. Once a Concept Paper is endorsed by the Assembly, an Implementation Working Group (IWG) should be established to develop the Q&A according to section 1.5 Establishment of the EWG/IWG of this SOP. The Management Committee (MC) will be responsible for overseeing the operations of the IWG and resolving any obstacles that may arise or elevating decisions to the Assembly when necessary. A Business Plan is not required for all Q&A documents however, for major implementation activities it is recommended that the MC consider whether a Business Plan should be required.
When an IWG is established, the ICH Secretariat will create a mailbox for the IWG that will be accessible through the public ICH website. Any questions sent to the mailbox, or raised by any of the ICH Members, and/or by the ICH Observer, will be brought to the attention of the appropriate Working Group. The regional questions and issues should first be handled by the Regulatory Member of the concerned region then shared and evaluated within the IWG, if applicable. Once the IWG has completed its work, the mailbox for that IWG will be deactivated.

The **Formal Step Process** outlined in section 2.1 of this SOP applies to the development of a Q&A document. The IWG Rapporteur in collaboration with the Regulatory Chair will send the questions to the members of his or her IWG. Based on this information, the IWG will prepare model questions and their responses for presentation at the Assembly meeting. An answer developed in response to a question must fall within the original scope of the Guideline, the answer cannot introduce new issues that were not previously discussed in the harmonized Guideline.

Based on the level of guidance given by the answers, the IWG will assess whether the Q&A document should proceed to Step 2b and then be published for comments or if it should be signed off by the regulatory experts at step 3 and submitted to the Assembly for adoption at Step 4 and published as final.

- The document should go through public consultation and proceed to Step 2b if, by the answers provided, it sets forth substantial new interpretations of the Guideline(s).
- The document should not go through public consultation and proceed to Step 3 sign-off if, by the answers provided, it sets forth existing practices or minor changes in the interpretation or policy of the guideline(s).

The IWG will provide its recommendation on the decision to go through public consultation to the ICH MC. The MC may in some circumstances where the Q&A document is of policy significance, elevate the decision for Assembly endorsement.

The Assembly will need to endorse the Q&A document and its (Step) status either through e-mail or during a meeting of the MC. The document will then follow the normal path of a Step 2b / Step 4 document as follows:

- **For documents going through public consultation:** Following agreement on the technical content of the Q&A through sign-off by the experts of the IWG as Step 1 and the endorsement of the ICH Members of the Assembly at Step2a, the IWG will proceed to Step 2b. In Step 2b, the Regulatory Members of the Assembly will
endorse the Q&A document as Step 2b. The document will then be published for comments in the ICH regions.

- For documents that will not go through public consultation: Following agreement of the technical content of the Q&A within the IWG, the Regulatory experts of the IWG will sign the Q&A document as a Step 3 Final Document and then the Regulatory Assembly members will be invited to adopt it as final at Step 4.

The Final Q&A document will be posted on the ICH website within four weeks after it has been endorsed by the Assembly.

If an IWG is working on several answers in a single Q&A document and it becomes apparent that some of the answers may require considerably more time than others, an IWG may decide, with MC approval, to publish the answers sequentially in batches so that some of the answers will be more readily available while the remaining answers are further deliberated. The IWG will assess, and obtain Assembly adoption at step 4, for each batch of questions published.

### 2.3. Revision Procedure

The revision procedure is used when the scientific/technical content of an adopted Guideline is no longer up-to-date or valid and needs to be revised or modified. Additionally, the revision procedure can be used in cases when there is new information to be added to an existing Guideline. The formal ICH step process in section 2.1 of this EWG/IWG SOP should be followed for all revision activities in conjunction with the process outlined below.

The Assembly, in consultation with the MC, will need to endorse all revision activities. Proposals for the revision of a guideline should be submitted by completing a new topic proposal template (see Annex 8) and following the process outlined in section 1.1 - Selection of New Topics of this SOP. The MC will review all Guideline revision proposals following this process and provide a recommendation to the Assembly on the decision to endorse the revision of an ICH Guideline.

If the Assembly endorses the revision of an existing Guideline, an informal Working Group should be established to develop a Concept Paper and Business Plan. The same process applies for the establishment of an informal Working Group and review of a Concept Paper and Business Plan as in section 1.2 - Establishment of an informal Working Group, section 1.3 - Developing a Concept Paper for a Selected Topic, and 1.4 Business Plan respectively, of this EWG/IWG SOP. Once a Concept Paper is endorsed by the Assembly, an Expert Working Group (EWG) should be established to develop the Q&A according to section 1.5 Establishment of the EWG/IWG of this SOP. The Management Committee (MC) will be
responsible for overseeing the operations of the EWG and resolving any obstacles that may arise or elevating decisions to the Assembly when necessary.

If an adopted Guideline needs to be revised, then the formal ICH step procedure should take place. However, if minor errors are discovered following implementation of a Guideline or if it becomes apparent that the use of certain terminology is causing misinterpretation of a Guideline, the EWG who developed the original Guideline may be reconvened to discuss any necessary revisions. The EWG will work with the Coordinators and MC to determine if the proposed revisions warrant the Formal Step Process.

There are two approaches for revision of an existing ICH Guideline.

- The first approach involves amendments being made directly to the content of the existing guideline e.g., in cases where the scientific/technical content is no longer up-to-date or valid.
- The second approach is where the existing text in the original guideline is not modified, but instead an Addendum or Annex to that guideline is developed. The latter approach is used where no amendments to the content of the existing guideline are necessary but there is a need to provide further complementary guidance.

In addition, there are two types of addenda: 1) an Addendum, and 2) an Integrated Addendum. For an Addendum, the additional or new text is added at the end of the current ICH Guideline. In contrast, an Integrated Addendum is developed when the purpose of the Addendum is to clarify or augment specific section(s) of an ICH Guideline and text is inserted right after the relevant paragraph(s) within the original guideline. Additionally, integration of the Addendum text into the original Guideline should be used to avoid many cross references and for easier reading of the Guideline. The clarifying content added after specific sections of the Guideline should be formatted in a specific way to facilitate its distinction from the original text by the reader. The format of the Addendum (i.e. which of the two types just described) should be recommended in the Concept Paper.

The “Revision Procedure” is almost identical to the formal ICH procedure, i.e., five ICH steps. The only difference, compared to the formal Step Process, is the final outcome. For a Guideline revision, the final outcome will be a revised version of a currently existing Guideline, whereas in the formal Step Process, the final outcome is a new Guideline.

In cases where an Addendum or Annex has been developed, upon reaching Step 4 the Addendum or Annex is added to the existing Guideline resulting in a revised Guideline.
The revision of a Guideline is designated by the letter R1 after the usual denomination of the Guideline. When a Guideline is revised more than once, the document will be named R2, R3, R4, (etc.) at each new revision.

If in the creation of a Q&A document it becomes apparent that a revision to the original Guideline is necessary, an EWG may provide a recommendation to the Assembly in consultation with the MC to establish an informal Working Group to discuss the type of modifications needed and develop a Concept Paper. To increase efficiency, the same members as those forming the IWG may develop both the Q&A document and revise the ICH Guideline.

In the case of Q4B, topic-specific Annexes are developed to provide information on how pharmacopoeial texts can be used at a national/regional level. Each Annex is issued as a stand-alone companion document to the Q4B Guideline, with each Annex assigned a number in sequential order e.g., Annex 1, Annex 2, Annex 3 etc.

2.4. Maintenance Procedure
This procedure specifically applies to the Q3C Guideline (residual solvents), Q3D Guideline (elemental impurities), Q4B Annexes, M7 (genotoxic impurities) and M2 Recommendations.

Updates to the Q3C, Q3D, and M7 Guidelines (Parent Guideline or Addenda) and the Q4B Annexes are considered as revisions and are designated by the letter R.

M2 Recommendations constitute an exceptional case, because no Step 2b Document is required. However, the Management Committee may request further clarification. In such cases, a Step 2b document may be necessary. Each new version of the M2 Recommendations is designated by a different version number.

The Maintenance Procedure also extends to any ICH Guideline which contains out-of-date information (e.g., out-of-date references, links etc...) which can be updated by the ICH Secretariat without the establishment of an EWG. Such updates require MC approval and are also considered revisions and assigned the letter R.

2.5. Error Correction
The ICH Secretariat may correct obvious typographical errors. In this case, no approval from the Management Committee is required.
In some cases where more substantial corrections are needed (e.g., editorial mistakes, errors/inaccuracies), a technical expert discussion may be necessary. This case would therefore undergo the Revision Procedure.

All editorial mistakes (i.e., changes in the wording, the grammar in order to keep with consistency and clarity) and errors/inaccuracies (i.e., wrong meaning needing correction), even if minor, should be corrected by the Working Group and require approval by the Management Committee and should be communicated to the Assembly.

2.6 Guideline Withdrawal
Under exceptional circumstances an ICH Guideline may be withdrawn. Such actions require substantial justification and endorsement by the ICH Assembly in consultation with the Management Committee.
3. Additional Activities during the Course of ICH Harmonization

During the course of the ICH harmonisation activities outlined in the previous sections, the Management Committee (MC) may authorize a Working Group to carry out other tasks intended to provide additional information complementary to a topic that is undergoing one of the above categories of harmonisation. These activities are outlined below and include development of an Options Paper, a Points to Consider document, a Proof of Concept, or an Implementation Package.

3.1 Options paper

An Options Paper is used when experts on a Working Group have differing viewpoints and cannot come to consensus on how to proceed with a harmonization activity. The Regulatory Chair should facilitate development of an Options Paper following a request from the MC. The Options Paper should clearly articulate the differing views of the Member’s experts of the WG, and the advantages and disadvantages of proceeding with the proposed options. The MC will use the Options Paper to provide a recommendation to the Assembly on how to best proceed for a given harmonization activity. All experts should sign-off on the Options Paper however, further endorsement is not necessary.

3.2 Points to Consider

A Points to Consider (PtC) document may be developed to provide additional clarity on an ICH document and/or to develop best practices. When proposing a new PtC document, a proposal and Concept Paper should be submitted to the ICH Assembly for approval. The PtC documents are not subject to regional implementation, but provide a best practice approach. The final document will need to be signed-off by the experts who developed the document and endorsed by the Assembly.

3.3 Proof of Concept

A Proof of Concept (POC) is used to test the viability of a specification such as enabling the transfer of regulatory information by electronic means. In the case of M2/M5/E2B(R3), the POC concerns testing the viability of using M2’s message specifications to exchange information.

3.4 Implementation Package

An Implementation Package may be developed following adoption of a Guideline to provide instruction on how a Guideline should be implemented (e.g. how to use a particular standard). The same Expert Working Group that developed the Guideline should be maintained or reconvened to develop the Implementation Package. The Implementation Package should include an Implementation Guide as the core document and this should describe how the standard will be implemented to meet ICH requirements. The Implementation Package should also include any associated technical files such as technical data standards, controlled
vocabularies for field usage, or additional supporting documentation (e.g. orientation materials) needed to fully implement a particular standard.

Development of the Implementation Package should follow the formal step process outlined in Section 2.1 Formal ICH Procedure by EWG of this SOP. Following completion of the Implementation Package, an Implementation Working Group may be established to maintain the standard and to address change requests.
Annex 1: Roles and Responsibilities

This Annex provides an overview of the roles and responsibilities of the ICH Management Committee, Assembly, Coordinators, Technical Coordinators, and Observers in the context of the ICH Working Groups.

I. ICH Management Committee

The ICH Management Committee is responsible for oversight of the Working Group (WG) process and operations to ensure the efficiency and timeliness of ICH Guideline completion and quality. The MC appoints a Regulatory Chair to each WG from one of the Regulatory Members represented on the WG. Additionally, the MC manages the size of WG appropriately and reserves the decision to allow additional Members to join a WG. The MC is also responsible for approving Business Plans created in alignment with an Assembly approved Concept Paper.

The MC is responsible for submitting recommendations and proposals to the ICH Assembly for new topics and decisions on the endorsement of an ICH document at its step status. Additionally, the MC makes a recommendation to the Assembly on the adoption of final Guidelines, revisions to existing Guidelines, or withdrawal of a Guideline. The MC serves as a conduit between the expert WG and the ICH Assembly. The MC should to the extent possible work with each WG to resolve any discrepancies or issues that may interfere with the harmonization process. In instances when an issue cannot be resolved, the MC should elevate the decision to the ICH Assembly. For more information on the role and responsibilities of the ICH MC please refer to the ICH Rules of Procedure of the Assembly and the ICH Rules of Procedure for the Management Committee.

II. ICH Assembly

The ICH Assembly has the responsibility for approving new topics for ICH Guidelines and adoption, amendment or withdrawal of ICH Guidelines. Additionally, the Assembly will endorse each Guideline at its step status as follows:

- The Assembly will endorse the final technical document at Step 2a
- The Regulatory Members of the Assembly will endorse the draft Guideline at Step 2b
- The Assembly will adopt the final harmonized Guideline at Step 4

Each WG will provide a report to the Assembly during biannual face-to-face meetings to provide an update on the status of the WG and request endorsement or adoption of the ICH document as appropriate. The Assembly may endorse the final technical document at Step 2a and Step 2b through an electronic process however, the adoption of a final harmonized
Guideline will need to occur during a face-to-face meeting of the Assembly. Additionally, the Assembly will endorse a Concept Paper developed following endorsement of a new topic proposal. For more information on the roles and responsibilities of the ICH Assembly please refer to the ICH Rules of Procedure of the Assembly.

III. ICH Coordinators

ICH Coordinators are designated by ICH Members and play a fundamental role in the efficient operations of the ICH Association. The role of a Coordinator is to act as the main point of contact with the ICH Secretariat and to ensure that ICH documents are distributed to the appropriate persons within their respective organization. The Coordinator also serves as a point of contact for communication to the experts within their own organization. Furthermore, the ICH Coordinator may support their respective MC Members in a subcommittee. The following lists specific responsibilities of the Coordinator and their role as a liaison, for teleconferences, and for biannual face-to-face meetings.

1) Liaison among experts, the Management Committee, and the ICH Secretariat

The ICH Coordinator is the central point of contact and liaison among experts, the Management Committee, and the ICH Secretariat. The ICH coordinator serves in the following capacity:

- The main point of contact between their respective Agency’s experts and the ICH Secretariat
- The initial point of contact between the Regulatory Chair/Rapporteur of its Member and the Management Committee when there is an issue to be raised
- Conveying comments and requests from experts to the ICH Secretariat and MC as appropriate.
- Ensuring proper distribution of ICH information, documents, and actions to the appropriate individuals from their Member delegation (MC Members, Topic Leaders, Experts, and any other representatives) within the area of their responsibility.

2) Tele/web conferences

a. Before a teleconference or web conference the ICH Coordinator should:
   - Notify the ICH Secretariat of any issues or topics to be discussed.
   - Consult with relevant experts on various topics and issues for discussion in order to be prepared to convey information as appropriate during the tele/web conference.

b. During a teleconference or web conference the ICH Coordinator may:
   - Give an oral report on the status and/or Member’s position on an issue or topic under discussion as appropriate.
• Take notes on actions for the responsible topics (e.g. if Co-Rapporteurs are designated from two Members, Coordinators from both Members will take responsibility for actions).

c. After a teleconference or web conference the ICH Coordinators should:
• Review and comment on the draft report of the tele/web conference circulated by ICH Secretariat respecting the designated deadline.
• Ensure proper follow up on actions by their respective Member within assigned deadlines.

3) Face-to-face Meetings

a. Before a face-to-face meeting the ICH Coordinators should:
• Notify the Secretariat about items/issues/topics for inclusion in the MC or Assembly Agenda, at least one month prior to the meeting whenever possible
• Distribute meeting announcements to representatives of their respective Member
• Verify, discuss, and distribute the meeting schedules to all representatives concerned, and comment on the draft schedule as appropriate.
• Provide the name(s) of nominated representatives for their Member (Topic Leader, Deputy Topic Leader, experts, etc.) for each topic under discussion
• Check the preliminary draft agendas (MC meeting, Assembly, Coordinators meeting, ICG or Regulators meeting as appropriate)

b. During a face-to-face meeting the ICH Coordinators should:
• Ensure that relevant information is conveyed to the expert of their region.
• Help the ICH Secretariat in the preparation of the draft provisional minutes of the MC meeting as needed (i.e., by providing notes, suggestions, comments and specific wording, in a continuous way during the meeting).
• Confirm the list of actions endorsed by the MC on each topic and subject.
• One of the Coordinators from the host region may help the ICH Secretariat to develop the Press Release after the Assembly meeting. The press release will be approved by the meeting chair in consultation with the MC.

c. After a face-to-face meeting the ICH Coordinators should:
• Ensure appropriate follow-up on every subject according to the list of actions endorsed at MC level
• Review the provisional report of the MC meeting distributed by the ICH Secretariat after the meeting, and coordinate comments from their Member (collect and consolidate comments from their respective representatives as appropriate) respecting the designated deadline.

IV. ICH Technical Coordinators
An ICH Technical Coordinator may be designated by an ICH Member but is not required. ICH Technical Coordinators support their Assembly/MC representative and Coordinator in Guideline harmonization activities, mainly by applying their scientific knowledge.

Examples of the types of functions a technical coordinator would perform include the following:

- Facilitating identification of new topic proposals from their respective organization
- Assisting in identification of appropriate expert representatives from their Member for a working group
- Liaising with experts during the Management Committee and Assembly meetings and communicating as necessary to the MC representative of his or her Member organization
- Ensuring that draft guidelines are reviewed for compliance with their regional regulations prior to endorsement in the Assembly
- Ensuring experts reflect the views and policies of the Member they represent
- Reviewing the guidelines and comments during discussion in ICH and before publication

V. ICH Observer

An ICH Observer may submit a request to appoint an Observer expert to a Working Group (WG) using the template provided in Annex 12. The ICH Secretariat will provide the Management Committee (MC) with any applications received and the MC will then make a decision on whether the Observer should be allowed to appoint an expert to the Working Group (WG). In the request, the Observer should include an explanation of their interest, information about their available expertise, and how they expect to contribute to the work of the WG. An Observer would need to submit a separate request for each WG that it is requesting to nominate an expert. The ability for an Observer to participate in a WG is based on the favorable decision of the Management Committee.

If the MC agrees that an Observer may appoint an expert to a WG, the Observer may appoint only one expert to actively participate in the WG; however, an alternate may also be named. The alternate may be copied on emails and may listen during teleconferences of the WG but would not participate in the discussion. In the event that the Observer expert cannot participate in the WG, the alternate would replace the Observer expert. The Observer should provide the contact information of any experts who will be participating in a Working Group to the ICH Secretariat. This information will be provided to the Regulatory Chair and Rapporteur of the relevant ICH WG. For the purposes of continuity, the same nominated expert should participate for the duration of the WG. If their participation
cannot be sustained and the Observer needs to replace the originally appointed expert, it is the responsibility of the departing expert to fully brief the new expert on the status of the WG and progress to date.

Observer experts participating in WGs retain Observer status and thus do not opine on WG decisions. Observer experts would be expected to attend the WG meetings and participate in the discussion when they are able to contribute new information on scientific technical content. While thus contributing to the technical discussion of the WG however, the Observer expert is expected to refrain from voting when key decisions are made. Based on the understanding that the Observer expert is joining the WG with technical expertise in the Guideline topic it is further expected that the expert would not request the WG to explain concepts under discussion or to revisit issues that have been previously decided on. With that said, the Observer expert may seek clarification outside of the WG meetings if necessary. Observer experts participating in the WG will be invited to sign off the Step 1 technical document and Step 3 ICH draft guideline. This sign-off will be on a voluntary basis; because Observers do not vote on key decisions the absence of a signature from an Observer will not lead to the suspension of a Guideline. Furthermore, the absence of an Observer from a WG meeting would not prevent a quorum from being established and would not prevent a WG meeting from taking place.
Annex 2: Ground Rules for Good Practices of ICH Working Groups

I. Conduct of Meetings

1) Materials to be presented at a meeting should be distributed a minimum of 24 hours prior to the meeting, if feasible and appropriate.

2) Meetings should be conducted in the most efficient manner possible. All participants will act in a respectful and professional manner. Excessive posturing by any Member should be avoided.

3) All positions taken during meetings should be based on facts, to the extent possible, and justifications either for or against provisions will be as fact-based as possible, recognizing that reasonable hypothetical solutions may be considered.

4) Although not required, it is considered a good practice to develop meeting minutes that will summarize key topics of discussion, including substantive proposals, as well as any significant controversies or differences of opinion, and their resolution. These minutes should be shared with all Members of the Working Group following the meeting.

5) At the end of each meeting, the Working Group should develop a plan for next steps.

6) The ICH Secretariat will conduct the initial call for nomination of Working Group experts; however, the Rapporteur should track attendance of experts for each meeting of the Working Group.

7) The Rapporteur may wish to obtain project management support from their respective ICH Member organization. The Project Manager would not contribute subject matter expertise to the discussion but would function to assist in organization of the EWG/IWG (coordination of meetings, agenda development, capture agreements and outcomes of EWG/IWG discussions, etc.) under the direction of the Rapporteur.

8) The Regulatory chair should ensure that the opinions of all Members are expressed and that the discussion remains in scope of the approved Concept Paper and in line with the Business Plan.

