



30th Anniversary Publication

ICH - the global platform
for harmonisation

“Coming together is a beginning
Keeping together is progress
Working together is success”

Henry Ford

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Welcome



On the left

Celia Lourenco

- ICH Assembly Vice-Chair (Health Canada, Canada)
- Director General of the Biologics and Radiopharmaceutical Drugs Directorate, Health Canada, Canada

On the right

Lenita Lindström-Gommers

- ICH Assembly Chair (EC, Europe)
- Senior Expert, Unit B4 – Medical products: quality, safety, innovation, Directorate General for Health and Food Safety, EC, Europe

MESSAGE BY ICH ASSEMBLY CHAIR AND VICE-CHAIR

“Harmonisation for better health” is the motto of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It truly captures the essence of our goal, over three decades, to develop harmonised ICH Guidelines and contribute to bringing safe, effective and high-quality medicines to market for the benefit of patients. Celebrating this 30-year milestone is a good opportunity to take stock.

Looking back, it is remarkable that during its first decade, ICH developed nearly 30 guidelines — clearly showing a need for harmonisation in a pharmaceutical sector that was much less global than it is today. ICH's second decade can best be characterised by continued harmonisation, consolidation and global outreach with some involvement of regulators from outside the ICH regions.

During our third decade and to remain on the forefront of cutting-edge science, work continued on updating earlier ICH Guidelines to keep up with scientific developments. However, focus shifted to reforming and transforming ICH into a truly global organisation. Today ICH has 18 Members and 33 Observers and is still growing.

With its own legal entity and an Assembly composed of all Members and Observers as the main decision-making body, ICH has established its independence with a clear governance structure that gives the final say on the guideline development process to regulatory authorities. ICH has left a distinct mark in the pharmaceutical world and is today internationally renowned for its high-level guidelines, referred to as international standards. It has been a long journey, during which ICH has grown into a respectable, global organisation, supported by a permanent Secretariat. None of this would have been possible without the dedication and commitment of all involved over the years and especially the experts who diligently work on developing ICH Guidelines, overcoming challenges and divergences, whilst ensuring that high standards are met.

Looking forward and with scientific and technical developments moving at an ever-growing pace, we are confident ICH will continue to thrive and meet the challenges ahead. ICH has demonstrated the value of international collaboration and the advantages of harmonising requirements by avoiding duplication of efforts, improving efficiency and bringing medicines to patients in the interest of public health. To quote the famous African proverb: “If you want to go fast, go alone but if you want to go far, go together.”

Please join us in celebrating ICH's important milestone and we hope you will enjoy reading this publication!

Lenita Lindström-Gommers
ICH Assembly Chair
(EC, Europe)

Celia Lourenco
ICH Assembly Vice-Chair
(Health Canada, Canada)



On the left

Theresa Mullin

- ICH MC Chair (FDA, United States)
- Associate Director for Strategic Initiatives, Center for Drug Evaluation and Research (CDER), FDA, United States

On the right

Nobumasa Nakashima

- ICH MC Vice-Chair (MHLW/PMDA, Japan)
- Associate Executive Director for International Programs, Pharmaceuticals and Medical Devices Agency, Japan

MESSAGE BY ICH MANAGEMENT COMMITTEE CHAIR AND VICE-CHAIR

On behalf of the ICH Management Committee (MC) Members, we would like to congratulate Members, Observers and stakeholders on your great success and achievements.

For 30 years, ICH has taken a leadership role in the international harmonisation of pharmaceutical regulatory standards. The result has been the publication of nearly 70 harmonised technical guidelines addressing safety, efficacy, quality, and multidisciplinary aspects of drug development, manufacturing, and post-market safety. In 2015, when ICH reform was carried out, the door to ICH was opened to the wider community of pharmaceutical regulators and global industry stakeholders and ICH work has been enriched by this broader range of perspectives. When asked to name the most impactful and successful international collaboration in the field of pharmaceutical products, many people think of ICH.

The ICH MC consisting of both Permanent and Elected Members from both regulatory authorities and industry, is the body that oversees operational aspects of ICH on behalf of all Members. One of the important roles of our committee is to submit recommendations or proposals for new topics, strategies, operational approaches and other enhancements for consideration by the ICH Assembly. In marking this 30th Anniversary, the ICH MC remains dedicated to driving and supporting ICH's mission of harmonisation for global health.

Moving forward, ICH is also exploring new engagement with patient advocates, academic researchers and other stakeholders who can bring valuable and relevant perspectives to inform our work. We are also pushing forward to build new relationships and pursue opportunities for collaboration with other international organisations, such as the International Coalition of Medicines Regulatory Authorities (ICMRA) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The ICH MC will work to ensure that these expanded efforts succeed in extending and increasing the benefits of international harmonisation work for patients and other public health stakeholders.

Thank you for your support and engagement.

Theresa Mullin
ICH MC Chair
(FDA, United States)

Nobumasa Nakashima
ICH MC Vice-Chair
(MHLW/PMDA, Japan)

02

About Us



ICH Assembly
at its last face-to-face
meeting in Singapore
(November 2019)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a unique harmonisation initiative involving regulators, the pharmaceutical industry and other stakeholders. Founded in 1990, it was reformed and established as a non-profit legal entity under Swiss Law on 23 October 2015. Its aim is to focus global pharmaceutical regulatory harmonisation work in one venue.

The purpose of ICH is the promotion of public health through international harmonisation that contributes to:

- Prevention of unnecessary duplication of clinical trials and post-market clinical evaluations
- Development and manufacturing of new medicines
- Registration and supervision of new medicines
- Reduction of unnecessary animal testing without compromising safety and effectiveness accomplished through technical guidelines implemented by the regulatory authorities.

The structure of the ICH Association includes the ICH Assembly, the ICH Management Committee (ICH MC) as well as the MedDRA (Medical Dictionary for Regulatory Activities) Management Committee (MedDRA MC). The Committees and the ICH Assembly are supported by the ICH Secretariat. In addition, the ICH Assembly appoints auditors.

The ICH Assembly is the overarching body of the Association that takes decisions regarding Articles of Association, Rules of Procedures, admission of new Members, adoption of ICH Guidelines, etc. It takes decisions by consensus and, in the absence of consensus, a vote is held in accordance with the Articles of Association. With regards to adoption of ICH Guidelines, only Regulatory Members have the right to vote.

The ICH MC is the body that oversees operational aspects of the Association on behalf of all Members, including administrative and financial matters and oversight of the ICH Working Groups (WGs). The ICH MC provides recommendations on the selection of new topics for harmonisation as well as on the adoption, withdrawal or amendments of ICH Guidelines.

