The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Standard Operating Procedures of the ICH Working Groups

Version 1.0

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ICH EWG/IWG SOP
Document History

Version number	Action	Date
v1.0	The ICH Management Committee endorsed Version 1.0 of the EWG/IWG Standard Operating Procedure with revisions to be included that were provided both prior to and during the meeting in Lisbon. *(Ref.: MC 2016/25)*	**June 2016**

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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.

Standing Regulatory Member: A former 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, this includes Health Canada and Swissmedic.

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

Type of Harmonization Procedure	Technical Discussion Group	Type of Work Conducted
Formal ICH Procedure	EWG	Development of a new Guideline
Q&A Procedure	IWG	Creation of Q&As to assist in the implementation of existing Guidelines
Revision Procedure	EWG	Revision/modification of existing Guidelines through amendments to content or a Guideline or addition of Addenda or Annexes
Maintenance Procedure	EWG	Updating existing Guidelines; adding standards to existing Guidelines and/or recommendations
Error Correction	EWG/IWG and/or ICH Secretariat	Correction of errors in ICH documents
Guideline Withdrawal	ICH Assembly	Withdrawal of an ICH document

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 harmonization 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 modifying 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 conferenceweb 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 conferenceweb 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 conferenceweb 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 conferenceweb 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 Organization (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 these EWG/IWG Rules of Procedure. 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 these Rules of Procedure. 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 these Rules of Procedure 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 these EWG/IWG Rules of Procedure 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 these Rules of Procedure. 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 these EWG/IWG Rules of Procedure. 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 these Rules of Procedure. 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 these rules of procedure. 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. <u>Before a teleconference or web conference the ICH Coordinator should:</u>
   - 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. <u>During a teleconference or web conference the ICH Coordinator may:</u>
   - 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. <u>After a teleconference or web conference the ICH Coordinators should:</u>

- 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. <u>Before a face-to-face meeting the ICH Coordinators should:</u>

- 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. <u>During a face-to-face meeting the ICH Coordinators should:</u>

- 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. <u>After a face-to-face meeting the ICH Coordinators should:</u>

- 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 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 (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 Rapportuer 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 these Rules of Procedure 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 these Rules of Procedure.

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 conferenceweb conference/e-mail. The group is asked to report at MedDRA Management Committee tele/web conferenceweb 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.

I. 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 with 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
Type of Harmonization Action: New guideline ☐ Revision of existing guideline ☐ Category of Harmonized Procedure: Quality ☐ Safety ☐ Efficacy ☐ Multidisciplinary ☐
Brief statement of perceived problem (caused by lack of harmonization):
Main technical and scientific issues to be addressed (which h 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?]

Annex 10 Business Plan Template

Final Business Plan
Title
date
Endorsed by the Assembly on day/Month/Year

1. **<u>The issue and its costs</u>**
   - *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. **<u>Planning</u>**
   - *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. **<u>The impacts of the project</u>**
   - *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. **<u>Post-hoc evaluation</u>**
   - *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)*

Completion Date	Deliverable
Day/Month/Year	*Step 2 Guideline*
Day/Month/Year	*Step 4 Guideline*

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

Date	Task / Activity	Details
Day/Month/Year	*e.g., EWG/IWG e-mail consultation, EWG/IWG teleconference etc…*	*Brief summary of task/activity objectives* *Brief summary of targeted deliverable /outcome*
Day/Month/Year		
Day/Month/Year		

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.

Date	**Task / Activity**	**Details**
Day 1 a.m.	*Task/Activity (short description)*	*Brief summary of task/activity objectives* *Brief summary of targeted deliverable /outcome*
Day 1 p.m.	*Task/Activity*	*Brief summary of task/activity objectives* *Brief summary of targeted deliverable /outcome*
…	…	…
Day 4 a.m.	*Task/Activity*	*Brief summary of task/activity objectives* *Brief summary of targeted deliverable /outcome*
Day 4 p.m.	*Task/Activity*	*Brief summary of task/activity objectives* *Brief summary of targeted deliverable /outcome*

Annex 12 Template for ICH Observer Request to Appoint an Expert to a Working Group

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***

CODE: GUIDELINE TITLE

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: .....

	Signature	*Name*	*Date*
Experts of Founding Regulatory Members			
EC	.....	.....	.....
FDA	.....	.....	.....
MHLW/PMDA	.....	.....	.....
Experts of Founding Industry Members			
EFPIA	.....	.....	.....
PhRMA	.....	.....	.....
JPMA	.....	.....	.....
Experts of Standing Regulatory Members			
Health Canada	.....	.....	.....
Swissmedic	.....	.....	.....

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

31 | **CODE: GUIDELINE TITLE** |
|---|

32 **All additional experts who participate in the Working Group are invited to sign-off the *Step 1***
33 **technical document in recognition of their contribution to the discussion.**

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

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

36 | | *Signature* | *Name* | *Date* |
|---|---|---|---|

37 ***Experts of Standing Observers***

38 | **IFPMA** | ..... | ..... | ..... |
|---|---|---|---|

39 | **WHO** | ..... | ..... | ..... |
|---|---|---|---|

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

42 | | ..... | ..... | ..... |
|---|---|---|---|

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

45 | | ..... | ..... | ..... |
|---|---|---|---|

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Annex 14 Step 3 Regulatory Experts Sign-Off

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

49 **CODE: GUIDELINE TITLE**

50 **Conclusion of *Step 3* of the ICH Process**[1]
51 ***Step 3* experts draft Guideline signed-off by the**
52 **DESIGNATED REGULATORY EXPERTS FROM THE ICH EXPERT WORKING GROUP**

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

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

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

58		*Signature*	*Name*	*Date*
59	***Experts of Founding Regulatory Members***			
60	**EC**	.....	.....	.....
61	**FDA**	.....	.....	.....
62	**MHLW**	.....	.....	.....
63	***Experts of Standing Regulatory Members***			
64	**Health Canada**	.....	.....	.....
65	**Swissmedic**	.....	.....	.....

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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).*

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

71 **CODE: GUIDELINE TITLE**

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

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

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

76 *Signature* *Name* *Date*

77

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

80 ....

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

83 ....

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85

86

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Annex 15 Step 3 Regulatory Experts Sign-Off without Public Consultation

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

CODE: GUIDELINE TITLE

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*.

Document Reference: .....

Document Date: .....

	Signature	*Name*	*Date*
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 adoption as a harmonised guideline (Step 4) without public consultation.*

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

CODE: GUIDELINE TITLE

Step 3 **of the ICH Process <u>without public consultation</u>**

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)*			
	.....	.....	.....