II. Participation

9) A quorum, consisting of representatives of those Members who are required to appoint an expert to all EWGs and IWGs, is required at minimum in order for an ICH EWG/IWG meeting to occur. The presence of at least one expert representative from each Founding Regulatory Member and if nominated, one expert from each Founding
Industry Member and, if nominated, one expert from each Standing Regulatory Member is required to constitute a quorum.

10) All Regulatory and Industry Members who have appointed experts to a Working Group are expected to actively participate in and contribute to the work of the Working Group on a continuous and regular basis until the work is completed to ensure continuity. If the appointed expert is absent from two consecutive meetings and is unable to resume participation in Working Group meetings, the Member should appoint another qualified expert to replace the original member. Experts should be replaced only in exceptional circumstances and should be minimized to the extent possible.

11) In the event that an expert is replaced, the original member has the responsibility to provide all relevant background information to the new expert to orient the new expert to the EWG’s work to date. This includes history on discussions and agreements of the EWG/IWG. The new expert should have the expertise needed to actively contribute to the EWG/IWG.

12) If a Member of an EWG/IWG has been absent for a significant number (e.g. two or more) of the Working Group meetings either face-to-face by via teleconference, the Regulatory Chair and Rapporteur should provide a report to the MC. The MC should seek an explanation from the Member whose representative has been absent and their plan for addressing the gap, e.g., through naming an alternate or replacement for their originally appointed expert(s).

13) A new member/expert to an EWG/IWG already in progress should not ask or expect the EWG/IWG to reconsider previous decisions made by the EWG/IWG prior to that expert’s membership.

14) If an ICH Member or Observer has not nominated (and obtained endorsement) for an appointed expert or observer to an EWG/IWG and wishes to attend a meeting of the EWG/IWG, then that Member should submit a request to the Rapporteur to attend the meeting as an Observer. A Member or Observer outside of a Working Group’s membership is not permitted to attend meetings of the EWG/IWG either in person or by teleconference unless prior approval is obtained from the Rapporteur. Additionally, individuals who are not affiliated with an official ICH Member or Observer are not permitted to attend EWG/IWG meetings either in person or by teleconference.
Annex 3: Procedure for the Organization of Interim Meetings

This procedure applies to exceptional interim face-to-face meetings outside of the regularly occurring biannual ICH meetings and may be convened for an ICH Working Group (WG), the ICH Management Committee (MC), or for a subcommittee of the ICH MC. In exceptional circumstances, an interim meeting may be necessary for a WG to achieve its assigned work objectives or to facilitate efficiency of the harmonisation process. Additionally, an interim meeting of the MC may be organised to address important and pressing procedural or organisational issues of the ICH Association. The arrangement of any interim face-to-face meeting will be subject to approval by the ICH MC.

1) Request to organise an interim meeting

If a WG is interested in holding an interim meeting, it can provide a request to the MC either during or between biannual face-to-face meetings. The request should include the reason for the meeting (including why teleconference or web conference options would not serve the purpose and why there is a need to meet before the next biannual meeting), the anticipated accomplishments, a Business Plan, a proposed location, and a tentative date. If a WG proposes to hold an interim meeting, this must be discussed and agreed by all members of the MC. The decision to hold an interim meeting is contingent on the ability of the Regulatory Members to fund any travel to the meeting. The Regulatory Coordinators should confirm the ability for their agency to attend the interim meeting within 2 weeks following the request to hold an interim meeting by the WG. Once the Regulatory Coordinators confirm the ability for their agency to attend the interim meeting, the ICH Secretariat should solicit endorsement by the MC.

2) Meeting Organization

The Rapporteur and Regulatory Chair, or MC Member representative, and their respective coordinator will work with the ICH Secretariat to organize the interim meeting. Once the MC endorses an interim meeting, the Rapporteur, Regulatory Chair, and coordinator of the hosting agency will identify a date by contacting all WG representatives and choosing a date in accordance with each participants’ availability.

The location of the meeting will be arranged with the ICH Coordinators of the hosting region and the ICH Secretariat. The meeting venue is to be financed or hosted by either an ICH Industry or Regulatory Member of the host region. The financing Member should be directly involved in any planning/logistical decisions associated with the meeting that would have meeting cost implications. Each Member will be responsible for funding the costs of travel, food, and accommodation for their individual experts.
Once a date and location have been determined, the ICH Secretariat will send out a request for nominations of experts to attend the interim meeting to each Member of the Working Group. Once the experts have been confirmed, a meeting confirmation will be sent to the WG experts with the meeting location and date.

3) Meeting Attendance

For meetings of a WG, a quorum is required at minimum in order for the interim meeting to occur. A quorum consists of at least one expert representative from each Founding Regulatory Member and if nominated, one expert from each Founding Industry Member and, if nominated, one expert from each Standing Regulatory Member. The same rules for meetings of the WGs, as outlined in section 1.5.5. Meeting Attendance of these rules of procedure apply to interim meetings. For meetings of the MC or for a MC subcommittee, each Member represented must be present for the meeting to occur.

4) Follow-up after the meeting

After the meeting, the WG or MC (in the case of an interim MC or MC subcommittee meeting) will prepare a report that summarises the progress made, the achievements and conclusions reached, and the list of actions with clear deadlines and responsible individuals. Draft reports shall be circulated to all experts who attended the meeting for discussion and adoption. Approved reports shall be sent by the Rapporteur of the WG or the Chair of the MC or lead of the Subcommittee to the ICH Secretariat for circulation to the MC and Coordinators.
Annex 4: Maintenance Procedure for Q3C, Q3D, and M7

This Maintenance Procedure applies to revision of the Q3C Guideline for Residual Solvents, Q3D Guideline for Elemental Impurities, and M7 Addendum for the Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. The procedure explains the process for revising the existing guidelines as new solvents, metals or impurities are accepted or new data become available. These changes include the following revisions for each Guideline:

- **Q3C** – Incorporation of Permitted Daily Exposure (PDE) for new solvents and revising the PDE for solvents already listed in Q3C as new toxicological data for solvents becomes available.
- **Q3D** - Incorporation of Permitted Daily Exposure (PDE) for new elemental impurities/routes of administration and revising the PDE for elemental impurities already listed in Q3D as new toxicological data for elemental impurities becomes available.
- **M7 Addendum** – Incorporation of acceptable limits (Acceptable Intakes (AIs) or PDEs) for new DNA reactive (mutagenic) impurities and revising acceptable limits for impurities already listed in the Addendum as new data becomes available.

Data and/or proposals pertaining to the revision of the Q3C, Q3D, or M7 Guidelines with supporting information can be submitted directly to the ICH Secretariat from either an ICH Member or Observer or other interested Member outside of ICH.

Information provided within a proposal should be based on significant toxicity data from studies such as repeat-dose studies, reproductive toxicity studies, genotoxicity studies, and carcinogenicity studies and/or other relevant studies. Single-dose toxicity data alone are not sufficient. The toxicity data should be of sufficient quality to calculate a PDE or AI. Gentoxicity and carcinogenicity data are of primary importance for revisions to the M7 Guideline.

A standing Expert Working Group (EWG) will be established to evaluate any proposals received. The EWG will be established according to the procedure outlined in section 1.5.1 – EWG/IWG Membership of these Rules of Procedure. As appropriate, an ICH Observer may be invited to join the EWG.

The Rapporteur should be a Founding Regulatory Member and will serve a two-year term. The role of the Rapporteur will rotate every two years to a new Founding Regulatory Member e.g., FDA (2017-2018, 2027-2028 etc...), MHLW/PMDA (2023-2024, 2033-2034 etc...), EU (2015-2016, 2025-2026 etc). Proposals will be evaluated once every 2 years following rotation of the Rapporteur. The ICH Secretariat will share any proposals received with the new Rapporteur.
and ICH Coordinators. The Rapporteur will facilitate the review of any proposals received by the EWG and the EWG will make a recommendation on whether the proposal should be supported by the Management Committee (MC).

If a proposal for maintenance is supported by an EWG, the ICH Secretariat will subsequently notify the ICH Coordinators and MC. The MC will then provide a recommendation to the Assembly on whether the EWG should be tasked with making the revision.

A revision will be considered only on presentation of new data or previously unrecognised toxicity data sufficient to result in a significant change, or because of convincing evidence that the existing data used to calculate a PDE are invalid. Minor changes in a PDE will not be considered. The Regulatory Chair, with the consensus of the EWG members, will assign data reviews to the EWG and request subsequent recommendations.

The Rapporteur will ordinarily rely on correspondence or teleconferencing to avoid unnecessary travel. Based on the discussion, with requests for further information to the proposing group and/or individual as appropriate, the Rapporteur will prepare an assessment report based on the EWG’s approval with a recommendation to accept, with or without modifications, or reject any proposed revisions.

After endorsement by the Assembly, either at the next formal meeting or by electronic endorsement, the recommendation of the EWG will be published in each region for public comment (Step 3 of the ICH process). In addition, the proposal will be provided to each pharmacopoeia for their publication.

After closure of the public comment period, the Regulatory Chair may convene a meeting of the EWG or will rely on correspondence or teleconferencing to consider the comments and finalise the proposal for the revised Guideline. The final recommendation for the Guideline and implementation is then forwarded to the Assembly for adoption in consultation with the MC. Implementation will follow regional practices. With approval of the ICH Assembly, the change will be provided to the pharmacopoeias at regional/national level for publication.

When a new or revised PDE or AI is recommended by the EWG, approval by the ICH MC is required. Once approval occurs, the information should be disseminated as quickly as possible to all ICH participants and other members of the chemical and pharmaceutical communities. It is recommended that the following actions should be taken by the MC to ensure rapid transmission of the new information:

- Publish relevant information on the ICH website;
- Request publication of revisions by the pharmacopoeias of the ICH regions in their Forums or websites;
- Request that each member publish the new or revised PDE or AI information on its respective websites.
Annex 5: Q4B Maintenance Procedure

The ICH Q4B Guideline *Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions* reached Step 5 in November 2007. Subsequently, the individual topic-specific Annexes reached Step 5 in accordance with the dates listed on the ICH website. Because the inputs to the Q4B process were from the Pharmacopoeial Discussion Group (PDG) harmonisation process, it is recognised that the pharmacopoeial texts could be updated as technology and requirements change, or for other reasons. Because changes to the pharmacopoeial texts could have an impact on the interchangeability assessment contained in the Annexes, it is necessary to have a maintenance procedure for updating the Annexes when needed.

The Pharmacopoeias (e.g., JP/Ph.Eur./USP) publish updates to the status of chapters in the PDG harmonisation work programme. Because of the potential impact of these chapters, the status of the work programme is regularly monitored by interested stakeholders, including industry. If PDG or any of the pharmacopoeias make revisions to any chapter that is the subject of an ICH Q4B Annex an assessment of the change(s) should be conducted by interested stakeholders, to determine whether a revision to the Annex may be necessary. As a result of this assessment, a recommendation from any stakeholder, including regulators, industry, or PDG, to revise the Annex will be communicated to ICH (for example through the ICH website), so that all ICH Members are alerted.

Following consideration by the ICH Management Committee (MC) and with the endorsement of the ICH Assembly, an informal Working Group may be established according to *section 1.2 – Establishment of an informal Working Group* of this SOP to formally review the revision proposal and, if necessary, make a recommendation to revise the Annex. The evaluation and revision work will be completed electronically through use of email and web-based technology. Any Annex revision would follow the revision procedure outlined in *section 2.3 - Revision Procedure* of this SOP.
Annex 6: MedDRA Points to Consider (PtC) Working Group

The MedDRA Points-to-Consider (PtC) Working Group (WG) was established with the scope of developing a PtC document on Good MedDRA Selection Practices and advising on standards for data output. The PtC WG develops and maintains the MedDRA Term Selection: Points to Consider and the MedDRA Data Retrieval and Presentation: Points to Consider documents synchronized with MedDRA version updates; its remit was later extended to enable the WG to provide guidance on ICH MedDRA initiatives on an as-needed basis.

If proposing an entirely new PtC document or further extension of its remit, the PtC WG will be asked to develop a draft Concept Paper with detailed information on the scope, need, benefits, deliverables, cost, time frame, membership, for consideration by the MedDRA Management Committee, followed by approval of the Management Committee.

I. Endorsement of PtC documents

The PtC documents are not subject to regional implementation, but provide a best practice approach. Generally the PtC WG releases a new version of the PtC documents for every version of MedDRA. PtC documents with major changes (i.e., significant new documents, new concepts in existing documents) will be signed off by the ICH Members of the PtC WG and by the ICH Management Committee. PtC documents with minor changes (e.g., simple revisions) will be signed-off by the Rapporteur/Co-Rapporteur.

Once signed-off, the PtC documents are available for public consultation. Any comments are forwarded to the PtC WG and will be taken into consideration for the release of the next version of the documents.

II. Membership

The PtC WG is similar to other ICH Working Groups, in that the ICH Members nominate up to two experts, one in the role of Topic Leader and the other as a Deputy Topic Leader. The PtC WG usually also includes a representative from both MSSO and JMO, as well as one representative from WHO (ICH Observer).

III. Working Procedures

The PtC WG has an on-going mandate from the ICH Management Committee (MC) to work by tele/web conference/e-mail. The group is asked to report at MedDRA Management Committee tele/web conference when there is a need for a face-to-face meeting. Justification will need to be provided for all face-to-face meetings, for MedDRA Management Committee consideration, followed by ICH Management Committee approval.
The PtC WG usually meets every 18 months during the week of the ICH face-to-face meeting; however, the WG may need to meet every 12 months, as the necessity for holding meetings depends on the feedback received from users and the time of release of MedDRA (March and September). The usual maintenance of both PtC documents on term selection and on data retrieval & presentation does not require frequent face-to-face meetings. A large part of the work is done by correspondence, and major and only complex changes to MedDRA are discussed during face-to-face meetings. The Rapporteur is asked to report on progress and issues to the ICH MC on a regular basis. Unresolved issues will be brought to the attention of the ICH MC.

I. Designation of the Rapporteur / Co-Rapporteur:

The nomination of Rapporteur/Co-Rapporteur proceeds via consultation for candidate(s) among the ICH Coordinators of ICH Members. The PtC WG should also be consulted and invited to discuss their leadership. The MedDRA MB will be asked to approve the nomination and the MC will be informed of the nomination. The Rapporteur/Co-Rapporteur should not be of the same region/affiliation (industry vs. regulatory authority) at any one time.

The MedDRA MB will reassess the term of Rapporteurship, as needed.
Annex 7: Streamlined Procedure

The purpose of the streamlined procedure is to develop a guideline in an accelerated timeframe in response to an emerging health care problem.

When it is critical for an ICH country/region to develop a guideline that other ICH Members share an interest in, then the task could be undertaken under the auspices of ICH. Under such circumstances the ICH Assembly in close consultation with the Management Committee (MC) would grant the use of the streamlined procedure in order to make the process as short and efficient as possible.

In addition to time constraints, the following conditions are required to make a document eligible for the streamlined procedure:

1) The presence of an emerging health issue, such as:
   a. A health problem that affects many persons
   b. A significant change in state of art of science.
2) A draft or final document should already exist in one of the ICH regions (including an Observer) that would provide a strong foundation for the development of the ICH guideline.

There should be consensus from the ICH Members that the draft document would be the starting point in the development of the ICH Guideline, no Concept Paper would be necessary and the country(s)/region(s) originating the document would lead the EWG responsible in developing the guideline. However, a Business Plan is still necessary.

ICH Industry Members are not required to participate in the development of the guideline.

The Assembly in close consultation with the MC will consider proposals for the streamlined procedure on a case-by-case basis.

1. Process for streamlined procedure

Upon approval of a streamlined process by the Assembly, the objectives and expected outcome of the harmonisation action is confirmed. Additionally, a timetable and Business Plan with an accelerated timeline will be developed.

The composition of the Expert Working Group (EWG) is confirmed, which can include outside experts if invited as an ad hoc Observer. The ICH Members designate a Topic Leader, as in the normal process and the region originating the documents nominates a Rapporteur, and one of the ICH Regulatory Members nominates a Regulatory Chair.
The step process for the streamlined procedure is the same as the normal ICH process with the exception of the absence of a Concept Paper. The form of communication to be used for the sign-off will be electronically or by postal mail.

II. **Streamlined procedure Step process**

1) In principle, the agreement of the ICH Members is necessary for initiating any ICH harmonisation activities. However, in exceptional cases when ICH Member consensus cannot be achieved, the Assembly will proceed to voting where a majority decision will make a determination.

   a. Step 1: Consensus building between the experts - The Rapporteur circulates the existing document to the EWG for comments and discussion. As the document has been agreed to in principle, the comments are unlikely to be major. The experts reach consensus on the document and sign-off at Step 1.

   b. Steps 2a and 2b: The Assembly and the ICH Regulatory Members, endorse the Technical Document and Draft Guideline, respectively, through an electronic approval process organised by the ICH Secretariat.

   c. Step 3: Regulatory consultation: The draft guideline is published for comments in each of the ICH regions (the comment period may be shortened to accommodate regulatory needs and timetables). After addressing all regulatory consultation results, the EWG regulatory experts reach consensus on the Step 3 Experts Draft Guideline and sign-off on it.

   d. Step 4: Adoption of a harmonised Guideline: The Assembly endorses the final harmonised guideline (via electronic process).

III. **Safeguard Clause**

In case of unexpected delays in the procedure that would jeopardize reaching consensus and finalising the ICH Guideline on time, the country/region from which the document originated may withdraw the document from the ICH process in order to meet its own deadlines at any time during the process in consultation with the other Members.
Annex 8 ICH Topic Proposal Template

1. ICH Topic Description

<table>
<thead>
<tr>
<th>Type of Harmonization Action:</th>
<th>New guideline</th>
<th>Revision of existing guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category of Harmonized Procedure:</td>
<td>Quality</td>
<td>Safety</td>
</tr>
</tbody>
</table>

Brief statement of perceived problem (caused by lack of harmonization):

Main technical and scientific issues to be addressed (which require harmonization):

Objective and expected outcome of proposed harmonization work:

2. Strategic Importance of Topic

Why is this important for international harmonization?

1. How does the proposal potentially conserve regulatory/industry resources? Which specific areas are likely to benefit more (e.g. generics, NCEs, biologics)?
2. How does the proposal potentially improve the timing of access of new drugs to patients?
3. Given the new construct, which industries and which regulators are likely to most benefit?

3. Feasibility

Would the proposal be in alignment with current laws and regulations in the ICH regions? (If not, identify regions in which incompatibilities or obstacles could be expected)

1. Level of effort required to complete the guideline
2. Time to complete the guideline
3. When benefits of the completed guideline would be realized
4. How does the proposed topic relate or potentially complement or conflict with existing guidelines
5. How would the proposed topic potentially compete for ICH resourcing within and across categories (Q, S, E, M)

4. Source of Proposed Topic

Topic proposed by:

ORGANIZATION: _____________________________________________________________
___________________________________________________________

CONTACT NAME: __________________________________________________________
Annex 9 ICH Concept Paper Template

Final Concept Paper

Title

Dated

Endorsed by the Assembly on day/Month/Year

Type of Harmonisation Action Proposed

[ Is a new harmonised guideline being recommended, or a revision of an existing guideline? What category of procedure would this fall into? ]

Statement of the Perceived Problem:

[ Provide a brief description with an indication of the magnitude of the problems currently caused by a lack of harmonisation, or - in the case of new scientific developments - anticipated if harmonisation action is not taken. ]

Issues to be Resolved:

[A summary of the main technical and scientific issues, which require harmonisation.]

Background to the Proposal:

[Further relevant information, e.g., the origin of the proposal, references to publications, and discussions in other fora.]

Type of Expert Working Group Recommended:

[Recommendation on whether the EWG (if needed) should be an extended EWG - for topics with implications beyond new drug research.]

Timing:

[When should the topic under consideration begin harmonization? How long is it anticipated to take to develop a harmonized guideline/revise existing guideline?]
1. **The issue and its costs**
   - What problem/issue is the proposal expected to tackle?
   - What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with “non action”?

2. **Planning**
   - What are the main deliverables?
   - What resources (financial and human) would be required?
   - What is the time frame of the project?
   - What will be the key milestones?

3. **The impacts of the project**
   - What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?
   - What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?

4. **Post-hoc evaluation**
   - How and when will the results of the work be evaluated?
Annex 11 Work Plan Template

ICH XX EWG/IWG Work Plan
Day Month Year

Topic Adopted: Day/Month/Year
Rapporteur: Name of Rapporteur / Co-Rapporteur
Regulatory Chair: Name of Regulatory Chair
Last Face-to-Face Meeting: Day/Month/Year

1. Anticipated Milestones (A high-level summary of the main deliverable(s) & timeframe(s) should be provided in the table below)

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day/Month/Year</td>
<td>Step 2 Guideline</td>
</tr>
<tr>
<td>Day/Month/Year</td>
<td>Step 4 Guideline</td>
</tr>
</tbody>
</table>

2. Timelines (Short-term timelines should be provided in the table below e.g., for work between now & next meeting)

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day/Month/Year</td>
<td>e.g., EWG/IWG e-mail consultation, EWG/IWG teleconference etc...</td>
<td>Brief summary of task/activity objectives Brief summary of targeted deliverable/outcome</td>
</tr>
</tbody>
</table>

3. Summary of Any Current Issues
Any issues which should be raised for the information of the ICH Management Committee, or on which ICH Management Committee guidance is needed should be mentioned here.