These guidelines are developed through a step-process. Following adoption of the topic and establishment of the WG, experts in the group develop the technical document, which is the first draft guideline text. To mark *Step 1*, this consensus document is signed off by the technical topic leads of the WG.

Step 2 involves decision-making on the draft ICH Guideline by the ICH Assembly, which is divided in two parts: at *Step 2a* all the ICH Members should reach consensus on the technical document. This involves both Industry and Regulatory Members. And as a second step – *Step 2b* - the draft ICH Guideline is then adopted by the ICH Regulatory Members for public consultation.

Step 3 includes the regulatory consultation in the ICH countries and regions, followed by discussions and consolidation of the comments received in the WG.

At *Step 4*, the final ICH Guideline is then adopted by the Regulatory Members of ICH Assembly.

Finally, the ICH Guideline is implemented in the countries and regions at *Step 5*.

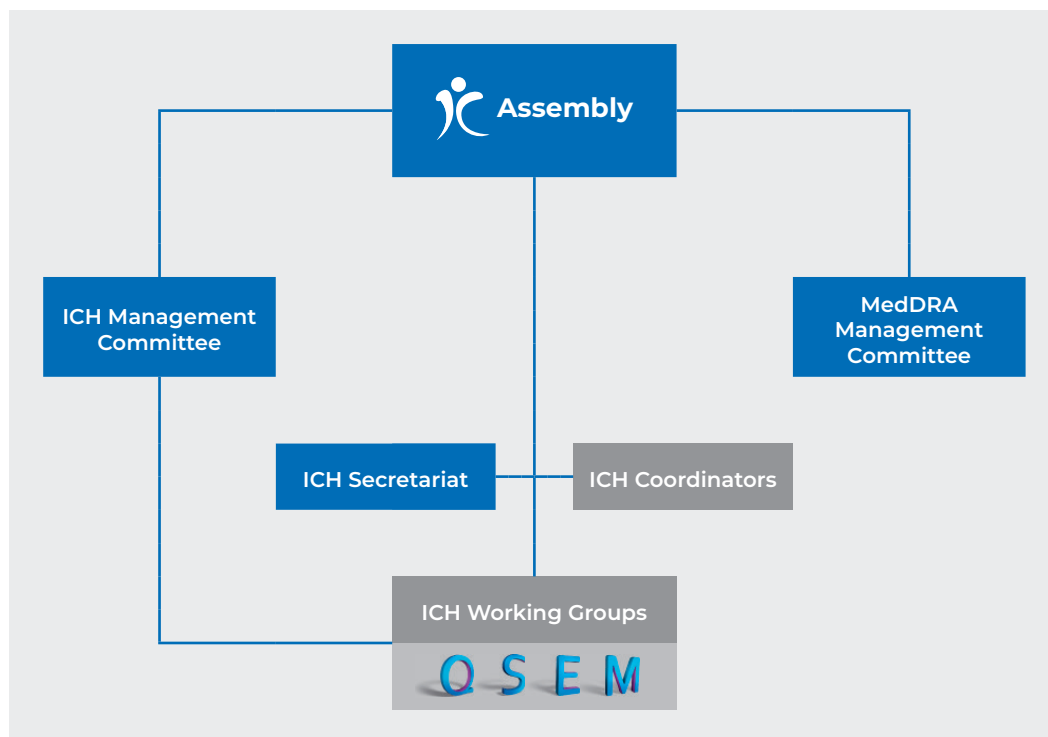


FIGURE 1
The structure of the ICH Association
The structure of the ICH Association includes the ICH Assembly, the ICH MC as well as the MedDRA MC and the WGs. The committees and the ICH Assembly are supported by the ICH Secretariat.