4. Necessity of Face-to-Face Meeting at the Next ICH Meeting
In line with the work plan presented above, the consensus view of the EWG/IWG on the necessity for the group to meet face-to-face at the time of the next ICH Assembly and EWG/IWG meetings should be presented here.
If there is agreement within the EWG/IWG on the need for a meeting, then a description of the work that would be undertaken during the meeting should be provided in the table below.

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Day 1 a.m.</td>
<td>Task/Activity (short description)</td>
<td>Brief summary of task/activity objectives</td>
</tr>
<tr>
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<td></td>
<td>Brief summary of targeted deliverable /outcome</td>
</tr>
<tr>
<td>Day 1 p.m.</td>
<td>Task/Activity</td>
<td>Brief summary of task/activity objectives</td>
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<td>Brief summary of targeted deliverable /outcome</td>
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<tr>
<td>Day 4 a.m.</td>
<td>Task/Activity</td>
<td>Brief summary of task/activity objectives</td>
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<td>Brief summary of targeted deliverable /outcome</td>
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<tr>
<td>Day 4 p.m.</td>
<td>Task/Activity</td>
<td>Brief summary of task/activity objectives</td>
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<tr>
<td></td>
<td></td>
<td>Brief summary of targeted deliverable /outcome</td>
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</table>
ICH OBSERVER – REQUEST TO APPOINT AN EXPERT TO A WORKING GROUP

1. Contact details for the applicant
   Name of Observer Organization:
   Contact Person:
   Title:
   Address:
   Phone:
   Email:
   Date:

2. Name of the Working Group the Observer organization is requesting to nominate an Observer expert:

3. Describe the Observer organization’s primary interest in participating in the Working Group:

4. Briefly describe the expertise of the individual being nominated and their expected contribution to the work of the Working Group:
Annex 13 Step 1 Experts Sign-Off

**Topic Reference:**  
**STEP 1 – EXPERTS**

<table>
<thead>
<tr>
<th>CODE: GUIDELINE TITLE</th>
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</table>
| Consensus on a technical document to be submitted to the ICH Assembly under *Step 1* of the ICH Process  
*Step 1* technical document signed-off by the  
DESIGNATED EXPERTS FROM THE ICH EXPERT WORKING GROUP |

The official ICH procedure specifies that a *Step 1* technical document can be submitted to the Assembly for endorsement when the designated experts of the ICH Members reach consensus and sign the *Step 1* sign-off sheet.

**Document Reference:** .................................................................

**Document Date:** .................................................................

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<thead>
<tr>
<th>Signature</th>
<th>Name</th>
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**Experts of Founding Regulatory Members**

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<td>MHLW/PMDA</td>
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**Experts of Founding Industry Members**

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**Experts of Standing Regulatory Members**

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<tr>
<th></th>
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<td>Swissmedic</td>
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</table>
All additional experts who participate in the Working Group are invited to sign-off the Step 1 technical document in recognition of their contribution to the discussion.

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<th>Signature</th>
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<th>Date</th>
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**Experts of Standing Observers**

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<tr>
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<tbody>
<tr>
<td>WHO</td>
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</table>

**Experts of Observers**
*(To be filled based on WG participants)*

|       |       |       |

**Experts of Other Participants**
*(To be filled based on WG participants)*

|       |       |       |

60
**Annex 14 Step 3 Regulatory Experts Sign-Off**

**Topic Reference:**  
**STEP 3 – REGULATORY EXPERTS**

**CODE: GUIDELINE TITLE**

Conclusion of Step 3 of the ICH Process

*Step 3 experts draft Guideline signed-off by the DESIGNATED REGULATORY EXPERTS FROM THE ICH EXPERT WORKING GROUP*

The official ICH procedure specifies that a *Step 3* experts draft Guideline can be submitted to the Assembly for adoption as an ICH Harmonised Guideline when the designated experts of the ICH Regulatory Members reach consensus and sign the *Step 3*.

---

**Document Reference:** ............................................................

**Document Date:** ..............................................................

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<thead>
<tr>
<th>Signature</th>
<th>Name</th>
<th>Date</th>
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**Experts of Founding Regulatory Members**

<table>
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<tr>
<th>Country</th>
<th>Signature</th>
<th>Name</th>
<th>Date</th>
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**Experts of Standing Regulatory Members**

<table>
<thead>
<tr>
<th>Country</th>
<th>Signature</th>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada</td>
<td></td>
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<tr>
<td>Swissmedic</td>
<td></td>
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</tr>
</tbody>
</table>

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1 The comments received by the ICH Regulatory Members on the regional consultation on the Step 2b Guideline have been considered for the preparation of a *Step 3* experts draft Guideline which, once signed-off by the experts designated by the regulatory Members, will be submitted to the Assembly for adoption as a harmonised guideline (Step 4 of the Process).
All additional regulatory experts who participate in the Working Group are invited to sign the Step 3 Experts Draft Guideline in recognition of their contribution to the discussion.

Experts of Observers
(To be filled based on WG participants)

................................................................. ................................................................. .................................

Experts of Other Participants
(To be filled based on WG participants)

................................................................. ................................................................. .................................
Step 3 of the ICH Process\(^2\) **without public consultation**

Step 3 Experts Document signed-off by the DESIGNATED REGULATORY EXPERTS FROM THE ICH EXPERT WORKING GROUP

The official ICH procedure specifies that a Step 3 Document can be submitted to the Assembly for adoption as an ICH Harmonised Guideline when the Designated Experts of the ICH Regulatory Members reach consensus and sign the Step 3.

**Experts of Founding Regulatory Members**

EC .......................................................... ................................. .................................

FDA .......................................................... ................................. .................................

MHLW .......................................................... ................................. .................................

**Experts of Standing Regulatory Members**

Health Canada .......................................................... ................................. .................................

Swissmedic .......................................................... ................................. .................................

\(^2\) Once signed-off by the experts designated by the Regulatory Members, this document will be submitted to the Assembly for adaption as a harmonised guideline (Step 4) without public consultation.
Step 3 of the ICH Process without public consultation

All additional Regulatory experts who participate in the Working Group are invited to sign the Step 3 Experts Draft Guideline in recognition of their contribution to the discussion.

Document Reference: .................................................................

Document Date: .................................................................

Signature          Name          Date

Experts of Observers
(To be filled based on WG participants)

.................................................................  .................................................................  ........

Experts of Other Participants
(To be filled based on WG participants)

.................................................................  .................................................................  ........
2. Membership and Observership

The ICH Management Committee (MC) will present to the Assembly its recommendation regarding Membership and Observership applications processed since the Lisbon meeting in June 2016.

**Action:**

- The Assembly is invited to take a **decision** regarding the applications for ICH Membership/Observership recommended by the MC.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The MC presented to the Assembly its recommendations regarding Membership and Observership applications processed to-date.

**Decisions/Actions:**

- The Assembly took note of the following former RHIs and DRAs/DoH who became Observers immediately after the establishment of the Association following submission of a confirmation letter to the ICH Secretariat according to Article 17(3) of the ICH Articles of Association:
  - The Brazilian Health Surveillance Agency (ANVISA, Brazil);
  - The Asia-Pacific Economic Cooperation (APEC);
  - The Association of Southeast Asian Nations (ASEAN);
  - The Central Drug Standards Control Organisation (CDSCO, India);
  - The East African Community (EAC);
  - The Gulf Cooperation Countries (GCC);
  - The Pan American Network for Drug Regulatory Harmonisation (PANDRH);
  - The Health Sciences Authority (HAS, Singapore);
  - The Ministry of Food and Drug Safety (MFDS, Korea);
  - The Roszdravnadzor (Russia);
  - The Southern African Development Community (SADC);
  - The Food and Drug Administration (TFDA, Chinese Taipei);
  - The Therapeutic Goods Administration (TGA, Australia);
The Assembly approved in Lisbon the following Observership applications on the basis of the recommendation of the MC:

**Legislative or Administrative Authority**
- The Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico);

**International Pharmaceutical Industry Organisation**
- The Biotechnology Innovation Organisation (BIO);

**International Organisations with an Interest in Pharmaceuticals**
- The Council for International Organizations of Medical Sciences (CIOMS);
- The European Directorate for the Quality of Medicines & HealthCare (EDQM);
- The International Pharmaceutical Excipient Council (IPEC);
- The United States Pharmacopeia (USP).

The Assembly approved the following Membership applications on the basis of the recommendation of the MC:

- The International Generics and Biosimilar Medicines Association (IGBA);

The Assembly did not approve the application for Observership from the Centers for Medicare and Medicaid Services (CMS);

The Assembly supported the request from MFDS to participate in the activities of the Q12 EWG on the basis of the recommendation from the MC.
3. Financial Matters

The ICH MC will provide an update on ICH financial matters including:

- Preparation of the 2017 ICH Budget;
- Reflections regarding the level of the annual fee for new Members;
- Development of a proposal for a participation fee for non-membership fee paying ICH meeting participants; and
- Development of a Donation Policy and recommendation of an auditing firm for appointment as ICH Auditors.

The MedDRA MC Chair or Chair’s delegate will provide an update on the preparation of the 2017 MedDRA Budget, including the 2017 subscription fees.

**Actions:**

- The Assembly is requested to take a decision to approve the 2017 ICH Budget;
- The Assembly is invited to take a decision to approve the annual fee for new Members for publication on the ICH website and confirm agreement to a 2018 implementation;
- The Assembly is invited to approve the publication of the Donation Policy (if adopted as part of the RoP, referred to under agenda item 1) on the ICH website;
- The Assembly is requested to take a decision to appoint an auditing firm as the ICH Auditors for an initial period of two years to audit the annual financial statements of the Association;
- The Assembly is requested to take a decision to approve the 2017 MedDRA Budget.
**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Assembly was updated on ICH financial matters including the 2016-2018 ICH Secretariat Budget, the proposed fees for new Members and the concept of participation fee for Observers.

**Decisions/Actions:**

- The Assembly noted the 2016-2018 ICH Secretariat budget and its publication to the financial section of the ICH website;
- The Assembly discussed a proposal for fees for new Members which proposed a range of fees for its consideration: from CHF19,200 to CHF48,000;
- The Assembly was invited to provide comments on the proposed fee range for new Members ahead of the Osaka meeting, in November 2016, where a final decision will be made on the level of new members fees;
- The Assembly also shared views on the concept of for a participation fee for non-membership fee paying parties (i.e., Observers) to cover costs of meeting participation such as catering. A proposal will be developed including how participation fees will be invoiced, processed and accepted.
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 4

4. Strategic Discussions

Actions:

➢ The Assembly is invited to hold a strategic discussion focusing notably on the following potential topics proposed by the MC:
  ○ Good Clinical Practice (GCP)
  ○ Compliance of Reliability for Electronic Data

➢ The Assembly is invited to discuss follow-up actions from this discussion.

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The MC reported on the development of a process for the selection of new ICH technical topics for use in future ICH Meetings.

In addition, the MC presented to the Assembly for its consideration and approval its recommendation to adopt for the following 2 new topics for the development as ICH Guidelines: Biopharmaceutics Classification System-based Biowaivers and Bioanalytical Method Validation.

The MC also presented a proposal to the Assembly regarding the organisation of strategic topics discussions at the next ICH meeting to be held in Osaka, Japan in November 2016.

Decisions/Actions:

➢ The Assembly noted the proposed ICH process for the selection of new ICH topics and supported that the process be run on a yearly basis (6-month process);

➢ The Assembly noted the Concept Paper outlines for the following 2 new ICH topics which were recommended by the MC to the Assembly for its approval:
  - Biopharmaceutics Classification System-based Biowaivers (proposed by EC)
  - Bioanalytical Method Validation (proposed by MHLW/PMDA)
The Assembly adopted the Concept Paper outline on Biopharmaceutics Classification System-based Biowaivers (code: ICH M9) and agreed on the establishment of an informal Working Group (with EC nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

The Assembly adopted the Concept Paper outline on Bioanalytical Method Validation (code: ICH M10) and agreed on the establishment of an informal Working Group (with MHLW/PMDA nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

The ICH Secretariat will launch the nomination process amongst ICH Members for the establishment of the 2 informal Working Groups;

Further to Article 17(5), any ICH Observer interested to participate in the activities of these new Working Groups (WGs) would need to inform the ICH Secretariat in writing and provide explanations for their interest in the specific Working Group, information about their available expertise and how they expect to contribute to the work of the WG;

Any request received by the ICH Secretariat, will be shared with the MC; and the Assembly may, on the basis of the recommendation by the MC, invite Observers to appoint experts in the WGs. The Assembly will be able to take a decision on such invitations at the Osaka meeting in November 2016;

The Assembly nominated EC as the Rapporteur for the ICH M9 EWG and MHLW/PMDA as the Rapporteur for the ICH M10 EWG;

The Founding Regulatory Members and the Standing Regulatory Members will confirm the respective Regulatory Chairmanship for these 2 new EWGs once established;

The Assembly also noted the following 2 additional new topic proposals considered by the MC in Lisbon and recommended that the MC further discussed and provide feedback on these in Osaka:

✧ Safety Data Collection (proposed by FDA);
✧ Adaptive Clinical Trials (proposed by PhRMA);

The Assembly also noted the general outline on the organisation of ICH Strategic discussions for which FDA was tasked to develop a proposed approach for the structure and organization of Strategic topics discussions;

The Assembly agreed on a recommendation that proposals are developed for strategic discussions in Osaka on Good Clinical Practices (to be led by FDA) and on Compliance of Reliability for Electronic Data (to be led by JPMA and supported by FDA).
5. New ICH Topics

The MC will highlight the overall status of ICH harmonisation activities on current ICH topics and the process agreed in Lisbon in June 2016 for the selection of new ICH topics. The MC will provide the Assembly with an update on its considerations since the Lisbon meeting in June 2016 of the new proposals on Safety Data Collection and Adaptive Clinical Trials.

**Action:**
- The Assembly will be invited to provide its views and consider approval of any new topics for ICH Guidelines recommended by the MC.

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**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The MC reported on the development of a process for the selection of new ICH technical topics for use in future ICH Meetings.

In addition, the MC presented to the Assembly for its consideration and approval its recommendation to adopt for the following 2 new topics for the development as ICH Guidelines: Biopharmaceutics Classification System-based Biowaivers and Bioanalytical Method Validation.

The MC also presented a proposal to the Assembly regarding the organisation of strategic topics discussions at the next ICH meeting to be held in Osaka, Japan in November 2016.

**Decisions/Actions:**
- The Assembly noted the proposed ICH process for the selection of new ICH topics and supported that the process be run on a yearly basis (6-month process);
- The Assembly noted the Concept Paper outlines for the following 2 new ICH topics which were recommended by the MC to the Assembly for its approval:
  - Biopharmaceutics Classification System-based Biowaivers (proposed by EC)
  - Bioanalytical Method Validation (proposed by MHLW/PMDA)
- The Assembly adopted the Concept Paper outline on Biopharmaceutics Classification System-based Biowaivers (code: ICH M9) and agreed on the establishment of an informal Working Group (with EC nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;
The Assembly adopted the Concept Paper outline on Bioanalytical Method Validation (code: ICH M10) and agreed on the establishment of an informal Working Group (with MHLW/PMDA nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

The Assembly nominated EC as the Rapporteur for the ICH M9 EWG and MHLW/PMDA as the Rapporteur for the ICH M10 EWG;

The Founding Regulatory Members and the Standing Regulatory Members will confirm the respective Regulatory Chairmanship for these 2 new EWGs once established;

The Assembly also noted the following 2 additional new topic proposals considered by the MC in Lisbon and recommended that the MC further discussed and provide feedback on these in Osaka:

- Safety Data Collection (proposed by FDA);
- Adaptive Clinical Trials (proposed by PhRMA);

The Assembly also noted the general outline on the organisation of ICH Strategic discussions for which FDA was tasked to develop a proposed approach for the structure and organization of Strategic topics discussions;

The Assembly agreed on a recommendation that proposals are developed for strategic discussions in Osaka on Good Clinical Practices (to be led by FDA) and on Compliance of Reliability for Electronic Data (to be led by JPMA and supported by FDA).
6. Communication

Communication Activities
The MC will provide an update on current communication activities including development of:

- A general slide deck on ICH;
- A transparency policy; and
- A stakeholder engagement plan.

The Assembly will also note recent updates to the ICH website.

Action:

- The Assembly will be invited to share its views.

ICH Regional Public Meetings

Action:

- The Assembly will be invited to share information on any ICH Regional Public Meetings in their respective regions prior to/following the ICH meeting in Osaka in November 2016.

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

Communication Activities
The Assembly noted the ongoing communication activities regarding the newly established ICH Association. It was noted that a Q&A document on Membership had been recently made available on the ICH website. In addition, the Assembly noted the development of a new slide deck on ICH which will also be made available on the ICH website once finalised, the development of a transparency policy and the development of a stakeholder engagement plan to receive feedback from various stakeholders. The Assembly also noted that the ICH website will continue to be improved in advance of the Osaka meeting in November 2016.
**ICH Workshops and Regional Public Meetings**

The Assembly noted the ICH Information Day organised by the EC/EMA in collaboration with DIA in Hamburg, Germany on April 6, 2016 and, which focused on the recent reform by ICH and its impact on global development of medicines.

The Assembly also noted that JPMA in collaboration with MHLW/PMDA will be organising an ICH regional public meeting in Tokyo, Japan, on July 21, 2016. In addition, JPMA in collaboration with DIA will be also organising in Tokyo, on November 12, 2016 an ICH workshop on ICH E6, E9 and E17 Guidelines.

The Assembly also noted that a U.S. public meeting was held at the FDA’s White Oak campus in Silver Spring, MD on May 6, 2016. The meeting was organised by the U.S. FDA and co-hosted with Health Canada (HC), with presenters from FDA, HC, and PhRMA.

In addition, the FDA will also be organising a regional public workshop on August 22-23, 2016 at FDA’s White Oak campus in Silver Spring, MD to elaborate key aspects of the ICH Q3D Guideline on *Elemental Impurities*, in order to facilitate a harmonised interpretation and implementation by industry and regulators. The workshop will have presenters from FDA, PhRMA, and USP.
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 7

7. Training
The MC will present to the Assembly on the development of an ICH Training Strategy.

**Action:**
- The Assembly will be invited to share its views.

**Chronicle:**

**Extract from the Assembly Meeting Final Minutes, Lisbon, Portugal, June 15 – 16, 2016:**

**ICH Cooperation with Other Organisations**
The Assembly received a status report on the AHC e-learning pilot project on the ICH E2 Series of Pharmacovigilance Guidelines. The Assembly noted that the E-Learning Center is expected to launch the pilot programme in Q3 2016 which would be open free of charge for a limited time period (up to 12 months).

**Decision/Action:**
- The Assembly congratulated the AHC on progress made in the development of the pilot programme on ICH E2 Guidelines in collaboration with ICH.

**ICH Training Strategy**
The Assembly also received a status report on the MC’s development of an ICH Training Strategy.

**Decisions/Actions:**
- The Assembly noted that the MC is in the process of developing an ICH Training Strategy;
- The AHC will continue discussing with the MC regarding the development of training materials.
8. Update on MedDRA

The MedDRA MC Chair or Chair’s delegate will provide a report on current MedDRA activities. The report will cover the following matters:

- Training in ICH regions and beyond;
- Tools to facilitate MedDRA’s use;
- Development of a patient friendly list of MedDRA terms;
- Development of Standardised MedDRA Queries (SMQs);
  - Status of SMQ development;
  - Collaboration with the Council for International Organizations of Medical Sciences (CIOMS).

Action:

- The Assembly will be invited to share its views on the report.

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Assembly received a report on the ICH MedDRA Management Board (MB) meeting held on 11 – 12 June 2016.

The report covered the following matters: establishment of the MedDRA Management Committee; completion of the MSSO Call for Tender; 2017 subscription rates; training; development of Standardised MedDRA Queries (SMQs) including status of SMQ development and collaboration with the Council for International Organizations of Medical Sciences (CIOMS); tools to facilitate MedDRA’s use; and the MedDRA 2016 Annual Work Plan.

The Assembly was updated on the inaugural MedDRA Management Committee (MC) meeting that was held virtually on April 19, 2016, although several formalities need to be completed before MedDRA can be transferred to the new ICH Association. Once transferred, the MedDRA MC, which is a body of the ICH Association, will become fully operational. Prior to the transfer, the MedDRA MC will only have responsibilities for MedDRA issues which pertain to the new ICH Association.

The Assembly noted the completion of the Call for Tender for the Maintenance and Support Services Organisation (MSSO) that was launched by ICH in August 2014, with bids invited by
October 31, 2014. ICH’s Tender Evaluation Panel made its recommendation of the selected bidder to the MedDRA MC and the contract is in the process of being signed off. A specific press release will be published shortly to announce the selected bidder.

The Assembly was informed of the MedDRA MB’s consideration to give a reduction in the 2017 Subscription rates, based on the continued growth of MedDRA subscribers throughout the world – currently numbering over 4,500 organisations – and increased efficiencies to contain costs of maintenance and development of MedDRA. The MedDRA MB will take a decision on the 2017 rates shortly.