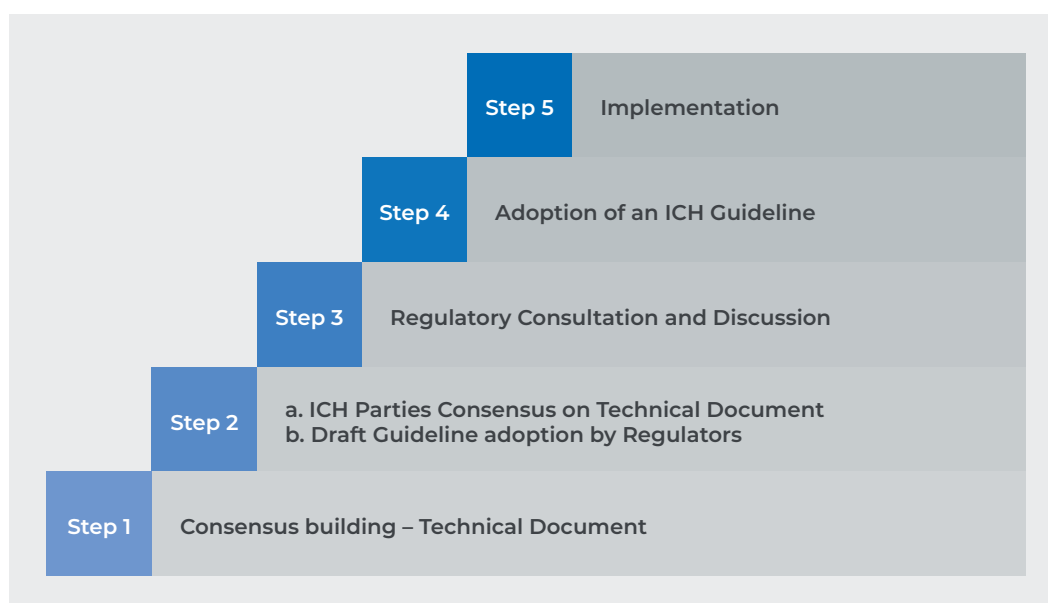
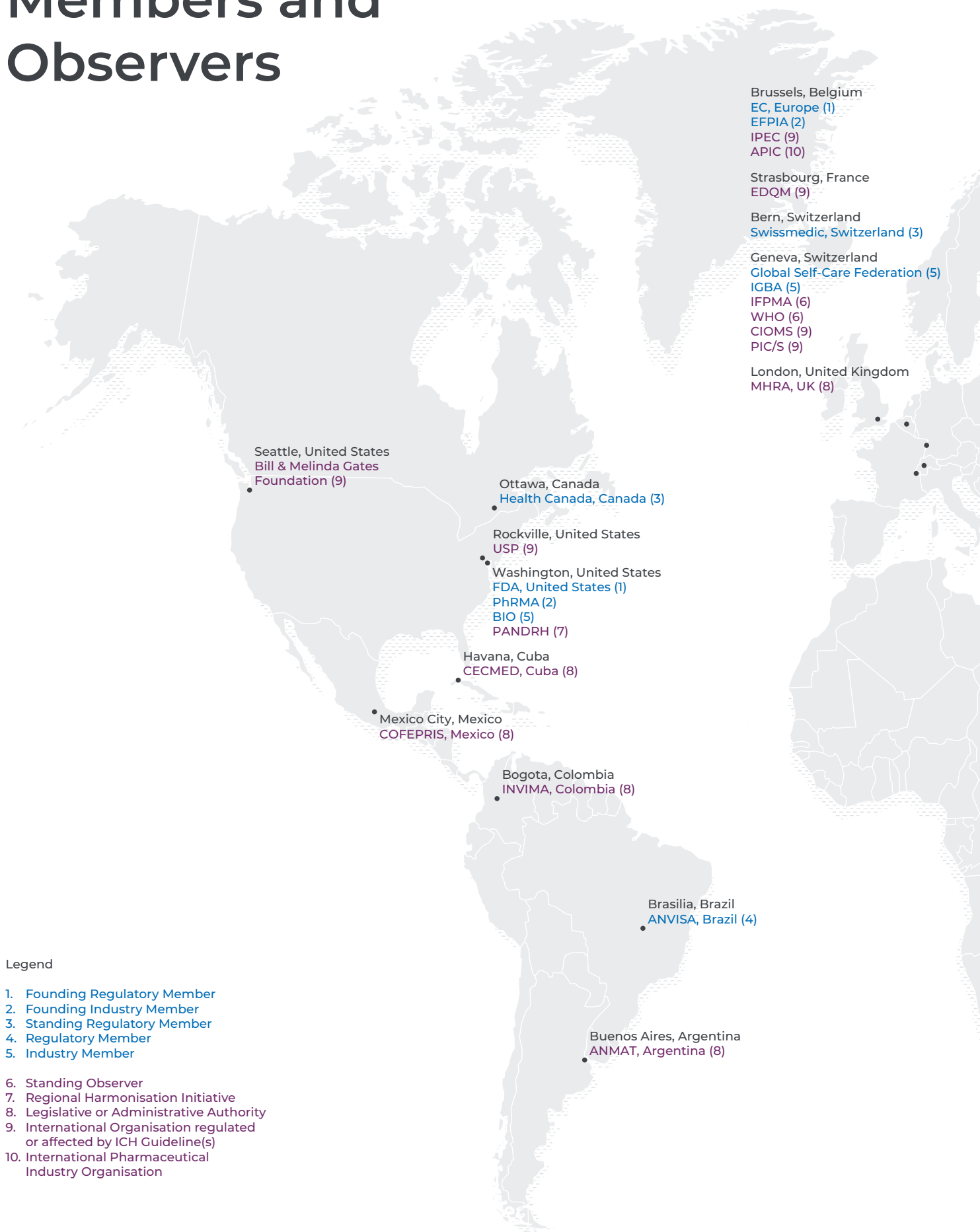


FIGURE 2
ICH Guidelines
These are developed through a step-process following adoption of the topic and establishment of the WG.

03

Members and Observers



Legend

1. Founding Regulatory Member
2. Founding Industry Member
3. Standing Regulatory Member
4. Regulatory Member
5. Industry Member
6. Standing Observer
7. Regional Harmonisation Initiative
8. Legislative or Administrative Authority
9. International Organisation regulated or affected by ICH Guideline(s)
10. International Pharmaceutical Industry Organisation



04 History

1990

Coming together is a beginning

April 1990

Birth of ICH

ICH was initiated by the regulators and research-based industries of the United States, European Union and Japan, with WHO, IFPMA, Health Canada, Canada and EFTA (represented by Swissmedic, Switzerland) as Observers.

1991

November 1991

ICH 1 (Brussels)

ICH 1-6

ICH organised Symposium-type meetings allowing general participants to disseminate information. United States, European Union and Japan took turns to host them.

1994

1994

MedDRA

ICH adopted MedDRA Version 1.0 as basis for international terminology. An ICH M1 Expert Working Group (EWG) was formed to further develop the terminology.

1995

1995

ICH 3 (Yokohama)

1993

ICH 2 (Florida)



Steering Committee (1993)

2000

Keeping together is progress

2000

CTD (ICH M4) presents the agreed upon common format for the preparation of a well-structured Common Technical Document (CTD) for applications that will be submitted to regulatory authorities.

ICH Q7 provides guidance regarding Good Manufacturing Practice (GMP) for the manufacturing of Active Pharmaceutical Ingredients (APIs) under an appropriate system for managing quality.

2003

2003

ICH 6 (Osaka)

eCTD (ver.3.0)

eCTD (ICH M8) Guideline facilitates electronic exchange of regulatory information prepared in accordance with the requirements of the CTD in the ICH regions.



ICH 6 (2003)

1996

1996

GCP

The first version of the ICH E6 Good Clinical Practice (GCP) Guideline described the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and Institutional Review Boards (IRBs). GCP covers aspects of monitoring, reporting and archiving of clinical trials, and incorporates addenda on the Essential Documents and on the Investigator's Brochure.

1997

ICH 4 (Brussels)

1997

1999

1999

Global Cooperation Group (GCG) established

Reflecting the globalisation of drug development and a need for common standards, ICH created the GCG to establish global linkages that extend beyond the three ICH regions. Regional Harmonisation Initiatives (RHIs), namely APEC, ASEAN, EAC, GHC, PANDRH and SADC, as well as Drug Regulatory Authorities, namely ANVISA, Brazil, CDSCO, India, HSA, Singapore, MFDS, Republic of Korea, NMPA, China, Roszdravnadzor, Russia, TFDA, Chinese Taipei and TGA, Australia joined GCG at different times.

2000

1999

MedDRA made available for MSSO and JMO

Maintenance and Support Services Organization (MSSO) and Japanese Maintenance Organization (JMO) maintain, distribute, and support MedDRA, under the oversight of the ICH MedDRA Management Committee.

2000

ICH 5 (San Diego)

10th Anniversary publication

10th Anniversary publication, "The Value and Benefits of ICH to Industry" detailed ICH's creation, procedures, and guideline development in the areas of safety, efficacy and quality.