The Assembly also noted the importance of training in helping to facilitate the use of MedDRA and that the MSSO provides free training to Regulators and other MedDRA users as part of their MedDRA subscription package, with training available in several forms: face-to-face training; webinars; and e-learning tools/videocasts. The Assembly heard that in 2016 the MSSO had scheduled a total of 99 training courses which included 68 face-to-face training classes and 31 webinars. It was noted that a similar scale of training is planned for 2017, with all training offerings advertised on the website www.meddra.org.

The Assembly was also updated on ICH’s work with CIOMS to develop Standardised MedDRA Queries (SMQs). In Lisbon, the MedDRA MB acknowledged the significant contributions of the CIOMS SMQ Working Group (WG) and the development to-date of 101 SMQs. In addition, the MedDRA MB also congratulated CIOMS for its work on the second edition of the CIOMS SMQ WG’s book on Development and Rational Use of Standardised MedDRA Queries, which is due shortly for publication.

The Assembly was also informed of the release of a new version of the MedDRA Web-Based Browser (WBB) in May 2016 which updates the user interface in all MedDRA languages, includes hierarchy information when exporting MedDRA terms, as well as search results displayed in more than one language. Additionally, the Assembly was updated on the coming soon Account Self-Service Application which is a web-based application which allows users to obtain subscription information; add/delete/change point of contact; change of password; download or print Training Certificates.

Decisions/Actions:

- The Assembly noted the decisions taken by the MedDRA MB;
- The Assembly approved MedDRA 2016 Annual Work Plan and supported its publication on the ICH website.
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 9

9. Annual Work Plan and Multi-Annual Strategic Plan of the Association

The ICH MC will present to the Assembly the 2017 ICH Work Plan and Multi-annual Strategic Plan.

**Action:**
- The Assembly is requested to take a decision to approve the 2017 ICH Work Plan and Multi-annual Strategic Plan.

The MedDRA MC Chair or Chair’s delegate will present to the Assembly the 2017 MedDRA MC Work Plan.

**Action:**
- The Assembly is requested to take a decision to approve the 2017 MedDRA MC Work Plan.

**Chronicle:**

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The ICH Secretariat presented to the Assembly the 2016 Work Plan and Multi-annual Strategic Plan of the Association.

**Decision/Action:**
- The Assembly approved the 2016 Work Plan and Multi-annual Strategic Plan for the Association and agreed to their publication on the ICH website.
10. Implementation of ICH Guidelines

**Action:**
- The Regulatory Members of the Assembly will be invited to share information on the status of implementation of the ICH Guidelines in their respective countries or regions.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Assembly noted that as per the Assembly RoP, there should be a process for the Assembly to monitor the progress of international harmonisation and coordinate efforts in this regard. All ICH Regulators were invited to update the Assembly on the status of implementation of ICH Guidelines in their respective countries and regions.

The Assembly noted that this item provides an opportunity for the Regulators to share their experience, explain challenges and how to overcome them; and develop good practice relating to the implementation of ICH Guidelines.

**Decision/Action:**
- The Assembly Members and Observers shared information on the status of implementation of ICH Guidelines in their respective countries and regions.
ICH2016/18

ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 11

REPORT ON EWGS/IWGS/DICUSSION GROUPS


Hereafter please find the status of ICH Topics, before the start of the current round of Expert/Implementation Working Group (EWG/IWG) meetings.

This is intended to assist the Assembly in setting a timetable for reports on the ICH Topics under Agenda items 12 to 21, and also to act as a background paper for that discussion:

<table>
<thead>
<tr>
<th>ICH Topics:</th>
<th>Status of EWG/IWG Activities:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S5(R3) EWG:</strong> Revision of Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility</td>
<td>The S5(R3) EWG to continue its work on the revision of the S5(R2) Guideline. <em>Step 1 sign-off and Step 2a/b endorsements are expected by Q3 2017.</em></td>
</tr>
<tr>
<td><strong>S11 EWG:</strong> ICH Guideline on Nonclinical Safety Testing in support of Development of Paediatric Medicines</td>
<td>The S11 EWG to continue its work on the development of the S11 Guideline. <em>Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.</em></td>
</tr>
<tr>
<td><strong>Q12 EWG:</strong> ICH Guideline on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management</td>
<td>The Q12 EWG to continue its work on the development of the Q12 Guideline. <em>Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.</em></td>
</tr>
<tr>
<td><strong>E2B(R3) IWG:</strong> Revision of the Electronic Submission of Individual Case Safety Reports</td>
<td>The E2B(R3) IWG to continue its work on items including completion of a document on how to use the EDQM routes of Administration, an editorial update to the Implementation Guide to reflect the Q&amp;A document, and the determination of any conflicts in ICSR messages based upon review of regional Implementation Guides. <em>Step 3 and Step 4 of the editorial changes made to the Implementation Guide to reflect the Q&amp;A document are expected in November 2016.</em></td>
</tr>
<tr>
<td>EWG/Commissioner</td>
<td>Description</td>
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<tr>
<td><strong>E9(R1) EWG:</strong> Addendum to Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses</td>
<td>The E9(R1) EWG to continue its work on the development of the E9 Addendum.</td>
</tr>
<tr>
<td><strong>E17 EWG:</strong> ICH Guideline on Multi-Regional Clinical Trials</td>
<td>The E17 EWG to continue its work on the finalisation of the E17 Guideline.</td>
</tr>
<tr>
<td><strong>E18 EWG:</strong> ICH Guideline on Genomic Sampling and Management of Genomic Data</td>
<td>The E18 EWG to continue its work on the finalisation of the E18 Guideline.</td>
</tr>
</tbody>
</table>
| **M8 EWG/IWG:** The Electronic Common Technical Document: eCTD | The M8 EWG/IWG to continue its work on activities including: updating the Implementation Package and Specification Change Request document; developing the v4.0 Q&A v1.0; and communication with vendors. | *Step 3 and Step 4 of the eCTD v4.0 Implementation Package v1.2 are expected in November 2016.*  
*Step 3 and Step 4 of the eCTD v4.0 Questions and Answers and Specification Change Request Document v1.0. are expected in November 2016.* |
| **M9 EWG:** Biopharmaceutics Classification System-based Biowaivers | The M9 EWG to meet for the first time and initiate its work on the M9 Guideline. | *Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.* |
| **M10 EWG:** Bioanalytical Method Validation | The M10 EWG to meet for the first time and initiate its work on the M10 Guideline. | *Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.* |
Under Agenda item 22, the Assembly will be invited to raise any issues regarding groups not meeting in Osaka. The following is intended to assist the Assembly with this discussion:

<table>
<thead>
<tr>
<th>ICH Topics:</th>
<th>Status of EWG/IWG/Discussion Group Activities:</th>
</tr>
</thead>
</table>
| S1 EWG: Revision of the Rodent Carcinogenicity Studies for Human Pharmaceuticals Guideline | The S1 EWG is not meeting in Osaka but is working on the collection and review of confidential submissions of Carcinogenicity Assessment Documents (CADs).  
*Step 1 sign-off and Step 2a/b endorsements are expected by June/November 2019.* |
| S3A IWG: Q&As on Note for Guidance on Toxicokinetics                      | The S3A IWG is not meeting in Osaka but is working by email/teleconference on the finalisation of the S3A Q&As.  
*Step 3 sign-off and Step 4 adoption are expected by June 2017.*                           |
| S9 IWG: Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals       | The S9 IWG is not meeting in Osaka but is working by email/teleconference on the finalisation of the S9 Q&As.  
*Step 3 postal sign-off is expected by December 2016.  
Step 4 is expected in June 2017 at the subsequent Assembly meeting.*             |
| Q3C(R6) Maintenance EWG: Maintenance of the Guideline for Residual Solvents | The Q3C(R6) Maintenance EWG is not meeting in Osaka but is working by email/teleconference.  
*Step 3 postal sign-off is expected in Q3/Q4 2016.  
Step 4 is expected in November 2016.*                                           |
| Q3D(R1) Maintenance EWG: Training Guideline for Elemental Impurities       | The Q3D(R1) Maintenance EWG is not meeting in Osaka but is initiating its new activity regarding the development of permitted daily exposures for all 24 elements included in the Q3D Guideline for the cutaneous and transdermal route of administration. |
| Q11 IWG: Q&As on API Starting Materials                                    | The Q11 IWG is not meeting in Osaka but is working by email/teleconference to develop the draft Q11 Q&As.  
*Step 1 postal sign-off is expecting in October 2016.  
Step 2a/b endorsements are expected in November 2016.*                           |
| E6(R2) EWG: Integrated Addendum to Good Clinical Practice (GCP)            | The E6(R2) EWG is not meeting in Osaka.  
*Step 4 is expected in November 2016.*                                           |
| E11(R1) EWG: Addendum to Paediatric Drug Development                      | The E11(R1) EWG is not meeting in Osaka but is working towards finalising the E11 Addendum.  
*Step 3 postal sign-off is expected in May 2017.  
Step 4 is expected in June 2017.*                                              |
<table>
<thead>
<tr>
<th><strong>E14/S7B DG</strong></th>
<th>The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs</th>
</tr>
</thead>
</table>
| **E14/S7B DG** | The E14/S7B DG is not meeting in Osaka but is working by email/teleconference.  
**E14/S7B DG recommendation on whether to reopen the E14 Guideline for a complete revision is expected by December 2017.** |
| **M1 PtC WG** | MedDRA Points to Consider  
The M1 PtC WG is not meeting in Osaka but is working to continue its work related to the update with each MedDRA release of the two PtC documents on Term Selection and Data Retrieval and Presentation; and the development of a proposal for a new area of work. |
| **M2 EWG** | Electronic Standards for the Transfer of Regulatory Information  
The M2 EWG is not meeting in Osaka. |
| **M4Q(R1) IWG** | Addressing CTD-Q Related Questions  
The M4Q(R1) IWG is not meeting in Osaka. |
| **M7(R1) EWG** | Addendum to Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk  
The M7(R1) EWG is not meeting in Osaka but is working towards finalising the M7 Addendum.  
**Step 3 sign-off is expected by December 2016 and Step 4 is expected in June 2017.** |
ICH2016/18

ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 12

REPORTS ON CURRENT TOPICS

12. S5(R3) EWG: Revision of Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility

The Acting Rapporteur will report on the outcome of the S5(R3) EWG meeting held on November 6 – 10, 2016 and progress made towards revising the ICH S5(R2) Guideline on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility. Step 1 sign-off and Step 2a/b endorsements are expected by Q3 2017.

Actions:
- The Assembly will be invited to provide its views on the report;
- The Assembly will be invited to approve the new Rapporteur for the S5(R3) EWG.

Background Document:
- S5(R3) EWG work plan, dated July 22, 2016.

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Rapporteur reported to the Assembly on the outcome of the S5(R3) EWG meeting held June 12 – 16, 2016 and progress made towards revising the ICH S5(R2) Guideline on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility. The Assembly noted the group’s progress related to the completion of the revision of the text for all sections where gaps were identified in the ICH S5(R2) Guideline, the compilation of a draft list of reference compounds, the agreement on: concept of qualification criteria, the exposure multiple for high dose selection, the placental transfer and lactational exposure, and the deferral strategies for Embryo-Foetal Development (EFD) testing. The Assembly also noted some remaining topics to be addressed by the EWG including the design of the reduced EFD study(ies), the foetal morphological variations and the harmonisation of assay qualification for regulatory acceptance.

The Assembly noted that the ICH S5(R3) EWG was expecting to reach Step 1 and Step 2a/b in June 2017.

Action/Decision:
- The Assembly endorsed the work plan of the S5(R3) EWG for activities to be undertaken.
ICH S5(R3) EWG Work Plan
22 July 2016

**Topic Adopted:** April 2014

**Last Face-to-Face Meeting:** Lisbon, Portugal – June 2016

### 1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Q-2Q 2016</td>
<td>Continuation of work on ICH S5(R3) via TCs in line with the identified work packages.</td>
</tr>
<tr>
<td>June 2016</td>
<td>F2F Meeting of the ICH S5 EWG Criteria for dose selection, criteria for species selection, performance criteria for possible regulatory acceptance of in vitro, ex vivo and non-mammalian in vivo (e.g. zebrafish) Embryo Fetal Development (EFD) assays, design of optional integrated testing strategies for EFD testing, combinations of <em>in vivo</em> study options for reproductive toxicity testing, integrated risk assessment, structure of the guideline</td>
</tr>
<tr>
<td>3Q-4Q 2016</td>
<td>Continuation of work on ICH S5(R3) via TCs in line with the identified action items.</td>
</tr>
<tr>
<td>November 2016</td>
<td>F2F Meeting of the ICH S5 EWG Discussion on reflections to the general concept received from EWG members Specific discussion of proposals for crafted and revised wording in the drafted guidance and appendix, including the content of the list of reference compounds in order to work towards a <em>Step 1</em> document</td>
</tr>
<tr>
<td>3Q 2017</td>
<td><em>Step 1</em> document</td>
</tr>
<tr>
<td>3Q 2019</td>
<td><em>Step 4</em> document</td>
</tr>
</tbody>
</table>

### 2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6 June 2014</td>
<td>ICH S5 Informal WG meeting in Minneapolis, US</td>
<td>➢ Discussion on the topic and agreement within IWG about concept-paper. <em>Post-hoc</em> discussion about the further process.</td>
</tr>
<tr>
<td>Date</td>
<td>Event</td>
<td>Details</td>
</tr>
<tr>
<td>------</td>
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<td>---------</td>
</tr>
<tr>
<td>10-13 November 2014</td>
<td>ICH S5 Informal WG meeting in Lisbon, Portugal</td>
<td>Re-discussion on the topic and agreement within IWG about revised concept-paper and way forward. Definition of work packages for revision ICH S5(R2).</td>
</tr>
<tr>
<td>2Q 2015</td>
<td>ICH S5(R3) EWG Telecons</td>
<td>Initiation of work on ICH S5(R3) in line with the identified workpackages.</td>
</tr>
<tr>
<td>8-11 June 2015</td>
<td>ICH S5(R3) EWG meeting in Fukuoka, Japan</td>
<td>Discussion on progress regarding the different work packages; including the drafting of new or revising of existing wordings in order to work towards a Step 1 document. Specific discussion on the scope, criteria for dose selection, criteria for species selection, basic principles for possible regulatory acceptance of in vitro, ex vivo and non-mammalian in vivo (e.g. zebrafish) EFD assays, design of optional integrated testing strategies for EFD testing, combinations of in vivo study options for reproductive toxicity testing.</td>
</tr>
<tr>
<td>24 September, 23 October, 17 November 2015</td>
<td>ICH S5(R3) EWG Telecons</td>
<td>Continuation of work on ICH S5(R3) in line with the identified workpackages.</td>
</tr>
<tr>
<td>7-10 December 2015</td>
<td>ICH S5(R3) EWG meeting in Jacksonville, US</td>
<td>Discussion on progress regarding the different work packages; including the drafting of new or revising of existing wordings in order to work towards a step 1 document.</td>
</tr>
<tr>
<td>1-2Q 2016</td>
<td>ICH S5(R3) EWG Telecons: multiple regional, 3 regulators only and 4 full EWG TCs</td>
<td>Continuation of work on ICH S5(R3) in line with the identified workpackages, drafting a new structure for guidance.</td>
</tr>
<tr>
<td>12-16 June 2016</td>
<td>ICH S5(R3) EWG meeting in Lisbon</td>
<td>Identified gaps and completed text for all sections; Compilation of a draft list of reference compounds; Work on concepts of qualification criteria and data review and discussion on exposure multiple for high dose selection, placental transfer and lactational exposure; mature options for deferral strategies for EFD testing;</td>
</tr>
<tr>
<td>Time Frame</td>
<td>Organizational Details</td>
<td>Tasks</td>
</tr>
<tr>
<td>------------</td>
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</tr>
</tbody>
</table>
| 3-4Q 2016  | ICH S5(R3) EWG Telecons | - Reiteration of controversial issues around the design of the reduced EFD study(ies), fetal morphological variations and harmonization of assay qualification for regulatory acceptance; Assignment of topics to craft wording and provide proposals;  
- Continuation of work on ICH S5(R3) in line with the assigned topics to mature text. |
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 13
REPORTS ON CURRENT TOPICS


The Rapporteur will report on the outcome of the S11 EWG meeting held on November 7 – 10, 2016 and progress made towards collecting data on juvenile animal studies and to develop the draft S11 Technical document on Nonclinical Safety Testing in Support of Development of Paediatric Medicines.

*Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.*

**Action:**
- The Assembly will be invited to provide its views on the report.

Background Document:
- [S11 EWG work plan](#), dated August 1, 2016.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Rapporteur reported to the Assembly on the outcome of the meeting of the S11 EWG held on June 13 – 16, 2016, and progress made towards collecting data on juvenile animal studies and developing the ICH Guideline on Nonclinical Safety Testing in Support of Development of Paediatric Medicines.

The Assembly noted the group continued to collect information on juvenile animal studies conducted to support paediatric programs in the last 7 years and reviewed the literature. The Assembly also noted that these data will add to the collective experience in conducting studies and point to areas where specific guidance is needed. Moreover, these data are expected to support the sections of the guideline on how to determine if juvenile animal studies are needed for those studies within scope of S11 and what design elements of juvenile animal studies are most useful.

In addition, the S11 EWG further progressed the development of the sections of the S11 Guideline and agreed with the S9 IWG on the scope regarding oncology products.

The Assembly noted that the ICH S11 EWG was expecting to reach *Step 1* and *Step 2a/b* in June 2017.

**Action/Decision:**
- The Assembly endorsed the work plan of the S11 EWG for activities to be undertaken.
ICH S11 EWG Work Plan
1 August 2016

**Topic Adopted:** November 2014

**Last Face-to-Face Meeting:** Lisbon, Portugal – June 2016

### 1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2017</td>
<td><em>Step 2b</em> Guideline</td>
</tr>
<tr>
<td>December 2018</td>
<td><em>Step 4</em> Guideline</td>
</tr>
</tbody>
</table>

### 2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>June – November 2016</td>
<td>Teleconferences</td>
<td>➢ Teleconferences of the EWG or subgroups as needed to accomplish objectives</td>
</tr>
<tr>
<td></td>
<td>Completion of data collection by EU and Industry</td>
<td>➢ Regulatory and industry experience with juvenile animal studies to support pediatric development should be completed and updated analysis discussed at the next face-to-face meeting in November</td>
</tr>
<tr>
<td>June – November 2016</td>
<td>Drafting and revision of guidance sections</td>
<td>➢ All sections of the document have been assigned for drafting, with discussions of the text at the teleconferences and November meeting</td>
</tr>
</tbody>
</table>
|                     | Continued review of literature relevant to juvenile animal toxicity studies | ➢ Developing systems  
➢ Regulatory process (needs, design of studies, impact on program)  
➢ Value of studies for pediatric programs |
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 14

REPORTS ON CURRENT TOPICS


The Rapporteur will report on the outcome of the Q12 EWG meeting held on November 6 – 10, 2016 and progress made towards developing the draft Q12 Technical document on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.

Step 1 sign-off and Step 2a/b endorsements are expected by June 2017.

Action:
- The Assembly will be invited to provide its views on the report.

Background Document:

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Rapporteur reported on the outcome of the Q12 EWG meeting held on June 12 – 16, 2016 and progress made towards developing the draft Q12 Technical document on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.

The Assembly noted the EWG’s progress made in Lisbon in the development of all Q12 chapters including, established conditions, Post Approval Change Management Protocols, Product Lifecycle Management Strategy, effective Pharmaceutical Quality System (Change Management), categorisation of change and data requirements/, and the application of Q12 for currently marketed products and lifecycle management plan.

The Assembly noted that the ICH Q12 EWG was expecting to reach Step 1 and Step 2a/b in June 2017.

Decision/Action:
- The Q12 EWG will provide a revised work plan for activities to be undertaken to the MC ahead of its teleconference to be held in autumn 2016.
ICH Q12 EWG Work Plan  
21 July 2016

**Topic Adopted:** 9 September 2014  
**Last Face-to-Face Meeting:** Lisbon, Portugal – June 2016

### 1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2015 - June 2016</td>
<td><strong>Four EWG meetings, via telecon,</strong> to assess progress on major issues, revise current draft, and produce Q12 Technical Document version 4. <strong>Interim informal 2-day meeting of the established conditions team April 6-8, 2016</strong> to prepare proposed text from June face-to-face meeting.</td>
</tr>
<tr>
<td>June 2016</td>
<td><strong>Face-to-face meeting,</strong> to review Q12 Technical Document version 4, and address disagreements and concerns. Agree on Q12 Technical Document version 5.</td>
</tr>
<tr>
<td>November 2016</td>
<td><strong>Face-to-face meeting,</strong> to review Q12 Technical Document version 6, and address disagreements and concerns. Agree on Q12 Technical Document version 7 to be shared with ICH parties and stakeholders.</td>
</tr>
<tr>
<td>November 2016 – June 2017</td>
<td><strong>Four EWG meetings, via telecon,</strong> to review input from ICH parties and stakeholders on issues that must be addressed before moving to Step 1 Technical Document.</td>
</tr>
<tr>
<td>June 2017</td>
<td><strong>Face-to-face meeting to finalize Step 1 and Step 2a/b Technical Document.</strong></td>
</tr>
</tbody>
</table>

### 2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2014 – November 2014</td>
<td><em>Step 1</em>: Consensus building, reviewing concept paper and business plan, and drafting the agenda for Lisbon meeting</td>
<td>EWG continued regular interactions by email</td>
</tr>
</tbody>
</table>
| November 2014 – June 2015 | Continue EWG discussion and meetings | The EWG will meet, via telecon, four times between January and May, 2015, to develop initial draft of guideline chapters, and to prepare for June Meeting:  
- Three sub-teams will be established to prepare |
proposals for consideration by the entire EWG

- January 21, 2015, EWG telecon to identify key topics for guideline and agree on an integrated approach for the guideline (Progress Report)
- February 23, 2015, EWG telecon to identify key elements of each chapter and agree on outline (Outline of Guideline) and initiate drafting of core guideline chapters
- March 31, EWG Telecon to discuss key issues and agreement on ‘bullet points’ content of guideline chapters, provide instructions to drafting teams to convert ‘bullet points’ to text, and to review EWG workplan (First Chapter Draft – Bullet points)
- May 13, 2015, EWG telecon to review draft of document, identify major challenges and prepare for June ICH F2F meeting (Chapters Draft)

<p>| June 2015 | EWG face-to-face meeting | EWG will meet face-to-face in June 2015, to address major challenges, develop guideline version 1 and agree on future milestones and timelines |
| June 2015 – December 2015 | Continue EWG discussion and meetings | The EWG will meet, via telecon, four times between June and December 2015 to review version 1, discuss major issues to produce updated Q12 Technical Document, and to prepare for December Meeting: |
| | | - Three sub-teams will continue to draft sections for consideration by the entire EWG |
| | | - July 8, 2015, EWG telecon to review Fukuoka progress and identified challenges and agree plan to address |
| | | - September 9, 2015, EWG telecon to review drafting teams materials, discuss common issues among drafting teams and address disagreements and concerns: |
| | | - October 14, EWG Telecon to review version 2 Technical document |
| | | - November 19, 2015, EWG telecon to review version 2 and agree on agenda for face-to-face meeting in December |
| December 2015 | EWG Face-to-face meeting | Face–to-face meeting to review updated Q12 Technical Document, and address disagreements and concerns. |
| December 2015 – June 2016 | Continue EWG discussion and meetings | Four EWG meetings, via telecon, to assess progress on major issues, revise current draft, and produce Q12 Technical Document |</p>
<table>
<thead>
<tr>
<th>Date Range</th>
<th>Event Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 6-8, 2016</td>
<td>Interim F2F Meeting of Established Conditions (EC) Team</td>
<td>Face–to-face meeting of EC team to advance the development of EC section. EC section is a pre-requisite for enabling further development of other Q12 elements including lifecycle management plans, expectations for life cycle approaches in managing to legacy (currently marketed) products and overall role of the PQS</td>
</tr>
<tr>
<td>June 2016</td>
<td>EWG face-to-face meeting</td>
<td>Face-to-face meeting, to review Q12 Technical Document version 4, and address disagreements and concerns</td>
</tr>
<tr>
<td>June 2016 – November 2016</td>
<td>Continue EWG discussion and meetings</td>
<td>Five EWG meetings, via telecon, to assess progress on major issues, revise current draft, and produce Q12 Technical Document version 6</td>
</tr>
<tr>
<td>November 2016</td>
<td>EWG face-to-face meeting</td>
<td>Face-to-face meeting, to review Q12 Technical Document version 6, and address disagreements and concerns</td>
</tr>
<tr>
<td>November 2016 – June 2017</td>
<td>Continue EWG discussion and meetings</td>
<td>Four EWG meetings, via telecon, to review input from ICH parties and stakeholders on issues that must be addressed before moving to Step 1 Technical Document</td>
</tr>
<tr>
<td>June 2017</td>
<td>EWG face-to-face meeting</td>
<td>Face-to-face meeting to finalize Step 1 and Step 2a/b Technical Document</td>
</tr>
<tr>
<td>June 2017 – November 2017</td>
<td>Continue EWG discussion and meetings</td>
<td>Receive Step 2a/b document comments, triage, and address significant issues</td>
</tr>
<tr>
<td>November 2017</td>
<td>EWG face-to-face meeting</td>
<td>Face-to-face meeting to finalize Step 3 and Step 4 document</td>
</tr>
</tbody>
</table>
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 15

REPORTS ON CURRENT TOPICS

15. E2B(R3) IWG: Revision of the Electronic Submission of Individual Case Safety Reports

The Rapporteur will report on the outcome of the E2B(R3) IWG meeting held on November 7 – 10, 2016 and progress made towards the completion of a document on how to use the EDQM routes of Administration; progress towards an editorial update to the Implementation Guide to reflect the Q&A document; and progress towards the determination of any conflicts in ICSR messages based upon review of regional Implementation Guides.

*Step 3 and Step 4 of the editorial changes made to the Implementation Guide to reflect the Q&A document are expected in November 2016.*

**Actions:**

- The Assembly will be invited to provide its views on the report;
- If *Step 3* of the editorial changes made to the Implementation Guide to reflect the Q&A document is reached in Osaka, the E2B(R3) Regulatory experts will be invited to sign-off; and the Regulatory Members of the Assembly will be invited to adopt as final under *Step 4* this document;
- The Assembly will note the temporary change in the Rapporteurship of the E2B(R3) IWG.

**Background Document:**

- E2B(R3) IWG work plan, dated August 4, 2016.

**Chronicle:**

**Extract from the Assembly Meeting Final Minutes, Lisbon, Portugal, June 15 – 16, 2016:**

The Rapporteur reported on the outcome of the E2B(R3) IWG meeting held on June 12 – 16, 2016 and progress made towards the finalisation of additional Q&As and the revision of documents in the Implementation Guide Package.

The Assembly noted the completion of the additional Q&As. *Step 3* was signed-off by the IWG in Lisbon and the Regulatory Members of the Assembly were invited to adopt as final under *Step 4* the additional Q&As in Lisbon, in June 2016.
The Assembly was updated on the current status of E2B(R3) implementation in the different regions with FDA and MHLW/PMDA having started the implementation, and EC and Health Canada to transition to E2B(R3) within the next years.

The Assembly also noted the need of the E2B(R3) IWG to have M2 EWG’s support regarding SDO monitoring and ISO standards.

The Assembly was also updated on E2B discussion with EDQM on Dose Forms (DF) and Routes of Administration (RoA) and was invited to endorse the designation of EDQM as the maintenance organization for DF and RoA TermIDs for E2B(R3), pending the approval of the EDQM governance board.
**Decisions/Actions:**

- The E2B(R3) Regulatory Experts signed-off Step 3 of the additional Q&As in the Implementation Guide Package;
- The Regulatory Members of the Assembly adopted Step 4 of the additional Q&As in the Implementation Guide Package;
- The EDQM will be designated as the maintenance organisation for DF and RoA TermIDs for E2B(R3) (pending the approval of the EDQM governance board);
- The E2B(R3) IWG will provide an updated work plan for activities to be undertaken to the MC ahead of its teleconference to be held in autumn 2016.
ICH E2B(R3) IWG/Subgroup Work Plan
4 August 2016

**Topic Adopted:** July 2013

**Last Face-to-Face Meeting:** Lisbon, Portugal – June 2016

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 2016</td>
<td>Sign off on editorial update to Implementation Guide to reflect the Q&amp;A document</td>
</tr>
<tr>
<td>November 2016*</td>
<td>Complete a document on how to use the EDQM dose form and route of Administration</td>
</tr>
<tr>
<td>August - November 2016*</td>
<td>Determine any conflicts in ICSR messages based upon review of regional Implementation Guides</td>
</tr>
</tbody>
</table>

*: anticipated, but it depends on regional implementation plan and external working group

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 August 2016</td>
<td>Development of draft work plan</td>
<td>➢ Submission of a draft work plan to cover activities between August and next ICH meeting in November 2016</td>
</tr>
<tr>
<td>August to October 2016</td>
<td>Monitor and discuss any comments received by the ICH Secretariat or within the regions</td>
<td>➢ Comments are going to be provided by each region and the ICH E2B mail box&lt;br&gt; ➢ Assess the need to address comments as Q&amp;As by the ICH. Determine a work plan to address the comments</td>
</tr>
<tr>
<td>August to October 2016</td>
<td>Update documents in the IG package and create Q&amp;As if needed</td>
<td>➢ According to the results of the comment resolution, the documents in the IG package are going to be updated and additional Q&amp;As are going to be created in line with the change control process if needed</td>
</tr>
<tr>
<td>August to October 2016</td>
<td><strong>Editorial update to the IG to reflect the Q&amp;A document</strong></td>
<td>✓ <strong>Making editorial corrections to the IG to reflect the Q&amp;A document.</strong></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>August to October 2016*</td>
<td>Prepare a draft document on how to use the EDQM dose form and route of Administration</td>
<td>✓ Drafting a guide document to explain how to use the EDQM dose form and route of Administration TermIDs for the E2B(R3) use.</td>
</tr>
<tr>
<td>August to October 2016*</td>
<td>Assess the need for cross-regional data exchange pilot</td>
<td>✓ Assess the need to conduct pilot testing to confirm whether regional ICSR messages can be accepted by other regions without causing parsing errors</td>
</tr>
<tr>
<td>August to October 2016*</td>
<td>Evaluate the progress of regional implementations to identify any potential conflict in ICSR messages</td>
<td>✓ Each region is responsible for evaluating impacts of other regional IGs and will summarize any regional issues for further discussion at the ICH</td>
</tr>
</tbody>
</table>

*: anticipated, but it depends on regional implementation and external working group
16. E9(R1) EWG: Addendum to Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses

The Rapporteur will report on the outcome of the E9(R1) EWG meeting held on November 4 – 8, 2016 and progress made towards developing the draft E9 Addendum on Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses.

Step 1 sign-off and Step 2a/b endorsements are expected by November 2016.

**Action:**
- The Assembly will be invited to provide its views on the report, and if Step 1 of the Addendum is signed-off by the E9(R1) EWG, the Assembly will be invited to endorse Step 2a of the E11 Addendum, following which the Regulatory Members of the Assembly will be invited to endorse Step 2b of the E11 Addendum.

Background Document:
- [E9(R1) EWG work plan](#), dated August 10, 2016.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Rapporteur reported on the outcome of the E9(R1) EWG meeting held on June 13 – 16, 2016 and progress made towards developing the draft E9 Addendum on Defining the Appropriate Estimand for a Clinical Trial/Sensitivity Analyses.

The Assembly noted the EWG progress made in Lisbon in the development of the Technical document for the Addendum to the E9 Guideline including the EWG agreement on content for the scope, the framework for positioning an estimands, the definition of estimands, and the classification for different choices of estimands. It was noted that the EWG proposes to promote specification and possibly discussion of the estimand choice in the trial protocol.

The Assembly noted the group’s proposal to insert footnotes in the Guideline where the existing guidance is superseded by E9 Addendum (e.g., on analysis sets, missing data and sensitivity analysis).

The Assembly also noted the impact of the Addendum on other ICH Guidelines: E3, E6(R2), and E8.

The Assembly also noted that the Addendum to ICH E9 was expected to reach Step 1 and Step 2a/b in November 2016; and that the EWG was reflecting on the organisation of the consultation process (Step 3) amongst stakeholders.
**Decisions/Actions:**

- The Assembly agreed that the E9(R1) EWG should further consider how the changes could be made in a clear manner and requested that the MC also consider how best to do this procedurally;
- The Assembly noted the impact of the work of the EWG on the E6(R2) Guideline and recommended that the comments received from the E9(R1) EWG be considered in Osaka when a strategic discussion will be organised at the Assembly level;
- The Assembly also noted the impact of the work of the EWG on the E8 Guideline and recommended that E9(R1) EWG develops a proposal for MC consideration;
- The Assembly agreed that the MC should discuss further the development of an engagement plan including the need of a broader consultation amongst stakeholders to facilitate understanding of the impact of the E9 Addendum on the E9(R1) Guideline;
- The Assembly endorsed the work plan of the E9(R1) EWG for activities to be undertaken.
ICH E9(R1) EWG Work Plan
10 August 2016

**Topic Adopted:** October 2014  
**Face-to-Face Meeting:** Lisbon, Portugal - June 2016

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
</table>
| Q4 2016         | *Step 1 and Step 2a* Finalisation of the Technical Document and sign-off by all ICH Parties’ members in the EWG and endorsement by the Assembly  
*Step 2b* Draft Addendum and endorsement by the ICH Regulatory Members of the Assembly. |
| Q1 2017         | *Step 3 phase* Publish draft Addendum |
| Q2 2017 – Q4 2017 | *Step 3 phase* Discuss regional consultation comments and consolidate the Draft Addendum |
| 2017 - 2018     | Finalisation of the Addendum and *Step 3* sign-off by topic leaders of the ICH Regulatory Members. *Step 4* adoption by the ICH Regulatory Members of the Assembly. |

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
</table>
| July to November 2016 | Progress towards *Step 1 and Step 2a* | ➢ Continue writing sections of the *Step 1* Technical Document.  
➢ Identify themes and aspects that would be more relevant in a technical appendix or scientific publication.  
➢ If needed, continue discussion of methodological issues to support drafting of Addendum.  
➢ Continue review of ICH E9 in relation with statements that relate to concepts to be developed in ICH E9 Addendum, and propose annotations or modifications. Continue review of other ICH ‘E’ Guidelines.  
➢ Prepare document(s) to support communication to the clinical community, including case studies.  
➢ Organise regional discussions, both with |
statisticians and non-statisticians, and discuss feedback from these meetings.

- Follow actions to be undertaken until the ICH meeting in November 2016, and that will contribute to the finalisation of the *Step 1* Technical Document.
- Discuss the need to meet in November at the ICH meeting in Japan. The Technical Document should be near final before the ICH November meeting.
- Monthly full group EWG teleconferences will be facilitated by the Rapporteur to ensure progress.
- Monthly full group EWG teleconferences will be facilitated by the Rapporteur to ensure progress.

<table>
<thead>
<tr>
<th>ICH Meeting November 2016</th>
<th><em>Step 1, Step 2a and Step 2b</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clarify outstanding issues and finalise the <em>Step 1</em> Technical Document.</td>
</tr>
<tr>
<td></td>
<td><em>Step 1</em>: Sign-off by all ICH Parties' members in the EWG.</td>
</tr>
<tr>
<td></td>
<td><em>Step 2a</em>: Sign-off by the Assembly.</td>
</tr>
<tr>
<td></td>
<td>Develop a presentation that helps users to understand the draft Addendum.</td>
</tr>
<tr>
<td></td>
<td>ICH Regulatory parties adapt the <em>Step 1</em> Technical Document into a draft Addendum which is then signed by the ICH Regulatory Parties.</td>
</tr>
<tr>
<td></td>
<td>Finalise the presentation of the Addendum.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>November 2016 to November 2017 (or later), including ICH Meeting June 2017</th>
<th><em>Step 3 phase</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deliverables set for this period will depend on the duration of the public consultation in each region and may be delayed.</td>
</tr>
<tr>
<td></td>
<td>Publish the draft Addendum in each region for a 3- or 6-month public consultation, under the <em>Step 3</em> procedure guidelines. The duration of public consultation, either 3 or 6 months, is subject to approval by each of the ICH Regulatory Parties.</td>
</tr>
<tr>
<td></td>
<td>Start discussing comments received in each region.</td>
</tr>
<tr>
<td></td>
<td>Discuss regional consultation comments and modification of the Addendum based on comments received. Outline plans for further progress towards finalisation.</td>
</tr>
</tbody>
</table>
| ICH Meeting November 2017 (or later) | **Step 3 and Step 4** | - Deliverables set for this period will depend on the duration of the public consultation in each region and may be delayed.  
- Finalisation of the Addendum.  
- *Step 3:* Sign-off by topics leaders of Regulatory ICH Parties.  
- *Step 4:* Sign-off by all ICH Regulatory Parties.  
- Develop a presentation that helps users to understand the Addendum. |
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 17

REPORTS ON CURRENT TOPICS

17. E17 EWG: ICH Guideline on Multi-Regional Clinical Trials

The Rapporteur will report on the outcome of the E17 EWG meeting held on November 7 – 10, 2016 and progress made towards updating the draft E17 Guideline on *Multi-Regional Clinical Trials* with comments received during the consultation period in the ICH regions.

*Step 3 sign-off and Step 4 adoption are expected by June 2017.*

**Action:**

- The Assembly will be invited to provide its views on the report.

**Background Document:**

- [E17 EWG work plan](#), dated August 9, 2016.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The E17 EWG did not meet in Lisbon.

The Assembly noted the current activities of the E17 EWG including the finalisation of the draft E17 Technical document on *Multi-Regional Clinical Trials* (MRCTs) and initiation of the consultation process. The Assembly noted that the primary focus of this guideline is on MRCTs designed to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval of additional indications, new formulations and new dosing regimens) and for studies conducted to satisfy post-marketing requirements.

The Assembly noted that the E17 EWG experts signed-off electronically *Step 1* in early June.

The Assembly also noted that the ICH E17 was expected to reach *Step 3* and *Step 4* in June 2017.

**Decisions/Actions:**

- The E17 Experts signed-off *Step 1* of the E17 Technical Document (via written postal procedure) in advance of the Assembly meeting;
- The Assembly Members endorsed *Step 2a* of the E17 Technical Document;
- The Regulatory Members of the Assembly endorsed *Step 2b* of the E17 Technical Document;
- The E17 EWG will provide a work plan to the MC (including the length of time for the public consultation period in each region) ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.
ICH E17 EWG Work Plan
9 August 2016

**Topic Adopted:** June 2014

**Last Face-to-Face Meeting:** Jacksonville, FL, USA - December 2015

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>2Q 2016</td>
<td><em>Step 1</em> Technical Document</td>
</tr>
<tr>
<td>2Q 2016</td>
<td><em>Step 2</em> Guideline</td>
</tr>
<tr>
<td>2Q 2017</td>
<td><em>Step 4</em> Guideline</td>
</tr>
</tbody>
</table>

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2016</td>
<td><em>Step 1</em> completed</td>
<td>➢ Experts signed off the document as <em>Step 1</em></td>
</tr>
<tr>
<td>June 2016</td>
<td><em>Step 2a/b</em> completed</td>
<td>➢ The <em>Step 2a/b</em> were completed at the ICH Lisbon meeting</td>
</tr>
<tr>
<td>July 2016-</td>
<td>Public consultation in each region</td>
<td>➢ The draft guideline was published for public consultation on July 15th in Japan and on July 28th in EU.</td>
</tr>
<tr>
<td>3Q 2016</td>
<td>Comments review</td>
<td>➢ Review public comments by e-mail and the web-conference.</td>
</tr>
<tr>
<td>November 2016</td>
<td>Fourth face-to-face EWG Meeting</td>
<td>➢ Revise the guideline based on comments received on the public consultation.</td>
</tr>
</tbody>
</table>
18. E18 EWG: ICH Guideline on Genomic Sampling and Management of Genomic Data

The Rapporteur will report on the outcome of the E18 EWG meeting held on November 7 – 10, 2016 and progress made towards updating the draft E18 Guideline on Genomic Sampling and Management of Genomic Data with comments received during the consultation period in the ICH regions.

*Step 3 sign-off and Step 4 adoption are expected by June 2017.*

**Action:**
- The Assembly will be invited to provide its views on the report.

**Background Document:**
- [E18 EWG work plan](#), dated August 5, 2016.

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The E18 EWG did not meet in Lisbon.

The Assembly noted the current activities of the E18 EWG including progress made towards updating the draft E18 Guideline on Genomic Sampling and Management of Genomic Data with comments received during the consultation period in the ICH regions.

The Assembly also noted that the ICH E18 was expected to reach *Step 3 and Step 4* in June 2017.

**Decision/Action:**
- *The E18 EWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.*
ICH E18 EWG Work Plan
5 August 2016

**Topic Adopted:** June 2014

**Last Face-to-Face Meeting:** Jacksonville, FL, USA - December 2015

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Q 2016</td>
<td>Complete regulatory consultations including consolidation of all the comments from each region</td>
</tr>
<tr>
<td>2Q 2017</td>
<td>Step 4 document sign off</td>
</tr>
</tbody>
</table>

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
</table>
| 2 Aug 2016               | Whole team discussion at the web-conference                                     | ➢ Agreed to request the next F2F meeting at Osaka to the MC  
➢ Discussed how to address comments received during regulatory consultations |
| By end of October 2016   | Whole team discussion at the web-conference (several times)                    | ➢ Prioritize high level comments to which consensus opinion from E18 EWG should be provided  
- Remaining comments except high level (e.g., editorial comments) would be handled after finishing discussion about high level comments |
| 4Q 2016                  | Clarify EWG’s opinion about every single comment prioritized as high level during Osaka meeting | ➢ Reach a consensus on amendment of draft E18 document based on high level comments (so called “EWG’s consensus document for Step 3 sign off”). |
| 2Q 2017                  | Step 4 document sign off                                                       | ➢ Finalization of E18 document based on the results of discussion at Osaka meeting and remaining comments except classified as high level. |
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 19

REPORTS ON CURRENT TOPICS


The Rapporteur will report on the outcome of the M8 EWG/IWG meeting held on November 7 – 10, 2016 and progress made on the current activities of the M8 EWG/IWG including: updating the Implementation Package and Specification Change Request document; developing the v4.0 Q&A v1.0; and communication with vendors.