2004

2004

RHIs allowed to observe WGs and SC

RHIs participating in GCG started to observe Working Groups (WGs) and ICH Steering Committee (SC).

2006

SDO Process (ICH M2) started

The ICH SC took a key decision that technical specifications should no longer be developed solely within ICH, but should be created in collaboration with Standards Development Organisations (SDOs) to enable wider inter-operability across the regulatory and health-care communities.

2006

2008

2008

Regulators Forum

Regulators Forum (RF) evolved from GCG. RHIs as well as individual Drug Regulatory Authorities (DRAs) joined. RF offered opportunities to discuss implementation of ICH Guidelines and their impact on regulatory systems in a regulator-only environment. RF evolved further into International Pharmaceutical Regulators Forum (IPRF) in 2013, which was later consolidated with the International Generic Drug Regulators Programme (IGDRP) to form the International Pharmaceutical Regulators Programme (IPRP) in 2018.

2009

2009

ICH Q Trio (ICH Q8(R2), 9, 10) completed

The guidelines on Pharmaceutical Development (ICH Q8), Quality Risk management (ICH Q9) and Pharmaceutical Quality System (ICH Q10) describe a risk and science based approach to pharmaceuticals in an adequately implemented quality system, different from the traditional approach.

2010

20th Anniversary publication

As part of its 20th Anniversary celebration, ICH launched a new logo, representing the letters "I", "C", "H", a new slogan "Harmonisation for Better Health", and renewed its website.

2010

Working together is success

2011

2011

EAC joined GCG

The ICH GCG welcomed for the first time representatives of the EAC, a RHI composed of Burundi, Kenya, Rwanda, Tanzania and Uganda.

Opening of EWGs to Non-ICH Regions

For the first time, non-ICH regulators were nominated to serve as experts in EWGs. The measure provided opportunities for non-ICH regulators to make direct technical contributions to the work of ICH and advance their implementation of ICH Guidelines.

2012

2012

“New Principles of Governance”

The SC agreed to strengthen the role of regulators in ICH by giving them the final say in the adoption of ICH Guidelines whilst recognising the ultimate responsibility of regulators in ensuring the protection of public health and the competence to issue regulatory guidelines. To solicit greater engagement of global regulators, the GCG was to serve as a better platform for dialogue.

2015

2016

2017

2017

2016

New Regulatory and Industry Members joined

ICH welcomed many new Members and Observers. The numbers of ICH Members and Observers were; 8 and 2 in 2015, 13 and 22 in 2016, 16 and 28 in 2018, and 18 and 33, as of June 2021.

2017

MedDRA transferred from IFPMA to ICH - ICH Training Pilot Programmes started

MedDRA enjoyed increasingly global uptake with the growing number of users to over 6,000 organisations in more than 125 countries. These users currently have access to MedDRA in 14 language translations.

ICH Training Programme started

Under ICH Recognised Training Programmes, ICH engages appropriate accredited non-profit training organisations to assist ICH in its efforts to address the training needs of its Regulatory and Industry Members and Observers in a strategic manner.

ICH E17

With the increasing globalisation of medicines development, ICH adopted a major guideline on the planning and design of multi-regional clinical trials (MRCTs). It is intended that the ICH E17 Guideline will facilitate the acceptability of MRCTs as part of global regulatory submissions in ICH and non-ICH regions, as well as making it easier to seek approval of global trials.

2013

2014

2015

2012

ICH E2B (R3)

The ICH E2B (R3) EWG on revision of the “Electronic Transmission of Individual Case Safety Reports (ICSR)” progressed its Implementation Guide (IG) to *Step 4*. It is the first ICH work item to be completed under a pilot process that involved work in parallel with standards development organisations.

2013

Measures for Transparency

More detailed information regarding the ongoing ICH activities became available to the public through the ICH website including the agenda and the report of the SC meetings as well as the Work Plans of active EWGs.

2014

Health Canada, Canada and Swissmedic, Switzerland became SC Members

New MedDRA website launched

2015

ICH Legal Entity Established as part of the ICH reform

The International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation (ICH) held the inaugural meetings of its new Assembly [and Management Committee] on 23 October 2015. The Members of the former GCG were invited to take the opportunity to automatically become Observers.

2015

ICH Q7 Guideline Q&A

The Question & Answer (Q&A) document on the ICH Q7 Guideline on Good Manufacturing Practices for APIs has been signed off at *Step 4*.



ICH Assembly (2015)

2018

2018

ICH Management Committee expanded

The first face-to-face meeting of the expanded ICH MC was held, with elected ICH MC Representatives from HSA, Singapore; MFDS, Republic of Korea; NMPA, China; BIO and IGBA joining ICH's Founding and Standing Members to play an active role in overseeing the Association's administrative, financial, and WG operations.

2019

2018

Reflection Paper “GCP Renovation”

The goal of the potential renovation was to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate.



ICH EWG (2019)

2020

2019

Implementation Survey results published

To better understand the state of implementation of ICH Guidelines by ICH Regulatory Members and Observers, with the help of an independent third-party, a survey was conducted in early 2019 monitoring adequacy of implementation and adherence to ICH Guidelines. The results of the survey were made available on the ICH website.

2020

ICH YouTube channel opened

05

Facts and Figures

The following metrics provide a sense of ICH's influence in promoting a global regulatory language and framework for the development, registration and surveillance of pharmaceuticals for human use.

FACT

THE WORLD'S OLDEST, LARGEST AND MOST PROLIFIC PHARMACEUTICAL HARMONISATION INITIATIVE.

Sphere of influence: Member and Observer economies represent approximately two-thirds of the world's population, not counting Regional Harmonisation Initiatives.

Output: To date, 67 state-of-the-art technical guidelines and standards have been produced spanning the pharmaceutical products lifecycle, with a further 10 guidelines under development at the time of writing. This impressive body of work is categorised along four broad workstreams:

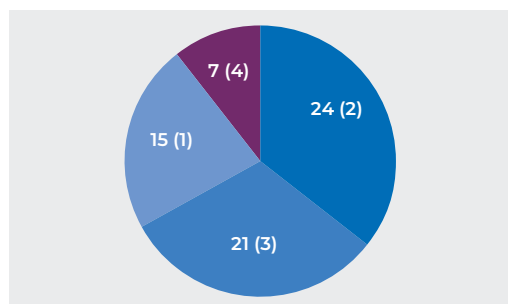


FIGURE 3
Guidelines: final (and under development)

- **Quality (Q)**
Manufacture, control and stability of products and ingredients
- **Efficacy (E)**
Design, conduct, safety and reporting of clinical trials
- **Safety (S)**
Nonclinical test strategies and methods
- **Multidisciplinary (M)**
Diverse cross-cutting topics, including CTD/eCTD, medical dictionary and e-standards for transfer of regulatory information.

In addition, ICH has developed an extensive set of Q&A documents and training materials to further clarify concepts and principles in ICH Guidelines.

Participation: ICH has grown over the years in terms of Members, Observers and experts, reflecting the global dimension and complexity of drug regulation and the importance of broad engagement to achieving its mission – considerations central to the ICH Reform.

Some specifics:

- Over 1,000 individuals are involved in ICH work
- 759 technical experts in 34 Working Groups (May 2021)
- Membership spans all six populated continents

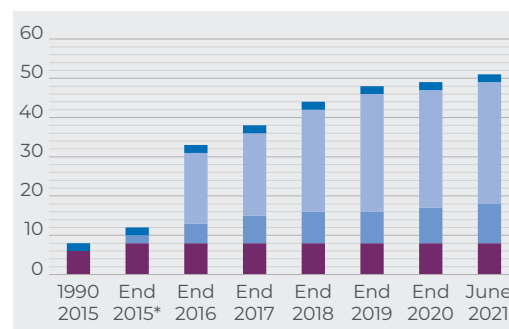


FIGURE 4
ICH Members and Observers

- Founding/Standing Member
 - Member
 - Observer
 - Standing Observer
- *Reform of the ICH

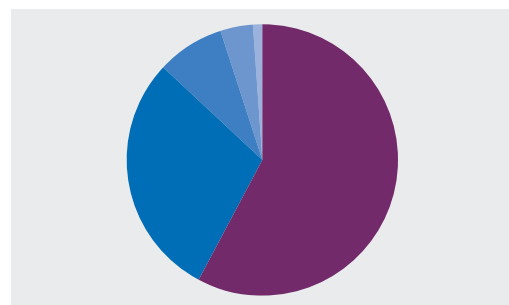


FIGURE 5
Numbers of experts in ICH WGs

- 58%
441 Founding/ Standing Member
- 29%
218 Member
- 8%
64 Observer
- 4%
31 Standing Observer
- 1%
5 Other

Meetings: The size and complexity of ICH requires efficient planning and operations to manage the number of parallel WG and meetings, which include:

Approximately 22 meetings of ICH governing bodies per year (ICH MC, ICH Assembly and MedDRA MC - 7 in person and 15 virtual)

FACT

IMPLEMENTATION-FOCUSED.

Guidelines, once implemented by ICH regulators, form a common backbone of technical requirements across the globe.

For ICH Guidelines to achieve the intended effect of promoting a greater level of harmonisation worldwide they are expected to be implemented by regulatory authorities. A commitment by ICH Regulatory Members to implement ICH Guidelines has been a core operating principle of ICH since its inception – one which is now reflected in the Articles of Association.

ICH has introduced measures to promote and monitor implementation and identify training needs. These include:

- Commitment and evidence of implementation as a pre-requisite to regulatory membership
- Reporting the status of implementation of ICH Guidelines on the ICH website
- Developing a common set of definitions on implementation
- Conducting an independent third-party survey in support of implementation efforts.

FACT

MODEL OF TRANSPARENCY AND CONSULTATION.

Transparency is key to raising awareness of and support for ICH goals, products and plans, promoting input on ICH Guidelines under development and garnering interest in becoming an ICH Member or Observer.

ICH has taken great efforts to enhance the transparency of its operations and consequently the material made available to stakeholders on its website.
www.ich.org/page/transparency

Consultation with stakeholders has also been an ICH priority to ensure broad input by those interested or impacted by ICH's work. This is accomplished through various mechanisms, including:

- *Step 3* of the ICH process, which calls for regulatory consultation on draft ICH Guidelines
- Active consultations by Members and Observers to ICH, including public meetings
- Workshops and other measures to secure engagement.

06

Harmonisation for better health

“Harmonisation for better health” – this is the motto that defines ICH’s vision. On our 30th anniversary, it is time to ask if and how ICH is delivering on this vision. Here is what different stakeholders believe ICH has achieved and what can still be done moving forward.

HOW DOES ICH/HARMONISATION CONTRIBUTE TO BETTER HEALTH AND THE HEALTH OF PATIENTS?



Cathy Parker

- Former Health Canada, Canada Representative
- Former Director General, Biologics and Genetic Therapies Directorate, Health Canada, Canada

ICH and the harmonisation initiative set new standards for drug manufacturing that raised the bar. In a world where there are hundreds of different regulatory bodies and manufacturers of different sizes, capacity and resources, it sent a clear message that all should strive for standards that are beyond the minimum.

Even if not capable of full implementation, any regulator striving to implement an ICH Guideline or manufacturer working to comply with one will be working towards reaching a standard they may never previously thought was attainable. The rewards will be directly felt to patients and consumers, via safer and more effective, high quality drugs.

HOW DO SPECIFIC GUIDELINES IMPROVE PATIENTS’ HEALTH?



Toshiyoshi Tominaga

- Former ICH Assembly Vice-Chair and ICH MC Vice-Chair (MHLW/ PMDA, Japan)

Of all the ICH Guidelines, ICH GCP could be judged to have had the greatest health impact. It has standardised clinical trials worldwide to form a basis for global development. Widening the development basis from individual countries to larger regions or, indeed, the whole world, has sped up the delivery of new drugs to patients and contributed to their health. The guideline’s impact has also reached beyond drug development; it has improved non-commercial clinical research and perhaps also “de-paternalised” the patient-doctor relationship regarding informed consent, again for the benefit of patients.

ICH Guidelines related to adverse drug reaction (ADR) reporting, i.e. MedDRA,

ICH E2B, and ICH E2D, have enabled quick sharing of untoward events among stakeholders across the globe, so that necessary countermeasures can be taken in a timely way, to minimise potential health damage to patients and society. Implementation of the named ICH products affords further benefit. Recently, urgently needed drugs, including those against COVID-19, have been authorised for marketing based on relatively limited pre-market evidence of their safety and efficacy, to be supplemented in the post-market phase. Such pathways are possible only when supported by a robust ADR reporting/sharing mechanism.

Cathy Parker

- Former Health Canada, Canada Representative
- Former Director General, Biologics and Genetic Therapies Directorate, Health Canada, Canada

ICH has moved guideline development into areas directly affecting patient, areas that were woefully unaddressed before. Guidelines such as Paediatric

Extrapolation, and Studies in Support of Special Populations: Geriatrics help ensure safe use of drugs in populations that have been neglected previously.