Step 3 and Step 4 of the eCTD v4.0 Implementation Package v1.2 are expected in November 2016.

Step 3 and Step 4 of the eCTD v4.0 Questions and Answers and Specification Change Request Document v1.0 are expected in November 2016.

Action:

- If Step 3 of the eCTD v4.0 Implementation Package v1.2 and the eCTD v4.0 Q&As and Specification Change Request Document v1.0 are reached in Osaka, the M8 Regulatory experts will be invited to sign-off; and the Regulatory Members of the Assembly will be invited to adopt as final under Step 4 these 2 documents.

Background Document:

- M8 EWG/IWG work plan, dated August 5, 2016.

Chronicle:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL,
JUNE 15 – 16, 2016:

The M8 EWG/IWG did not meet in Lisbon.

The Assembly noted the current activities of the M8 EWG/IWG, including Q&As session with eCTD Tool Vendors; finalisation of the eCTD v4.0 Orientation Materials; finalisation of the revised Granularity Document included in the M4(R3) Guideline on Organisation with M4Q(R1) IWG agreement; and work on an updated version of the eCTD v3.2.2 Q&As/Change Request document.

The Assembly also noted the eCTD v4.0 Q&As and Change Request Document is expected to reach Step 3 and Step 4 at the next meeting in Osaka in November 2016.
Decisions/Actions:

- The M8 Regulatory Experts signed-off Step 3 of the revised Granularity Document included in the M4(R3) Guideline on Organisation and the eCTD v3.2.2 Q&As and Specification Change Request v1.28 Document;
- The Regulatory Members of the Assembly adopted under Step 4 the revised Granularity Document included in the M4(R3) Guideline on Organisation and the eCTD v3.2.2 Q&As and Specification Change Request v1.28 Document;
- The M4(R4) Guideline on Organisation will be published on the ICH website;
- The eCTD v3.2.2 Q&As and Specification Change Request v1.28 Document will be published on the ICH website;
- The M8 Experts signed-off the Support Document and Orientation Materials;
- The Assembly endorsed the Support Document and Orientation Materials;
- The Assembly noted that these documents will be published on the ESTRI website;
- The M8 EWG/IWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.
ICH M8 EWG/IWG Work Plan
5 August 2016

Topic Adopted: 11 November 2011
Last Face-to-Face Meeting: Jacksonville, FL, USA - December 2015

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 November 2016</td>
<td>Step 4 eCTD v4.0 Implementation Package v1.2.</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>July – Nov 2016</td>
<td>Update the Implementation Package. Update SSF document.</td>
<td>Discuss change requests&lt;br&gt;Update and agree to the documents&lt;br&gt;Ask M2/HL7/Lawyer for their review prior to Osaka Meeting</td>
</tr>
<tr>
<td>July – Nov 2016</td>
<td>Develop v4.0 Q&amp;A v1.0.</td>
<td>Discuss change requests&lt;br&gt;Develop and agree to the Q&amp;As</td>
</tr>
<tr>
<td>July – Nov 2016</td>
<td>Determine how/whether to continue communication with vendors.</td>
<td>Develop and agree to the communication plan&lt;br&gt;Contact the vendors</td>
</tr>
</tbody>
</table>
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 20

REPORTS ON CURRENT TOPICS

20. M9 EWG: Biopharmaceutics Classification System-based Biowaivers

The Rapporteur will report on the outcome of the first meeting of the M9 EWG held on November 7 – 10, 2016 and progress made towards developing the draft guideline on Biopharmaceutics Classification System-based Biowaivers. 

*Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.*

**Action:**

- The Assembly will be invited to provide its views on the report.

Background Documents:

- [Final M9 Concept Paper](#), dated October 7, 2016;

**Chronicle:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The MC reported on the development of a process for the selection of new ICH technical topics for use in future ICH Meetings.

In addition, the MC presented to the Assembly for its consideration and approval its recommendation to adopt for the following 2 new topics for the development as ICH Guidelines: *Biopharmaceutics Classification System-based Biowaivers* and *Bioanalytical Method Validation.*

The MC also presented a proposal to the Assembly regarding the organisation of strategic topics discussions at the next ICH meeting to be held in Osaka, Japan in November 2016.

**Decisions/Actions:**

- The Assembly noted the proposed ICH process for the selection of new ICH topics and supported that the process be run on a yearly basis (6-month process);
- The Assembly noted the Concept Paper outlines for the following 2 new ICH topics which were recommended by the MC to the Assembly for its approval:
  - *Biopharmaceutics Classification System-based Biowaivers* (proposed by EC)
  - *Bioanalytical Method Validation* (proposed by MHLW/PMDA)
- The Assembly adopted the Concept Paper outline on *Biopharmaceutics Classification System-based Biowaivers* (code: ICH M9) and agreed on the establishment of an informal Working
Group (with EC nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

- The Assembly adopted the Concept Paper outline on Bioanalytical Method Validation (code: ICH M10) and agreed on the establishment of an informal Working Group (with MHLW/PMDA nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

- The ICH Secretariat will launch the nomination process amongst ICH Members for the establishment of the 2 informal Working Groups;

- Further to Article 17(5), any ICH Observer interested to participate in the activities of these new Working Groups (WGs) would need to inform the ICH Secretariat in writing and provide explanations for their interest in the specific Working Group, information about their available expertise and how they expect to contribute to the work of the WG;

- Any request received by the ICH Secretariat, will be shared with the MC; and the Assembly may, on the basis of the recommendation by the MC, invite Observers to appoint experts in the WGs. The Assembly will be able to take a decision on such invitations at the Osaka meeting in November 2016;

- The Assembly nominated EC as the Rapporteur for the ICH M9 EWG and MHLW/PMDA as the Rapporteur for the ICH M10 EWG;

- The Founding Regulatory Members and the Standing Regulatory Members will confirm the respective Regulatory Chairmanship for these 2 new EWGs once established;

- The Assembly also noted the following 2 additional new topic proposals considered by the MC in Lisbon and recommended that the MC further discussed and provide feedback on these in Osaka:
  - Safety Data Collection (proposed by FDA);
  - Adaptive Clinical Trials (proposed by PhRMA);

- The Assembly also noted the general outline on the organisation of ICH Strategic discussions for which FDA was tasked to develop a proposed approach for the structure and organization of Strategic topics discussions;

- The Assembly agreed on a recommendation that proposals are developed for strategic discussions in Osaka on Good Clinical Practices (to be led by FDA) and on Compliance of Reliability for Electronic Data (to be led by JPMA and supported by FDA).
Final endorsed Concept Paper
M9: Biopharmaceutics Classification System-based Biowaivers
7 October 2016

Type of Harmonisation Action Proposed

This proposed new multidisciplinary guideline will address Biopharmaceutics Classification System (BCS)-based biowaivers. This guideline will provide recommendations to support the biopharmaceutics classification of medicinal products and will provide recommendations to support the waiver of bioequivalence studies.

This will result in the harmonisation of current regional guidelines/guidance and support streamlined global drug development.

Statement of the Perceived Problem:

Biopharmaceutics Classification System (BCS)-based biowaivers may be applicable to BCS Class I and III drugs, however BCS-based biowaivers for these two classes are not recognized worldwide. Regulatory guidelines/draft guidance which includes the possibility of BCS-based biowaivers have been issued in, for instance, the EU, US, Canada and within the WHO. Also, Japanese guideline includes the possibility of biowaivers based on the extent of formulation change. However, it appears from these guidelines that BCS based biowaivers may not be recognized globally or that the requested supportive data for such applications differs. In addition, even the classification itself may differ. This means that pharmaceutical companies have to follow different approaches in the different regions.

Current bioequivalence/biowaiver guidelines/guidances include:

- **EU**
  Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1, 2010)

- **US**
  Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry (draft 2015)

- **Japan**
  Guideline for Bioequivalence Studies of Generic Products (2012)

- **Canada**
  Guidance Document: Biopharmaceutics Classification System Based Biowaiver (2014)

- **WHO**
Issues to beResolved:

The main issues to be resolved can be divided into supportive data for the classification of the medicinal products into one of the 4 classes of BCS and supportive data for the waiver itself. The guidance/recommendations in the guideline will address the following issues:

1. Supportive data for classification

- **Solubility:** Considering a drug highly soluble or low soluble, the highest therapeutic dose as mentioned in the product label for the specific medicinal product can be taken into account or the highest dose strength of the medicinal product.

- **Permeability:** Different methods exist to estimate permeability. Harmonisation is sought on whether the estimation of permeability should be based upon *in vitro* data, *in vivo* data or both. Furthermore, when identified the most suitable method, cut-off values should be established to consider a medicinal product highly permeable or low permeable.

- Are literature data acceptable to support the BCS classification?

2. Supportive data for a waiver

- Establish cut-off values of dissolution criteria depending on whether the drug is considered a BCS Class I or a BCS Class III drug (note: depending on the applicability/acceptability of a BCS waiver for Class I and III drugs).

- With regard to comparability of the Test or proposed formulation versus the Reference formulation or Comparator formulation, establishing what are critical excipients which may influence the rate and/or extent of absorption of a drug. Additionally, criteria to consider formulations quantitatively comparable may be established, and the type of data needed to demonstrate that an excipient is non-critical may be clarified.

Additionally, the following issues will be resolved if possible:

- As *in vitro* dissolution testing is required for a BCS-based biowaiver, the conditions for dissolution testing should be established. Can different criteria be applied than the default conditions, e.g. a higher or lower agitation speed? If so, what kind of justification could be considered acceptable?

- Clarify if a BCS based biowaiver is only applicable for pharmaceutical equivalents. Furthermore, in case the Reference formulation or Comparator formulation is marketed with more than 1 strength, for example 10 and 20 mg IR release tablets, clarify whether the BCS based biowaiver should be matched 1 to 1, i.e., comparability should be shown between the 10 mg of the Reference/Comparator and 10 mg Test formulation and between the 20 mg of the Reference/Comparator and 20 mg Test formulation. Or is a full BCS based biowaiver sufficient for 1 strength and the other strength can be accepted based upon a biowaiver for additional strength.
Background to the Proposal:

Although the scientific data that can be used to support BCS-based biowaivers is the same, it seems that interpretation of these data differs. Harmonisation will create a common understanding of the applicability of BCS-based biowaivers and the conditions of waiving, which in addition can be used also outside ICH countries developing and/or introducing BCS-based biowaivers.

Strategic Importance of the Topic

BCS-based biowaivers may prevent unnecessary exposure of mostly healthy volunteers to medicinal products. It will reduce the costs and time of developing, as in vivo studies to prove the biopharmaceutical quality of the medicinal product would not needed. Furthermore, it may be an effective way to facilitate introduction of medicinal products of good quality, especially in developing countries. Harmonisation would simplify the requirements by reducing in vivo studies, and therefore, facilitate the patient’s access to medicines or post-approval changes.

Harmonisation would allow pharmaceutical companies to follow the same approach in all jurisdictions and help regulatory agencies in the timely authorization and availability of safe, effective and quality drugs based upon common and harmonised accepted criteria.

Type of Expert Working Group Recommended:

The EWG will require biopharmaceutic experts and clinical pharmacologists/pharmacokineticists to be nominated from the Members and Observers in line with the applicable Rules of Procedure.

Timing:

- Adoption of the topic by Approval of ICH Assembly: June 2016
- First EWG meeting (Osaka, Japan): Nov. 2016
- Adoption of Step 2 a/b Document: 1 - 2Q 2018
- Adoption of Step 4 Document: 2Q 2019
Final endorsed Business Plan
M9: Biopharmaceutics Classification System-based Biowaivers
7 October 2016

1. **The issue and its costs**
   - *What problem/issue is the proposal expected to tackle?*
     From current regulatory guidelines/draft guidance which includes the possibility of Biopharmaceutics Classification System (BCS) based biowaivers, it appears that BCS based biowaivers may not be recognized or that the requested supportive data for such applications differs. In addition, even the classification itself may differ. This means that pharmaceutical companies have to follow different approaches in the different regions. This lack of harmonisation may imply that additional bioequivalence studies should be carried out, depending on the region/guideline. Furthermore it may hamper a streamlined global drug development.

   - *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with “non action”?*
     The conflicting regional recommendations on the acceptability of BCS based biowaiver are leading to different requirements and possible the need of *in vivo* data (bioequivalence study) instead of *in vitro* studies (dissolution data). This results in increased drug development costs overall and sometimes to unnecessary exposure of healthy volunteers to medicinal products.

2. **Planning**
   - *What are the main deliverables?*
     The main deliverable is a guideline document on BCS-based biowaivers, which provides clear requirements on the applicability of BCS-based biowaivers and on supportive data for such application.

   - *What resources (financial and human) would be required?*
     It is anticipated that the *Step2 a/b* document will be approximately completed in 1 - 2Q 2018. It is envisaged that a WG member needs 18 - 24 days/year to work on the development of this guideline.
• What is the time frame of the project and what will be the key milestones?

The request will be submitted to the ICH Management Committee (MC) in September 2016 with expectation of the EWG meeting face-to-face in November 2016 at Osaka.

It is anticipated that the Step 2 a/b document will be completed in 1 - 2Q 2018 and that Step 4 will be reached in 2Q 2019.

3. The impacts of the project

• What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?

Clarifying the basic requirements for accepting and applying BCS-based biowaivers by establishing a guideline, reduces the need for carrying out additional clinical (bioequivalence) studies in humans. As a result, international harmonisation on the topic can accelerate the development of new drugs, line extensions of new drugs and generics and can lower the costs significantly.

• What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?

The proposal is consistent with current laws and regulations of the ICH regions. Regulatory authorities responsible for reviewing pharmacokinetic (bioequivalence) data will need to agree globally on accepting and applying BCS-based biowaivers. This guideline will supersede regional guidelines, and mutual use of the data in different countries/regions based on the guideline will become possible.

4. Post-hoc evaluation

• How and when will the results of the work be evaluated?

In case scientific data become available which may support the classification of other BCS classes as mentioned in the guideline, or in case supportive data become available resulting in a change of the requirements of BCS based biowaivers, after the topic reaches Step 5 in each region, the EWG may need to evaluate/update the guideline, if any.
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 21

REPORTS ON CURRENT TOPICS

21. M10 EWG: Bioanalytical Method Validation

The Rapporteur will report on the outcome of the first meeting of the M10 EWG held on November 7 – 10, 2016 and progress made towards developing the draft guideline on Bioanalytical Method Validation.

*Step 1 sign-off and Step 2a/b endorsements are expected by June 2018.*

**Action:**
- The Assembly will be invited to provide its views on the report.

Background Documents:
- [M10 Concept Paper](#), dated October 7, 2016;

**Chronicle:**

*EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:*

The MC reported on the development of a process for the selection of new ICH technical topics for use in future ICH Meetings.

In addition, the MC presented to the Assembly for its consideration and approval its recommendation to adopt for the following 2 new topics for the development as ICH Guidelines: *Biopharmaceutics Classification System-based Biowaivers* and *Bioanalytical Method Validation*.

The MC also presented a proposal to the Assembly regarding the organisation of strategic topics discussions at the next ICH meeting to be held in Osaka, Japan in November 2016.

**Decisions/Actions:**
- The Assembly noted the proposed ICH process for the selection of new ICH topics and supported that the process be run on a yearly basis (6-month process);
- The Assembly noted the Concept Paper outlines for the following 2 new ICH topics which were recommended by the MC to the Assembly for its approval:
  - *Biopharmaceutics Classification System-based Biowaivers* (proposed by EC)
  - *Bioanalytical Method Validation* (proposed by MHLW/PMDA)
- The Assembly adopted the Concept Paper outline on *Biopharmaceutics Classification System-based Biowaivers* (code: *ICH M9*) and agreed on the establishment of an informal Working
Group (with EC nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

- The Assembly adopted the Concept Paper outline on Bioanalytical Method Validation (code: ICH M10) and agreed on the establishment of an informal Working Group (with MHLW/PMDA nominated as Lead) to finalise the Concept Paper and develop a Business Plan ahead of the MC Teleconference to be held in autumn 2016;

- The ICH Secretariat will launch the nomination process amongst ICH Members for the establishment of the 2 informal Working Groups;

- Further to Article 17(5), any ICH Observer interested to participate in the activities of these new Working Groups (WGs) would need to inform the ICH Secretariat in writing and provide explanations for their interest in the specific Working Group, information about their available expertise and how they expect to contribute to the work of the WG;

- Any request received by the ICH Secretariat, will be shared with the MC; and the Assembly may, on the basis of the recommendation by the MC, invite Observers to appoint experts in the WGs. The Assembly will be able to take a decision on such invitations at the Osaka meeting in November 2016;

- The Assembly nominated EC as the Rapporteur for the ICH M9 EWG and MHLW/PMDA as the Rapporteur for the ICH M10 EWG;

- The Founding Regulatory Members and the Standing Regulatory Members will confirm the respective Regulatory Chairmanship for these 2 new EWGs once established;

- The Assembly also noted the following 2 additional new topic proposals considered by the MC in Lisbon and recommended that the MC further discussed and provide feedback on these in Osaka:
  - Safety Data Collection (proposed by FDA);
  - Adaptive Clinical Trials (proposed by PhRMA);

- The Assembly also noted the general outline on the organisation of ICH Strategic discussions for which FDA was tasked to develop a proposed approach for the structure and organization of Strategic topics discussions;

- The Assembly agreed on a recommendation that proposals are developed for strategic discussions in Osaka on Good Clinical Practices (to be led by FDA) and on Compliance of Reliability for Electronic Data (to be led by JPMA and supported by FDA).
Final endorsed Concept Paper
M10: Bioanalytical Method Validation
7 October 2016

Type of Harmonisation Action Proposed
The proposed new multidisciplinary guideline will apply to the validation of bioanalytical methods and study sample analyses in non-clinical and clinical studies. This guideline will provide recommendations on the scientific regulatory requirements for bioanalysis conducted during the development of drugs of both chemical and biological origins. This will result in the harmonisation of current regional guidelines/guidances and support streamlined global drug development.

Statement of the Perceived Problem
Bioanalysis herein means the quantification of drugs and their metabolites in biological matrices such as plasma, serum, blood, urine or other body fluids, which are conducted in non-clinical and clinical studies. Reliable data derived through validated bioanalytical methods are key for the review of marketing authorisation application.

In the EU, US and Japan, regulatory guidelines or draft guidelines for bioanalytical method validation (BMV) have been issued and recommendations on basic requirements are established for these nations/regions. However, several differences in method validation and study sample analysis exist among these guidelines/guidances and remain hurdles for the mutual use of bioanalytical data in global drug development. This means that sponsors, pursuing global approvals, are required to reconcile multiple guidelines/guidances in different countries and often requires unnecessary duplicative testing in order to meet the variable requirements.

Current BMV guidelines/guidances:
- EU Guideline on Bioanalytical Method Validation (2011)
- Japan Guideline on Bioanalytical Method Validation in Pharmaceutical Development (2013)
- Guideline on Bioanalytical Method (Ligand Binding Assay) Validation in Pharmaceutical Development (2014)

Issues to be Resolved
The main technical and scientific issues in BMV can be categorized as method validation, study sample analysis and other issues as described below. The recommendations provided in the guideline will address the issues by considering the characteristics of the analytical methods used in bioanalysis, e.g., chromatographic assay and ligand binding assay.
1. Method validation

- Define each validation characteristic (e.g., specificity, selectivity, calibration curve, sensitivity, reproducibility, accuracy, precision, total error, recovery, range, dilution integrity/linearity, matrix effect, carry-over, stability), their appropriate evaluation method and acceptance criteria, with respect to methods used to support non-clinical and clinical studies
- Clarify the cases where partial or cross validation are necessary and the validation characteristics that need to be evaluated
- Establish the requirements for reference standard and critical reagents
- Consolidate scientific experience and progress of instrumentation/technology

2. Study sample analysis

- Establish the requirements for ensuring the validity of each analytical run (e.g., setting the calibration standards and QC samples and their acceptance criteria)
- Clarify the conditions where reanalysis can be done
- Establish the required percentage of samples to be tested for incurred samples reanalysis (ISR) and its acceptance criteria

3. Other issues

- Establish the recommended documentation of validation and study sample analysis reports

This topic is not specifically relevant to any special subpopulation.

**Background to the Proposal**

During the development of chemical and biological drugs, bioanalytical methods are used in non-clinical and clinical studies such as pharmacokinetic, toxicokinetic, bioavailability, bioequivalence, dose finding and drug-drug interaction studies, etc., in order to describe the exposure to the drugs and their metabolites.

It is important that these bioanalytical methods are well characterised throughout the analytical procedures to establish their validity and reliability and ensure reliable review of the marketing authorisation application. In order to enable the mutual use of bioanalytical data set obtained in each region, international harmonisation of requirements for BMV is critical. Without their harmonisation, pharmaceutical companies must validate the bioanalytical methods and analyze samples to satisfy the different requirements of the guidelines/guidances in each region, thereby causing delay in global drug development and adding additional resource and cost burden.