HOW SHOULD/COULD PATIENTS CONTRIBUTE TO ICH?



Fernand Sauer

- Former EC, Europe Representative
- Former Executive Director of the EMA

As part of their mission to protect and promote health, public health authorities and health professionals have always felt they could legitimately represent the interests of patients. Over the years, patient representatives have acquired the right to be heard and later to get actively involved in health policies and as users of health care services. Their role has become very prominent in the United States, Europe and more recently in Japan but less so in other regions of the world.

Under present ICH rules, global international patient organisations can apply to become ICH Observers. Once they join ICH they can express their wishes on how they want to effectively participate in ICH Harmonisation activities.

Patient feedback is essential for the quality and safety of complex health technologies as well as quality of life issues. Patient organisations can contribute to innovative health research and recruitment for clinical trials, amply demonstrated in the field of rare diseases.

In November 2020, the ICH launched a wide consultation process on patients' perspectives to improve drug development and inform regulatory decision-making. The draft paper "ICH Guideline Work to Advance Patient Focused Drug Development" explains why patients should get involved and discusses interesting aspects of methodology to facilitate their input.

Two new ICH Guidelines are foreseen, on patient-reported outcome tools and on acceptability to patients of specified alternative outcomes. Patient representation already exists at local level in several ICH regions. Direct patient representation in ICH would bring major advantages to all concerned parties.

The European experience illustrates how the role of patients evolved progressively from consultation to effective participation, for the benefit of all concerned parties. This experience, together with similar developments in other ICH regions, has inspired improvements in ICH governance.

In the late 1980s, when the International Conference on Harmonisation emerged, only a handful of patient organisations were given a voice on specific patient needs at the national level. The ICH Regulatory Founding Members considered that the WHO was best placed to represent the collective needs of patients and health interests worldwide. Therefore, I approached WHO colleagues to become an ICH permanent Observer in the margins of two meetings of the International Conference of Drug Regulatory Authorities (Paris 1989 and Ottawa 1990). The World Health Assembly (WHA) endorsed that position in a 1992 WHA Resolution.

In the 1990s, the active involvement of patients suffering from diabetes, rare diseases or AIDS started having an impact beyond national borders. The European Commission of the European Union decided to hold regular consultations with consumers and patient organisations on new initiatives (legislative or guidelines), including all ICH drafts at *Step 2* and *Step 4*. The FDA, United States did the same. When the European Medicines Agency (EMA) was established in 1995, with a strong support from patient organisations, we continued this tradition and organised quarterly meetings between the EMA scientific committee and all interested parties. The publication of European Public Assessment Reports following every European wide marketing authorisation drew a lot of attention, and sometimes constructive criticism from patient organisations.

The US Orphan Drug Act (1983) illustrated the need to benefit from patients' expertise and patient mobilisation in an area at the time neglected by health professionals. A similar trend led to the adoption of the EU Regulation on orphan medicinal products (EC/141/2000) and similar moves in Japan and elsewhere. A common platform for rare orphan diseases associations in the EU was created in 1999: EURORDIS.

The first meeting of the Committee for Orphan Medicinal Products (COMP) was held at the EMA in London in 2000, with representatives from patient groups sitting alongside representatives from Member States. A patient representative was elected as vice chair of that Committee. At the EMA, in following years, patient representatives became full members of the EMA Management Board, of the Pharmacovigilance Risk Assessment Committee (PRAC), of the Committee for Advanced Therapies (CAT) and of the Paediatric Committee (PDCO).

In 2006, the EMA created a special liaison structure, the Patients' and Consumers' Working Party, to provide a platform for exchange of information and discussion of issues of common interest between EMA and patients and consumers. The revised rules of procedure for this Working Party, published in 2019, provide useful details about interactions with patient groups. In 2001, as director for public health at the European Commission, I saw the need to involve patient groups in health policy developments with the creation of the European Health Forum (50 NGOs and representative associations). In 2003, I invited various specialised patient groups to create a common platform, the European Patient Forum (EPF) to participate in high level meetings with health ministers (Pharmaceutical Forum) and in the Advisory Forum of the European Centre of Disease Control (2005).

Studies consistently suggest that about 10% of hospital admissions involve harm to patients and that their active involvement can reduce these risks. To address such issues, patient groups have provided a significant input in projects funded under the European health and health research programmes. Health and medical institutions are realising that people deserve to have input on the procedures

that affect them as shown in an interesting White Paper of the International Hospital Federation: "The institutional role of patient organisations in Healthcare", December 2014.

Speaking at two Drug Information Association events celebrating ICH achievements in 2013 and 2020, and for the 20th anniversary of the EMA in 2015, I expressed the wish that patient organisations should find a place in the new ICH structures. Based on my professional experience, this is a logical follow up to the present ICH consultation process.

I sincerely hope that global patient organisations will take this new opportunity to join ICH. I strongly believe that direct patient participation will enhance the operational capacities as well as the reputation of ICH, as has been the case for EMA.



Lembit Rägo
• CIOMS Representative
• Secretary-General, CIOMS

Thinking about patients' role in drug development and safe use has evolved. Today, it is generally agreed that patients' expertise and input can be helpful during the whole lifecycle of medicines starting from early stages of product development until its retirement from the market. There is still room for ICH to better benefit from patients' expertise and support. As many ICH topics are very technical, the direct involvement of patients in most of

them may not be appropriate. However, involving patient experts directly in new topics for which they could provide added value should be considered and piloted in the future. Patients can also be of more support in achieving ICH goals. In order to best benefit from patients' support e-training opportunities about ICH and its importance designed for patients as target audience should be created.

Cathy Parker
• Former Health Canada,
Canada Representative
• Former Director General,
Biologics and Genetic
Therapies Directorate,
Health Canada, Canada

I think it would be difficult to have patients directly involved in the ICH process, firstly because the ICH Guidelines are very technical and secondly because it would be difficult to have a population that would be globally representative. To conduct even an online patient survey may require

availability of the survey in multiple languages. However, the ICH initiative could encourage drug manufacturers to involve patients in specific areas of drug development, such as labelling, packaging and risk tolerance and acceptance.



Patricia Oliveira Pereira Tagliari
• Former ANVISA, Brazil
Representative
• Deputy Director, Second
Directorate, ANVISA,
Brazil

It is fair to say harmonisation has different positive impacts for the industry and for regulators, both directly benefitting the health of patients.

For the industry, harmonisation favours innovation as well as the development of generic drugs. Instead of putting effort and money in generating different sets of data for distinct regions, the industry should maximise its effort in developing large-scale safe, quality and effective medicines at lower prices. In addition, local and international industries, complying with shared guidelines, can easily access different markets more efficiently.

drug development, inspection and post-market activities, adopted by different regions, also allows better regulatory interaction, cooperation and information sharing. At the same time the exchange of information among regulators can decrease redundant activities as well as improve pharmacovigilance activities and drug quality and safety assurance. ICH favours the implementation of good review practices, transparency, and consistency by regulators worldwide.

The end result will be quicker access to better, safer, lower-priced therapies and new or generic drugs.

For regulators, having ICH-provided harmonised high-standard guidelines for



Wassim Nasabeh
• BIO Representative
• Global Head, Regulatory
Policy & International
Operations, Roche

The single most important contribution of ICH over the last 30 years is its profound impact in enabling availability and access to safe and effective medicines to patients worldwide. This was largely done through the development and global adoption of harmonised science-based regulatory standards that guide the clinical development, control, manufacture and supply of quality medicines. The ICH Guidelines quickly became the gold standard in defining proper risk-benefit analysis and acted

as an effective road map to streamline the drug development and registration process, supported the elimination of redundant country-specific clinical trials while always ensuring appropriate safety and quality standards are maintained and enhanced with the advancement of knowledge and scientific evolution. This has cemented the public trust in the safety and efficacy of medicines developed to the ICH standards, thus providing an immeasurable contribution to public health.

HOW DOES ICH CONTRIBUTE TO A MORE EFFICIENT ACCESS TO MEDICINES?

Patricia Oliveira Pereira Tagliari

- Former ANVISA, Brazil Representative
- Deputy Director, Second Directorate, ANVISA, Brazil

It is of utmost importance that all effort be made to improve access to affordable medicines worldwide. By promoting harmonisation amongst its Members, Observers or even regulators not directly involved with ICH activities, ICH favours a more efficient resources allocation by industry and regulators, which tends to make prices decrease.

ICH also plays an important role contributing to a more efficient access to medicines by strengthening national drug

regulatory authorities. The environment provided by ICH, guided by technical and scientific discussions among peers from different regulators and diverse industries' representatives, contributes to each national regulatory authority on the adoption of high standards, best regulatory practices, and the necessary structure to perform the regulatory activities focused on medical product lifecycle. In strengthened regulatory authorities, it is less likely to find significant substandard or falsified medicines.



Thomas Cueni

- Former IFPMA Representative
- Director General, IFPMA

The development of harmonised scientific and technical guidelines was the keystone in advancing biopharmaceutical innovation. Through ICH, a more efficient drug development process yielded greater access to medicines while improving patient health.

Before 1990, individual country requirements governed drug development, creating inefficiencies, redundancies, and conflicting requirements – leading to multi-decade processes to bring new medicines to patients. Alignment of regulatory guidelines through ICH acknowledged the commonalities within safety, efficacy, and quality disciplines irrespective of geography.

This transformed our approach to a harmonised, predictable, and efficient development process, saving time and resources that translated into greater access to new medicines.

ICH also facilitated regulator-to-regulator engagement and capability building. Shared interactions built trust and led to regulatory review procedures in which reliance and work-sharing models have created both time and resource savings. This approach shortened review timelines and sped access to medicines without sacrificing patient safety or individual country public health responsibilities.

Toshiyoshi Tominaga

- Former ICH Assembly Vice-Chair and ICH MC Vice-Chair (MHLW/PMDA, Japan)

ICH contributes to efficiency in multiple ways. Most importantly ICH Guidelines have eliminated duplicative country-by-country studies, as they represent the globally accepted standards required to register and manufacture drugs. A single data set made to the guidelines can thus earn market authorisation of a drug from multiple authorities. Drugs, raw materials or final products can now be sourced globally. The common norms have also expanded regulatory cooperation to give another boost in the efficiency of regulatory processes.

More recently ICH Guidelines have assumed a role as a driver of global development in accordance with the latest science. One ICH Guideline addresses multi-regional clinical trials, which contributes to efficiency with quicker subject recruitment. Newer ICH Guidelines clarify how the latest science (e.g. concept of Quality by Design (QbD), estimand, continuous manufacturing, etc.) should be used in drug development and encourage their use, thereby pre-empting disharmony.



Tomas Salmonson
• Former EC, Europe Representative
• Partner, Consilium Salmonson & Hemmings

The remarkable development of vaccines against SARS-CoV-2 demonstrates what can be achieved when stakeholders collaborate globally: developing, authorising and giving access to effective products without compromising the rigour of testing. The pandemic also shows the importance of defending scientific standards and regulatory assessments against political expediency.

Developments in science provide hope for cures or slowing disease progression in areas previously treated symptomatically. Developments in evidence generation promise more speed, but with the risk of reduced quality.

For 30 years ICH has been successful in setting standards for medicines, becoming a truly global platform. This should be recognised, but ambitions should not be reduced. The role of ICH in translating advances by academic and industry researchers into contemporary regulatory guidance will be even more important in the next 30 years to ensure patients around the world benefit from new products in a timely manner.

Lembit Rägo
• CIOMS Representative
• Secretary-General, CIOMS

ICH has reduced duplicative efforts in data generation and has been very successful in eliminating barriers to markets, due to higher rate of harmonisation of technical requirements based on ICH standards. To achieve more, there is a need to proactively involve academic research to study the impact of ICH Guidelines on product development, map the difficulties of guideline implementation and suggest new guideline development, better synergy between different guidelines

and timely revisions. These are just some potential study areas to be considered. ICH alone or in cooperation with partners should establish a research fund that could be used by ICH governing bodies to deliver grants for projects identified by them or proposed by academics with the aim of financing scientific research. This would be a shift from expert opinion-based decision-making to more evidence-based decision-making.

WHAT WILL ICH LOOK LIKE AT 40?



John CW Lim
• Executive Director, Centre of Regulatory Excellence, Duke-NUS Medical School, Singapore

As ICH turns 30, its renowned guidelines form the foundation of international regulatory evaluations while the globally accepted CTD format demonstrates the effectiveness of ICH's mission in promoting harmonisation of technical requirements and scientific rigour in decision-making. The current emphasis on capacity building is a critical step in translating knowledge of guidelines into effective implementation in developed and developing countries.