As a guideline for the validation of analytical procedures, the ICH Q2 Guideline “Validation of analytical procedures: text and methodology” was endorsed (Oct. 1994 / Nov. 1996) and has been used in the quality evaluation of drug substances and drug products where complex matrices are usually not included. In contrast to analyses aimed at drug quality evaluation, bioanalysis conducted during non-clinical and clinical studies deals with the analyte in very complex biological matrices such as serum, plasma or other body fluids, where variations of conditions among individuals can be quite large. Therefore, a guideline specific for bioanalytical methods needs to be established separately from ICH Q2. To date, requirements for method validation of bioanalysis and study sample analysis have been discussed and
BMV guidelines/guidances have been issued in each region, although there are some differences among them as described above.

A harmonised BMV guideline will promote the prompt, rational and effective non-clinical and clinical studies, thereby advancing the mission of the ICH.

**Type of Expert Working Group Recommended**

The EWG will require experts in bioanalytical methods such as chromatography-based and ligand-binding assays to be nominated from the Members and Observers in line with the applicable Rules of Procedure.

**Timing**

- Adoption of the topic by Approval of ICH Assembly: June 2016
- First EWG meeting (Osaka, Japan): Nov. 2016
- Adoption of Step2 a/b Document: 2Q 2018
- Adoption of Step4 Document: 2Q 2019
1. The issue and its costs

- **What problem/issue is the proposal expected to tackle?**
  Regional guidelines/guidances on bioanalytical method validation pertaining to chromatographic and ligand binding assay methods have been publicised to ensure the reliability of bioanalytical data regarding conditions/requirements for reference standard, validation characteristics, study sample analysis and several additional considerations such as reanalysis justification. However, there are some differences among these guidelines/guidances such as incurred sample reanalysis (for the required percentage of samples to be tested). This lack of harmonisation can lead to conducting validation experiments under several acceptance criteria, repetition of similar studies, the use of additional animals in toxicokinetic studies, which is direct contradiction to the 3R principles, and may delay of drug application.

- **What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with “non action”?**
  The conflicting regional recommendations on the need for bioanalytical method validation and design for study sample analysis are leading to inconsistent requirements of measurements and animal use. The uncertainty around requirements is responsible for extended drug development and application timeline and general increase in the costs overall. Possible ambiguity in the scope of regional guidelines/guidances may also cause extra costs in the drug development.

2. Planning

- **What are the main deliverables?**
  The main deliverable is a harmonised guideline document on bioanalytical method validation and its application to study sample analysis that will provide clarity regarding the conditions and requirements for bioanalysis in non-clinical and clinical drug development.
• **What resources (financial and human) would be required?**

Formation of an Expert Working Group (two or three experts nominated by each Member). One expert can also be nominated by each Observer (if requested). It is desirable to include representatives with expertise in chromatography-based and ligand-binding assays.

• **What is the time frame of the project?**

The request will be submitted to the ICH Management Committee (MC) in September 2016 with expectation of the first EWG meeting face-to-face in November 2016 at Osaka.

• **What will be the key milestones?**

It is anticipated that the *Step 2 a/b* document will be completed in 2Q 2018 and that *Step 4* will be reached in 2Q 2019.

3. **The impacts of the project**

• **What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?**

Clarifying the fundamental issues to ensure the reliability of bioanalytical data by establishing a harmonised guideline leads to assurance in the quality of drug/metabolites concentration data used in non-clinical and clinical evaluation, which will contribute to the appropriate dose finding and evaluation of safety and efficacy of the drugs to be developed. A harmonised guideline will also enable the creation of simplified, more efficient and resource sparing testing strategies. Consequently, international harmonisation of the guideline can accelerate the efficient and prompt development of safe and effective drug products with lowered cost.

• **What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?**

The proposal is consistent with current laws and regulations of the ICH regions. Regulatory authorities responsible for reviewing pharmacokinetic/toxicokinetic data will need to agree globally on the recommendations for bioanalytical method validations and analysis of study samples from non-clinical and clinical studies by validated methods. This guideline will supersede regional guidelines, enabling the mutual usage of bioanalytical data set in different countries/regions based on the harmonised guideline.
4. **Post-hoc evaluation**

- *How and when will the results of the work be evaluated?*

  When certain amount of study data are accumulated for novel bioanalysis techniques or innovative molecules that exceed the principles of this guideline after the topic reaches *Step 5* in each region, the EWG may need to evaluate/update the guideline, if any.
ICH ASSEMBLY MEETING
November 9-10, 2016
OSAKA, JAPAN

AGENDA ITEM 22

REPORTS ON CURRENT TOPICS

22. EWGs/IWGs Not Meeting in Osaka, Japan

The following groups will not be meeting in Osaka:

- S1 EWG
- S3A IWG
- S9 IWG
- Q3C(R6) Maintenance EWG
- Q3D(R1) EWG
- Q11 IWG
- E6(R2) EWG
- E11(R1) EWG
- E14/S7B DG
- M1 PtC WG
- M2 EWG
- M4Q(R1) IWG
- M7(R1) EWG

Actions:

- **S1 EWG: Revision of the Rodent Carcinogenicity Studies for Human Pharmaceuticals Guideline**
  The Assembly will be updated on the current activities of the S1 EWG including the progress made towards the collection and review of confidential submissions of Carcinogenicity Assessment Documents (CADs) and summary report submissions by sponsors to DRAs within each region and considerations regarding the timeframe for drafting the S1 Technical document.
  *Step 1 sign-off and Step 2a/b endorsements are expected by June/November 2019.*

- **S3A IWG: Q&As on Note for Guidance on Toxicokinetics**
  The Assembly will be updated on the current activities of the S3A IWG and the progress made by the group to collect comments on the draft S3A Q&As in the respective ICH regions.
  *Step 3 sign-off and Step 4 adoption are expected by June 2017.*

- **S9 IWG: Q&As on Nonclinical Evaluation for Anticancer Pharmaceuticals**
  The Assembly will be updated on the current activities of the S9 IWG and the progress made by the group to collect comments on the draft S9 Q&As in the respective ICH regions.
  *Step 3 postal sign-off is expected by December 2016.*
  *Step 4 is expected in June 2017 at the subsequent Assembly meeting.*
Actions:

- Q3C(R6) Maintenance EWG: Maintenance of the Guideline for Residual Solvents
  The Assembly will be updated on the current activities of the Q3C(R6) EWG including: the progress made towards reaching Step 3 and Step 4.
  The Assembly will note that a new Q3C Rapporteur will be nominated for the period 2017-2018 in line with the Q3C maintenance procedure.
  - If Step 3 is reached ahead of Osaka, the Regulatory Members of the Assembly will be invited to adopt Step 4 of the Q3C(R6) Guideline.
  
  Step 3 postal sign-off is expected in Q3/Q4 2016.
  Step 4 is expected in November 2016.

- Q3D(R1) Maintenance EWG: Guideline for Elemental Impurities
  The Assembly will be updated on the current activities of the Q3D(R1) Maintenance EWG including the finalisation of the Q3D training package, the outcome of the regional Q3D workshops held in the different ICH regions in 2016 and the initiation of its new activity regarding the development of permitted daily exposures for all 24 elements included in the Q3D Guideline for the cutaneous and transdermal route of administration.

- Q11 IWG: Q&As on API Starting Materials
  The Assembly will be updated on the current activities of the Q11 IWG including progress made including progress made towards reaching Step 2a/b for the Q11 Q&A document on API Starting Materials.
  - If Step 1 of the Q&A document is signed-off by the Q11 IWG, the Assembly will be invited to endorse Step 2a of the Q11 Q&A document, following which the Regulatory Members of the Assembly will be invited to endorse Step 2b of the Q11 Q&A document;
  - The Assembly will be invited to endorse the nomination of a new Regulatory Rapporteur for Q11 IWG, recommended by the MC.

  Step 1 postal sign-off is expecting in October 2016.
  Step 2a/b endorsements are expected in November 2016.

- E6(R2) EWG: Integrated Addendum to Good Clinical Practice (GCP)
  The Assembly will be updated on the status of the finalisation of the draft E6 Integrated Addendum on Good Clinical Practice.
  - The Regulatory Members of the Assembly will be invited to adopt as final the E6(R2) Integrated Addendum.

  Step 4 is expected in November 2016.

- E11(R1) EWG: Addendum to Paediatric Drug Development
  The Assembly will be updated on the current activities of the E11(R1) EWG including progress made towards collecting comments on the draft E11 Addendum on Paediatric Drug Development which was endorsed by the Regulatory Members of the Assembly under Step 2b of the ICH process in September 2016.
  
  Step 3 postal sign-off is expected in May 2017.
  Step 4 is expected in June 2017.
Actions:

- **E14/S7B Discussion Group (DG): The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs**
  
  The Assembly will be updated on the current activities of the E14/S7B DG to review advances in science and methods related to the clinical assessment of QT prolongation and to monitor the progress of the discussion of the Comprehensive In vitro Proarrhythmia Assessment Initiative.

  *E14/S7B DG recommendation on whether to reopen the E14 Guideline for a complete revision is expected by December 2017.*

- **M1 PtC WG: MedDRA Points to Consider**
  
  The Assembly will be updated on the current activities of the M1 PtC WG with respect to the updating with each MedDRA release of the two PtC documents on Term Selection and Data Retrieval and Presentation; and the development of a proposal for a new area of work.

- **M2 EWG: Electronic Standards for the Transfer of Regulatory Information**
  
  The Assembly will be updated on the outcome of MC discussions in Osaka regarding M2 activities.

- **M4Q(R1) (CTD-Quality) IWG: Addressing CTD-Q-Related Questions**
  
  The MC will provide its recommendation to the Assembly on whether the group should be disbanded or continue its work depending on whether questions have been received following the implementation of the M4 Granularity Document.

- **M7(R1) EWG: Addendum to Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**
  
  The Assembly will be updated on the current activities of the M7(R1) EWG including the progress made towards finalising the M7(R1) Addendum on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

  *Step 3 sign-off is expected by December 2016 and Step 4 is expected in June 2017.*

Background Documents:

- [S1 EWG work plan](#), dated August 9, 2016;
- [S3A IWG work plan](#), dated August 7, 2016;
- [S9 IWG work plan](#), dated July 17, 2016;
- [Q3C(R6) Maintenance EWG work plan](#), dated August 2, 2016;
- [Q3D IWG work plan](#), dated August 10, 2016;
- [Q11 IWG work plan](#), dated August 3, 2016;
- [E6(R2) EWG work plan](#), dated August 10, 2016;
- [E11(R1) EWG work plan](#), dated July 25, 2016;
- [E14/S7B Discussion Group (DG) work plan](#), dated August 26, 2016;
- [M1 PtC WG work plan](#), dated July 14, 2016;
- **M2 EWG work plan**, dated August 26, 2016;
- **M4Q(R1) IWG work plan**, dated August 9, 2016;
- **M7(R1) EWG work plan**, dated August 5, 2016.

**Chronicle S1 EWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The S1 EWG did not meet in Lisbon.

The Assembly noted the current activities of the S1 EWG including the progress made towards the collection and review of confidential submissions of Carcinogenicity Assessment Documents (CADs) and summary report submissions by sponsors to Drug Regulatory Authorities (DRAs) within each region and considerations regarding the timeframe for drafting the S1 Technical document. A CAD addresses the carcinogenic potential of an investigational pharmaceutical and predicts the outcome and value of the planned 2 year rat carcinogenicity study, and based on the level of certainty a company is expected to indicate the need for such a study or to claim a (virtual) waiver. The predicted value and outcome of the 2 year rat study in the CADs will be then checked against the actual value and outcome of the 2 year rat studies as they are completed and reported to the DRAs.

The Assembly noted that the ICH S1 document was expected to reach Step 1 and Step 2a/b in June or November 2019.

**Decision/Action:**

- The S1 EWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

**Chronicle S3A IWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The S3A IWG did not meet in Lisbon.

The Assembly noted the current activities of the S3A IWG which reached Step 2b upon electronic endorsement by the Regulatory Members of the Assembly in May 2016. The Assembly also noted that the public consultation (under Step 3) had been launched by ICH Regulatory Members.

The Assembly noted that the ICH S3A Q&As document was expected to reach Step 3 and Step 4 by June 2017.

**Decision/Action:**

- The S3A IWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

**Chronicle S9 IWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The S9 IWG did not meet in Lisbon.

The Assembly noted the current activities of the S9 IWG including the finalisation of the Technical Document for the S9 Q&As.

The Assembly noted that the S9 IWG experts signed-off electronically Step 1 in early June.

The Assembly noted that the ICH S9 Q&As document was expected to reach Step 3 and Step 4 by June 2017.
Decisions/Actions:

- The S9 Experts signed-off Step 1 of the S9 Q&As (via written postal procedure) in advance of the Assembly meeting;
- The Assembly Members endorsed Step 2a of the S9 Q&As;
- The Regulatory Members of the Assembly endorsed Step 2b of the S9 Q&As;
- The S9 IWG will provide a work plan to the MC (including the length of time for the public consultation period in each region) ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

Chronicle Q3C(R6) Maintenance EWG:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Q3C(R6) Maintenance EWG did not meet in Lisbon.

The Assembly noted the current activities of the Q3C(R6) EWG, including the progress made towards finalising the maintenance of the Q3C(R5) Guideline to revise PDE for methylisobutylketone and include PDE for triethylamine and maintenance procedure for collecting new Q3C/Q3D proposals.

The Assembly noted that the ICH Q3C(R6) Guideline was expected to reach Step 3 and Step 4 after June 2016.

It was noted that the leadership of the Maintenance EWG is changing every 2 years and that it will rotate to FDA in 2017-2018.

Decisions/Actions:

- Once Step 3 is reached, the Secretariat will organise a postal sign-off (under Step 3) at the Regulatory expert level;
- The Assembly noted that the Regulatory Members of the Assembly would be invited to adopt as final under Step 4, the ICH Q3C(R6) Guideline at the next Assembly meeting in Osaka in November 2016;
- The Q3C(R6) Maintenance EWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

Chronicle Q3D EWG:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Q3D EWG/IWG did not meet in Lisbon.

The Assembly noted the current activities of the Q3D IWG, and the finalisation of Modules 8-9 of the Q3D training package.

It was noted that a regional Q3D workshop will be organised on August 22-23, 2016 at FDA’s White Oak campus in Silver Spring, MD, USA (see also Section 4 of this report).

Decisions/Actions:

- The Q3D Experts signed-off the final training modules 8 and 9;
- The Assembly endorsed the final training modules 8 and 9;
- The Assembly noted that these training modules would be made available on the ICH public website;
- The Q3D IWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016.

Chronicle Q11 IWG:

EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:

The Rapporteur reported to the Assembly on the outcome of the Q11 IWG meeting held on June 13 – 16, 2016 and progress made towards developing the draft Q11 Q&A document on API Starting Materials.
The Assembly noted the IWG progress made in Lisbon regarding assessing and editing the 16 Q&As based on constituent feedback received, including clarifying and proposing revised text for the Question 6.

The Assembly also noted that the ICH Q11 IWG was expecting to reach Step 1 and Step 2a/b by November 2016.

**Action/Decision:**

- The Assembly endorsed the work plan of the Q11 IWG for activities to be undertaken.

**Chronicle E6(R2) EWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Rapporteur reported on the outcome of the E6(R2) EWG meeting held on June 13 – 16, 2016 and progress made towards finalising the draft E6 Integrated Addendum on Good Clinical Practice.

The Assembly noted that in Lisbon the EWG went through all comments received during the public consultation and finalised the draft Integrated Addendum under Step 3 of the ICH process. The content of the Integrated Addendum was presented to the Assembly.

**Decisions/Actions:**

- The E6(R2) Regulatory Experts signed-off Step 3 of the E6 Integrated Addendum;
- Step 4 of the E6 Integrated Addendum will be for adoption at the next Assembly meeting in Osaka in November 2016 following the completion of MHLW/PMDA internal consultation.

**Chronicle E11(R1) EWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Rapporteur reported on the outcome of the E11(R1) EWG meeting held on June 13 – 16, 2016 and progress made towards developing the draft E11 Addendum on Paediatric Drug Development.

The Assembly noted that some additional work would be needed to ensure clarity/accuracy of new sections, especially Extrapolation and Modelling & Simulation, based on comments received after an internal review amongst Members and the output of 3 Extrapolation workshops held in 2015 and 2016.

The Assembly noted that Step 1 and Step 2a/b for the Addendum to ICH E11(R1) were expected by August 2016.

The Assembly also noted the EWG proposal to update the Concept Paper template with some text to ensure early consideration of paediatric populations in the development of any future new ICH Guidelines.

**Decisions/Actions:**

- The Assembly requested that once Step 1 is reached, the Secretariat organises a written postal sign-off (under Step 1) at the expert level which will be followed by Step 2a electronic endorsement by the Assembly and Step 2b electronic endorsement by the Regulatory Members of the Assembly;
- The Assembly supported the proposed update of the Template Concept Paper to include considerations of paediatric populations in ICH Guidelines;
- The Assembly endorsed the work plan of the E11(R1) EWG for activities to be undertaken.

**Chronicle E14/S7B DG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The E14/S7B DG did not meet in Lisbon.

The Assembly noted the current activities of the E14/S7B DG including its proposal to review advances in science and methods related to the clinical assessment of QT prolongation and to monitor the progress of the discussion of the Comprehensive In vitro Proarrhythmia Assessment Initiative.

The Assembly noted that the E14/S7B DG recommendation on whether to reopen the E14 Guideline for a complete revision was expected by December 2017.
**Decision/Action:**
- The E14/S7B DG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

**Chronicle M1 PtC WG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The Rapporteur reported on the outcome of the M1 PtC WG meeting held on June 13 – 16, 2016 and the group’s current activities with respect to the updating with each MedDRA release of the two PtC documents on Term Selection and Data Retrieval and Presentation.

The Assembly noted the current activities of the M1 PtC WG including the review and update of PtC documents for MedDRA version 19.1 to be released on September 1, 2016, the review of proposed revisions to the Medication error and Product use issue hierarchy and the development of condensed versions of both PtC documents in order to translate them in the 9 other MedDRA languages (to be released in 2017). The Assembly noted that the full documents will remain in English and Japanese and will continue to be maintained with each MedDRA version.

**Decision/Action:**
- The Assembly endorsed the work plan of the M1 PtC WG for activities to be undertaken.

**Chronicle M2 EWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The M2 EWG did not meet in Lisbon.

The Assembly noted the current activities of the M2 EWG and the progress made towards development of a new M2 Operating Model; finalisation of the Information Paper on Redaction by June 2016; harmonisation of the PDF Specification; finalisation of the Technology Watch Report by June 2016; finalisation of report of M8 SDO Project survey results by M8 EWG/IWG for its review and comments.

**Decision/Action:**
- The M2 EWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.

**Chronicle M4Q(R1) IWG:**

**EXTRACT FROM THE ASSEMBLY MEETING FINAL MINUTES, LISBON, PORTUGAL, JUNE 15 – 16, 2016:**

The M4Q(R1) IWG did not meet in Lisbon.

The Assembly noted that the M4Q(R1) (CTD-Quality) IWG completed its work regarding the revision of the Granularity Document with the M8 EWG, and the development of a process to address future CTD-Q related questions.

The Assembly noted that in Osaka, the MC will provide its recommendation to the Assembly on whether the group should be dissolved or continue its work depending on whether questions would have been received following the implementation of the M4 Granularity Document.

**Decision/Action:**
- If needed, the M4Q(R1) IWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016.
The M7(R1) EWG did not meet in Lisbon.

The Assembly noted the current activities of the M7(R1) EWG including the progress made towards addressing comments received on the M7(R1) Addendum on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. The Assembly noted that the draft Addendum presents calculated Acceptable Intake (AI) or Permissible Daily Exposure (PDE) values derived for 15 chemicals that are mutagens and carcinogens and are selected because they are commonly used in pharmaceutical manufacturing, or are useful to illustrate the principles for deriving compound-specific intakes described in ICH M7.

The Assembly noted that the ICH M7(R1) work plan indicated that the Addendum was expected to reach Step 3 and Step 4 by December 2016, however, the EWG will try to complete its work ahead of the next Assembly meeting in November so that the Addendum could be presented to the Assembly for adoption in November.

It was also noted that following the finalisation of the Addendum, the EWG would propose to the Assembly to assess 10 remaining compounds and determine whether PDEs or AI’s should be developed for these remaining compounds.

**Decisions/Actions:**

- Once Step 3 is reached, the Secretariat will organise a written postal sign-off (under Step 3) at the Regulatory expert level;
- The Assembly noted that the Regulatory Members of the Assembly would be invited to adopt as final under Step 4 the M7(R1) Addendum at the next Assembly meeting in Osaka in November 2016;
- The M7(R1) EWG will provide a work plan to the MC ahead of its teleconference to be held in autumn 2016 for activities to be undertaken.
ICH S1 EWG Interim Work Plan Update
9 August 2016

Topic Adopted: May 2012
Last Face-to-Face Meeting: Jacksonville, FL, USA – December 2015

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>June or November 2019</td>
<td>Step 2 Guideline</td>
</tr>
<tr>
<td>June or November 2020</td>
<td>Step 4 Guideline</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2016 - June 2017</td>
<td>EWG members to meet every other month by teleconference. Regulatory members to meet periodically to discuss all new Carcinogenicity Assessment Document (CAD) submissions and all new final summary report submissions.</td>
<td>EWG to review progress, feedback, on CAD submissions and align on plans for meeting face-to-face in Jun 2017 to review regulatory member conclusions from final reports derived from 6/7 category 3, and 10 category 2 expected final study report submissions; and to review Drug Regulatory Authorities (DRA) conclusions on all (expecting approximately 16) new CAD submissions following Jan 2016 RND revisions posting</td>
</tr>
</tbody>
</table>
ICH S3A IWG Work Plan
7 August 2016

**Topic Adopted:** October 2014

**Last Face-to-Face Meeting:** None

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 May 2017</td>
<td><em>Step 3</em> Expert draft Guideline</td>
</tr>
<tr>
<td>30 June 2017</td>
<td><em>Step 4</em> Final Guideline</td>
</tr>
</tbody>
</table>

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 March 2016</td>
<td><em>Step 1</em> sign off</td>
<td>➢ <em>Step 1</em> sign off was completed.</td>
</tr>
<tr>
<td>12 May 2016</td>
<td><em>Step 2a</em> sign off</td>
<td>➢ <em>Step 2a</em> sign off was completed.</td>
</tr>
<tr>
<td>19 May 2016</td>
<td><em>Step 2b</em> sign off</td>
<td>➢ <em>Step 2b</em> sign off was completed and draft Q&amp;A was publicized on ICH Web site.</td>
</tr>
<tr>
<td>31 December 2016</td>
<td>Public consultation</td>
<td>➢ Public consultation will be finished in all countries/region (details as next section)</td>
</tr>
<tr>
<td>31 January 2017</td>
<td>E-mail or teleconference</td>
<td>➢ Summarize all the comments and will discuss by e-mail or teleconference.</td>
</tr>
<tr>
<td>31 March 2017</td>
<td>E-mail meeting</td>
<td>➢ Revised draft Q&amp;A will be distributed to the IWG members for consultation.</td>
</tr>
</tbody>
</table>
ICH S9 IWG Work Plan
17 July 2016

**Topic Adopted:** October 2014

**Last Face-to-Face Meeting:** Jacksonville, FL, USA - December 2015

### 1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 June 2016</td>
<td><em>Step 2a</em> Technical Document</td>
</tr>
<tr>
<td>08 June 2016</td>
<td><em>Step 2b</em> Draft Guideline</td>
</tr>
<tr>
<td>Q4 2016</td>
<td><em>Step 3</em> Expert draft Guideline</td>
</tr>
<tr>
<td>Q1-2 2017</td>
<td><em>Step 4</em> final Guideline</td>
</tr>
</tbody>
</table>

### 2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>08 June 2016</td>
<td><em>Step 2b</em></td>
<td>➢ Draft Q&amp;A posted to the ICH website with regional publication by the 5 parties pending.</td>
</tr>
<tr>
<td>Q4 2016</td>
<td><em>Step 3</em></td>
<td>➢ Address input from Constituents through email and telecons; prepare <em>Step 4</em> document.</td>
</tr>
<tr>
<td>Q1-2 2017</td>
<td><em>Step 4</em></td>
<td>➢ Regional publication of final document.</td>
</tr>
</tbody>
</table>
ICH Q3C(R6) EWG Work Plan
2 August 2016

Topic Adopted: November 2013
Last Face-to-Face Meeting: none (written procedure)

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 June 2015</td>
<td>Step 2 Guideline</td>
</tr>
<tr>
<td>Q3/4 - 2016</td>
<td>Step 4 Guideline</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 June 2015</td>
<td>Approval by Steering Committee under Step 2</td>
<td>➢ Release for public consultation</td>
</tr>
<tr>
<td>September 2015 - January 2016</td>
<td>Step 3</td>
<td>➢ Internal/external consultation in ICH regions</td>
</tr>
<tr>
<td>February 2016 - April 2016</td>
<td>EWG telecon/e-mail consultation</td>
<td>➢ Reviewing and resolving comments received from consultation process; preparing Step 3/4 document</td>
</tr>
<tr>
<td>Q3/4 - 2016</td>
<td>Step 3 signoff</td>
<td>➢ Postal signoff Step 3 by the Regulatory Experts.</td>
</tr>
<tr>
<td>November 2016</td>
<td>Step 4</td>
<td>➢ Adoption by the Regulatory Members of the Assembly.</td>
</tr>
</tbody>
</table>
ICH Q3D(R1) IWG Work Plan
10 August 2016

Topic Adopted: October 2009
Last Face-to-Face Meeting: Fukuoka, Japan – June 2015

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 August 2016</td>
<td>Completion of training modules</td>
</tr>
<tr>
<td>23 August 2016</td>
<td>Completion of Training Workshops in 3 ICH regions</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sept. 2016</td>
<td>IWG to submit a revised Concept Paper to ICH Coordinators for consideration at the next Coordinators’ conference call.</td>
<td>IWG needs Management Committee approval to begin working on permitted daily exposures for the dermal route of administration.</td>
</tr>
<tr>
<td>Upon Management committee approval</td>
<td>Initiate development of permitted daily exposures for the dermal route of administration for all 24 elements in the ICH Q3D Guideline.</td>
<td>Regulators and industry representatives have identified the dermal route of administration as a potential challenge for the implementation of Q3D going forward. This issue was conveyed to ICH coordinators prior to the 2016 Lisbon meeting. The Q3D IWG was informed that the ICH Management Committee approved the continued discussion of the topic within the existing Q3D Implementation Working Group.</td>
</tr>
<tr>
<td>18 months after approval</td>
<td>Finalize PDEs for dermal route of administration.</td>
<td>It is anticipated that this work will require 12-18 months to complete.</td>
</tr>
</tbody>
</table>

172
ICH Q11 IWG Work Plan
3 August 2016

**Topic Adopted:** November 2014

**Last Face-to-Face Meeting:** Lisbon, Portugal - June 2016

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 13-17, 2016</td>
<td>Deliver a <em>Step 1</em> Q&amp;A draft Q11 technical document for Constituent review</td>
</tr>
<tr>
<td>August 15 - October 31, 2016</td>
<td>Edit and finalize <em>Step 1</em> Q&amp;A document</td>
</tr>
<tr>
<td>November 2016</td>
<td>Deliver a <em>Step 2a/b</em> Q&amp;A document to the ICH Assembly to seek endorsement for public consultation</td>
</tr>
<tr>
<td>November 2016</td>
<td>Deliver a <em>Step 4</em> Q&amp;A document</td>
</tr>
</tbody>
</table>

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
</table>
| June 2016             | Face-to-face (F2F) meeting in Lisbon                                            | ➢ F2F meeting to further develop and understand the new concepts proposed and their practical implementation within Regional regulatory frameworks. To discuss and resolve all issues including those for the remaining Q&As  
 ➢ Discussion, consensus building and convergence on complex issues  
 ➢ Goal to come out of this meeting with a Q&A document as a *Step 1* draft for Constituent review |
| June 24 - August 15, 2016 | Constituent review                                                           | ➢ Constituent review of revised 16 Q&As as agreed March MC meeting                                                                                                                                                                                                 |
| August 15 - October 31, 2016 | Review constituent comments and make edits as appropriate                   | ➢ Assess feedback from Constituents and prepare a finalized *Step 1* draft Q&A document  
 ➢ Reach agreement on the finalize *Step 1* draft Q&A document for public comment                                                                                                                                             |
| November 2016 - November 2017 | ➢ *Step 2b*: public comments  
 ➢ Revise and edit                                                           | ➢ Post *Step 2a/b* document for public consultation  
 ➢ Work to prepare a *Step 4* document                                                                                                                                                                                                 |
ICH E6(R2) EWG Work Plan
10 August 2016

Topic Adopted: April 2014
Last Face-to-Face Meeting: Lisbon, Portugal – June 2016

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2015</td>
<td>Step 1 Technical Document</td>
</tr>
<tr>
<td>June 2015</td>
<td>Step 2a Technical Document</td>
</tr>
<tr>
<td>June 2015</td>
<td>Step 2b Draft Guideline</td>
</tr>
<tr>
<td>June 2016</td>
<td>Step 3 Expert draft Guideline</td>
</tr>
<tr>
<td>November 2016</td>
<td>Step 4 Final Guideline</td>
</tr>
</tbody>
</table>

2. Timelines

Expert discussion in E6 EWG was finished at Lisbon meeting (June 2016).
ICH E11(R1) EWG Work Plan
25 July 2016

**Topic Adopted:** August 2014

**Last Face-to-Face Meeting:** Lisbon, Portugal - June 2016

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early September 2016</td>
<td>Electronic sign off by E11 EWG to complete <em>Step 1</em></td>
</tr>
<tr>
<td>Mid-September 2016</td>
<td><em>Step 2a</em> Technical Document</td>
</tr>
<tr>
<td>End September 2016</td>
<td><em>Step 2b</em> Draft Guideline</td>
</tr>
<tr>
<td>May 2017</td>
<td><em>Step 3</em> Expert draft Guideline</td>
</tr>
<tr>
<td>November 2017</td>
<td><em>Step 4</em> Final Guideline</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2016 to 1 September 2016</td>
<td>E11 EWG agreement that final draft of <em>Step 1</em> Technical document is complete and ready for electronic sign-off.</td>
<td>➢ ICH Secretariat to assist with process for electronic expert sign off of <em>Step 1</em> Technical document on or before 1 September 2016 to advance document to the ICH Assembly/Regulatory members for electronic sign-off and advancement to <em>Step 2</em>.</td>
</tr>
</tbody>
</table>
ICH E14/S7B IWG/DG Work Plan
26 August 2016

Topic Adopted: December 2015
Last Face-to-Face Meeting: Jacksonville, FL, USA - December 2015

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2017</td>
<td>Preliminary recommendation to ICH Assembly regarding whether to re-open ICH E14 and S7B for complete revision</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
</table>
| Quarterly Teleconferences   | Track Progress of CiPA Initiative | ➢ Discuss progress of CiPA initiative, review data as it emerges, and provide guidance on developing a path towards using these assays for regulatory decision making.  
➢ When CiPA initiative is ready for widespread implementation, the discussion group will assess the scope of the effort required to re-open ICH E14 and S7B for complete revision and make a recommendation. |
ICH M1 PtC (Points to Consider) EWG Work Plan
14 July 2016

**Topic Adopted:** 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 (remit extended April 2014 per EU/EMA request for PtC expert consultation).

**Last Face-to-Face Meeting:** Lisbon, Portugal – June 2016

1. **Anticipated Milestones**

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st March 2017</td>
<td>Release of “MedDRA Term Selection: Points to Consider” and “MedDRA Data Retrieval and Presentation: Points to Consider” documents, including updates for MedDRA Version 20.0 via MedDRA and JMO websites</td>
</tr>
<tr>
<td>2017</td>
<td>Condensed Versions of the “MedDRA Term Selection: Points to Consider” and “MedDRA Data Retrieval and Presentation: Points to Consider” documents available for translation into all MedDRA languages (except English and Japanese)</td>
</tr>
</tbody>
</table>

2. **Timelines**

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
</table>
| November – December 2016 | Review user comments on PtC documents  
Review complex changes for MedDRA Version 20.0 | ➢ Decide on relevant changes to be made to PtC documents based on user feedback  
➢ Determine if any changes are necessary to PtC documents based on approved complex changes for MedDRA Version 20.0 |
| 5-6 November 2016 | Present final draft of condensed PtC documents at MMB meeting in Osaka, Japan | ➢ Obtain approval for condensed PTC documents to be translated into 9 MedDRA languages in 2017 |
**ICH M2 EWG Work Plan**  
*26 August 2016*

**Topic Adopted:** 1994  
**Last Face-to-Face Meeting:** Jacksonville, FL, USA – December 2015

### 1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
</table>
| 10 Sept. 2016   | **Revise M2 Operating Model Proposal**  
M2 Projects are generally not traditional ICH EWG projects and an alternative operating model is needed. M2 developed a proposal for their new operating model that provides more structure for the MC and other stakeholders. The M2 proposal was discussed by the MC at the ICH Lisbon meeting June 2016, and MC response was provided to M2 in July. The Proposed Operating Model will be reviewed and revised in accordance with the responses from the MC. |
| 30 Sept. 2016   | **ICH Project Opportunities Proposals**  
An assessment will be made of key opportunities with potential relevance to ICH and how these might impact existing guidance and/or specifications and the current or future work of ICH. Based on this assessment, potential (non-consensus) technological project proposals will be developed for MC review and discussed with the MC. |
| 10 Oct. 2016    | **Evaluation of existing ICH topics for technical opportunities**  
We evaluate existing ICH topics for technical opportunities. We review EWG material twice – first as individual parties before or at Step 1, and secondly as a WG at or around Step 3 (or Step 4) when the EWG has fully established its thinking in the topic. |
| 30 Oct. 2016    | **Finalized Information Paper on Redaction**  
The efficient and correct redaction with respect to the regional legal requirements is crucial. M2 EWG identified a set of requirements for redaction and used these to evaluate the usability of electronic formats and tools within the ICH regions. The findings will be provided in this paper. |
| 30 Oct. 2016    | **PDF Specification update**  
Current M2 recommendation is only on the use of specific PDF versions and agreed restrictions, but each regulator maintains separate PDF specification. We investigate opportunity to further harmonize existing PDF requirements and revise M2 PDF recommendation as necessary. |
Since ICH M8 IG reached Step 4 in Jacksonville ICH, December 2015, M2 will conduct a survey based on the ICH SDO projects evaluation criteria. The survey results will be reported to the MC.

### 2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
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<th>Details</th>
</tr>
</thead>
</table>
| Continuous         | Coordination of ICH use of Controlled Vocabularies                              | ➢ M2 facilitates harmonization of ICH use of CVs with appropriate experts.  
➤ The process for coordination will be defined.                                                                                                    |
| 10 Sept. 2016      | Revision of M2 Operating Model                                                   | ➢ M2 Operating Model is revised in accordance with responses from the MC.                                                                                                                              |
| 12 Sept. 2016      | Evaluation of existing ICH topics for technical opportunities                   | ➢ Each party will discuss a topic with its experts in each group that is still in the concept development stage (or Step 1).  
➤ Discuss and understand the topic and consider whether there’s a technology element for immediate or future action.  
➤ Review Step 3-4 documents for project opportunities.                                                                                           |
| 15 Sept. 2016      | Draft potential project opportunities                                           | ➢ Discuss individual party observations and proposals.  
➤ Develop potential (non-consensus) technological project opportunity proposals for MC review.                                                                                                         |
| (no later than)    | 30 Sept. 2016                     | Communicate with the MC ➢ Project opportunities proposal for ICH is discussed with a small group of the MC.                                                                                         |
| 30 Sept. 2016      | Further revision of Information Paper on Redaction                              | ➢ Information Paper on Redaction is revised further.                                                                                                                                                    |
| 30 Sept. 2016      | Update M2 PDF specification for possible ESTRI recommendation revision          | ➢ To further harmonize existing PDF requirements, review/remove any differences/discrepancies.  
➤ M2 PDF specification is updated further for possible ESTRI recommendation.                                                                        |
➤ Discuss initially with M8 Rapporteur and Regulatory Chair.                                                                                      |
<p>| 10 Sept. 2016      | Finalize a list of project opportunities for ICH                                 | ➢ A (non-consensus) list of Project opportunities is proposed to the MC.                                                                                                                                  |</p>
<table>
<thead>
<tr>
<th>Date</th>
<th>Task Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Oct. 2016</td>
<td>Communicate with the MC</td>
<td>➢ Project opportunities proposal is discussed with a small group of the MC.</td>
</tr>
<tr>
<td></td>
<td>Evaluation of existing ICH topics for technical opportunities</td>
<td>➢ Finalize and bring our findings to the MC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Joint discussions with some of these groups in Osaka might be useful depending on what we find during individual party discussions.</td>
</tr>
<tr>
<td>30 Oct. 2016</td>
<td>Finalize Information Paper on Redaction</td>
<td>➢ Information Paper on Redaction is finalized and signed off by M2 EWG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Submit to the MC for information.</td>
</tr>
<tr>
<td>30 Oct. 2016</td>
<td>Finalize PDF Specification update</td>
<td>➢ M2 PDF Specification update is finalized and signed off by the M2 EWG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Submit to the MC for endorsement.</td>
</tr>
<tr>
<td>30 Oct. 2016</td>
<td>Finalize report of M8 SDO Project survey results</td>
<td>➢ A report of M8 SDO project survey results is finalized.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➢ Submit to the MC for information.</td>
</tr>
</tbody>
</table>
ICH CTD-Q / M4Q(R1) - IWG Work Plan
9 August 2016

Topic Adopted: November 2014
Last Face-to-Face Meeting: Not applicable

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2016</td>
<td>The <em>Step 4</em> M4(R4) Guideline document was published on the ICH website, and now enters <em>Step 5</em> of the ICH process and is recommended for implementation in the ICH regions: the European Union, Japan, the USA, Canada and Switzerland.</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug-Oct/2015</td>
<td>Compare alternative regional proposals and begin consensus development with regard to responses due back to the M8 EWG/IWG.</td>
<td>Multiple teleconferences to try to reach agreements on proposed revisions to the Granularity document and proposals for which attributes (keywords) to include in sections 2.3 and 3 of v.4.0 of the eCTD. (Completed.)</td>
</tr>
<tr>
<td>Nov/2015</td>
<td>Written response to M8 EWG/IWG</td>
<td>IWG provides written response to M8 EWG/IWG. (Completed.)</td>
</tr>
<tr>
<td>Dec/2015</td>
<td>Written response to ICH SC on final issue, dealing with potential future questions pertaining to CTD-Q</td>
<td>IWG provides draft written proposal to ICH Secretariat for dealing with potential future questions pertaining to CTD-Q. (Completed.)</td>
</tr>
</tbody>
</table>
ICH M7(R1) EWG Work Plan
5 August 2016

Topic Adopted: November 2011
Last Face-to-Face Meeting: Fukuoka, Japan – June 2014

1. Anticipated Milestones

<table>
<thead>
<tr>
<th>Completion Date</th>
<th>Deliverable</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 December 2016</td>
<td>Step 3 for Addendum is anticipated in December 2016.</td>
</tr>
</tbody>
</table>

2. Timelines

<table>
<thead>
<tr>
<th>Date</th>
<th>Task / Activity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 July 2014</td>
<td>EWG 1st WebEx / Discussed Addendum work plan detail and process</td>
<td>Agenda and Actions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Goal of Addendum is to provide acceptance limits for reagents to use between applicants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and regulators i.e. consistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Scope of reagents to include in Addendum,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Consistent approach in collecting and reviewing the data, data quality and robustness,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Agreed to focus on Category 1&amp;2 reagents, although draft monographs have been developed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for all reagents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- EMA proposed to review/discuss threshold alternatives when more conservative linear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>approach is used</td>
</tr>
<tr>
<td>13 Aug. 2014</td>
<td>EWG 2nd WebEx / Continue discussion of monographs and discussion on methodology</td>
<td>Agenda and Actions:</td>
</tr>
<tr>
<td></td>
<td>approach and data/limit selection for reagents</td>
<td>- Agreed to add method section to addendum describing how data were collected, consistency</td>
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<td></td>
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<td>of methodology and analysis across monographs</td>
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<td>- Agreed to review alternative monograph versions that use threshold MOA to derive AIs</td>
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<td>for hemosiderosis (hydroxylamine), forstomach (epichlorhydrin), and hydrogen peroxide. If</td>
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<td>accepted, will serve as template for remaining category 1&amp;2 reagents with proposed thresholds</td>
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<td>- Regulatory parties to provide status update on acceptability/inclusion of reagents and</td>
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<td>draft monographs in category 1&amp;2</td>
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<td>- Monthly WebExs will be scheduled through December 2014</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
<td>Notes</td>
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<tr>
<td>11 Sept. 2014</td>
<td>EWG 3 WebEx</td>
<td>Introduced new title to the addendum and accepted by the EWG members. Continue to revise and incorporate edits/comments from EWG members and included an Introduction section. Discussed individual monographs</td>
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<tr>
<td>5 Nov. 2014</td>
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<tr>
<td>10 Dec. 2014</td>
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<tr>
<td>4 Feb. 2015</td>
<td>Final EWG WebEx before Step 2</td>
<td>Continue discussion of introduction/method sections and monographs with anticipation to reach Step 2 end of February.</td>
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<tr>
<td>11 June 2015</td>
<td>Reached Step 2</td>
<td>Document open for Public comment period in the 3 Regions.</td>
</tr>
<tr>
<td>3 Feb. 2016</td>
<td>Receipt and discussion of Public comments</td>
<td>Public comment period was closed in the US and Japan with the EU last to close on February 3rd, 2016. Comments collated by the FDA and distributed to the EWG for discussion.</td>
</tr>
<tr>
<td>6 April 2016</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; WebEx to discuss Public comments</td>
<td>Collated Public comments from all three regions were discussed. No major issues identified.</td>
</tr>
<tr>
<td>11 May 2016</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; WebEx continue discussions of Public comments</td>
<td>Continue discussion of Public comments.</td>
</tr>
</tbody>
</table>