Over the next ten years, ICH is well placed to forge and strengthen strategic partnerships among industry, regulators and

academia to effectively develop guidelines addressing key contemporary issues and advance regulatory science. Expanding membership will create a more inclusive stakeholder community and provide a strategic platform for advocating regulatory convergence, cooperation and collaboration. ICH's enabling of countries and agencies, regardless of size and capability, to advance harmonisation initiatives will become increasingly critical for addressing international health products and health systems challenges of the future.

Patricia Oliveira Pereira Tagliari

- Former ANVISA, Brazil Representative
- Deputy Director, Second Directorate, ANVISA, Brazil

In ten years, it is possible ICH will have progressed in two areas. The first one, already under discussion, would be the consolidation of the voice of patients in the ordinary process of regulating drug development. Despite the clear and strong desire to advance on this topic, finding the right parameters and mechanisms to make it a reality are still a challenge.

The second one may require some changes in the way ICH currently operates, but there is certainly room for advancement on discussions related to reliance within ICH Members. Once great harmonisation is achieved among peers, it will be natural to explore concrete ways and tools to make better and more efficient decisions that benefit the world's population.



Sue Forda

- EFPIA Representative
- Vice President GRA-International, Eli Lilly and Company Ltd

When we celebrate ICH's 40th year of progressing regulatory cooperation in 2030, I hope we will reflect on a decade that introduced the most substantial changes in ICH's important history. In traversing the unprecedented obstacles of the COVID-19 pandemic, medicine development stakeholders, brought together by ICH, will have offered concrete improvements for vexing issues uncovered during this global battle. ICH will have engaged new regulator collaborators, enabled important discussions and connections,

issued multiple harmonised guidelines and elevated regulatory science capabilities worldwide. I foresee ICH offering contributions to support the next wave of medicine development advances including in the fields of cell and gene therapies and digital health, just to name a few. In sum, ICH should mark its 40th year, empowered by enthusiasm from the decade's successes, charged by conviction from the obstacles it overcame and motivated by momentum to move towards its 50th year – ICH's "golden anniversary".



Joerg Schlaepfer

- Swissmedic, Switzerland Representative
- Head Sector Management Services and International Affairs, Swissmedic, Switzerland

We at Swissmedic, Switzerland, the Swiss Agency for Therapeutic Products strongly believe the impact of ICH will be even greater in ten years' time. We see an increasing role of ICH in embedding patients over the entire lifecycle of medicines from the beginning of drug development to maintenance of mature products. As good examples, the reflection paper on Patient-Focused Drug Development or the modernisation and renovation of

the Good Clinical Practices have paved the road already. Here ICH continues to build on its foundations, which were put in place by its founding agencies 30 years ago. The incorporation of the patient's perspective could contribute to enhanced quality, relevance, safety and efficiency of drug development processes, to informed regulatory decision-making and, in consequence to the faster access to high quality, safe and effective medicines.

HOW COULD ICH IMPACT BE INCREASED?

Cathy Parker

- Former Health Canada, Canada Representative
- Former Director General, Biologics and Genetic Therapies Directorate, Health Canada, Canada

ICH Guidelines should play a key role in regulatory capacity building. In low- and middle-income countries, both regulators and manufacturers should have development plans with full implementation of key

ICH Guidelines as their goal. The focus should not be on minimal standards or capacity, but on attaining ICH compliant goals and standards.

Sue Forda

- EFPIA Representative
- Vice President GRA-International, Eli Lilly and Company Ltd

Even with many reasons to celebrate ICH's 30th anniversary, all of us involved envisage its brighter, more dynamic future. From its initial 1990 meeting in Brussels, who could have imagined then ICH's current reach to all corners of the world or its impact on all areas of medicine development? To accelerate this progress, it is imperative that the extensive range of ICH Guidelines evolve as rapidly as science is advancing today. We should think of a continual improvement mindset during each

ICH meeting and project. Regulator authority participants should expedite efforts to implement – in spirit and practice – any ICH Guidelines not yet adopted. Finally, ICH needs to maintain a laser-sharp focus on its core business, guideline development and revision. Since ICH has been on the frontline of global regulatory cooperation for over 30 years, its central role and opportunity to further increase its impact are within view.



Mike Ward

- Former Health Canada, Canada Representative
- Former WHO Representative

ICH has progressively introduced measures aimed at increasing the impact of ICH Guidelines, including through the expansion of ICH membership. Further impact will come from refinement and amplification of existing measures.

Noteworthy among these are the following five:

- Training: As noted elsewhere, training is fundamental to a proper understanding of ICH Guidelines and their translation into predictable regulatory practice. Authoritative training, underpinned by a strategy and network of trusted partners, assumes greater significance with the increasing complexity of topics and the global audience.
- Diversity: Great strides have been made in building a more diverse, global ICH community. A natural evolution of this trend would see the increased responsibility of new Members in the governing bodies of ICH, thereby promoting further ownership and change.
- Stakeholder engagement: ICH Guidelines impact a wide range of stakeholders.

Effective engagement with researchers, patient organisations and other communities will enable the development, relevance, and broader use of ICH Guidelines.

- Optimising strategic alliances: ICH promotes pharmaceutical harmonisation through the development and implementation of technical guidelines. Other international initiatives such as ICMRA, IPRP and PIC/S perform distinct but complementary roles in ensuing sound regulatory oversight of pharmaceuticals. Deliberate, sustained collaboration between these initiatives will ensure most effective use of resources and collective impact.
- A focus on low- and middle-income countries (LMICs): For ICH to have a truly global impact, relevant ICH Guidelines should define registration requirements for LMICs. This will require continued support in the form of regulatory system strengthening and regional harmonisation efforts, including through the RHIs represented at ICH.



Analía Porrás

- PAHO Representative
- Unit Chief, Medicines and Health Technologies, Health Systems and Services, PAHO/WHO

ICH constitutes an invaluable reference for regulatory standards not only for its Members but for all regulatory bodies across the globe. By opening the forum to new Members and Observers such as the Pan American Network for Drug Regulatory Harmonisation (PANDRH) and several member states from Latin America, the ICH has expanded its

influence and made its mission even more relevant, enabling access to quality, safe and effective medicines. In this important milestone in its history, we encourage the ICH to continue to embrace new members from across all regions to accelerate harmonisation and efficiencies as a means to strengthen the regulatory systems across the world.

07

ICH's technical work: process and products

THEME 1 - LIFTING THE VEIL: HOW ARE ICH GUIDELINES DEVELOPED?



Peter Honig

- Former PhRMA Representative
- Board member, Sesen Bio; Member of Board of Directors, Drug Information Association



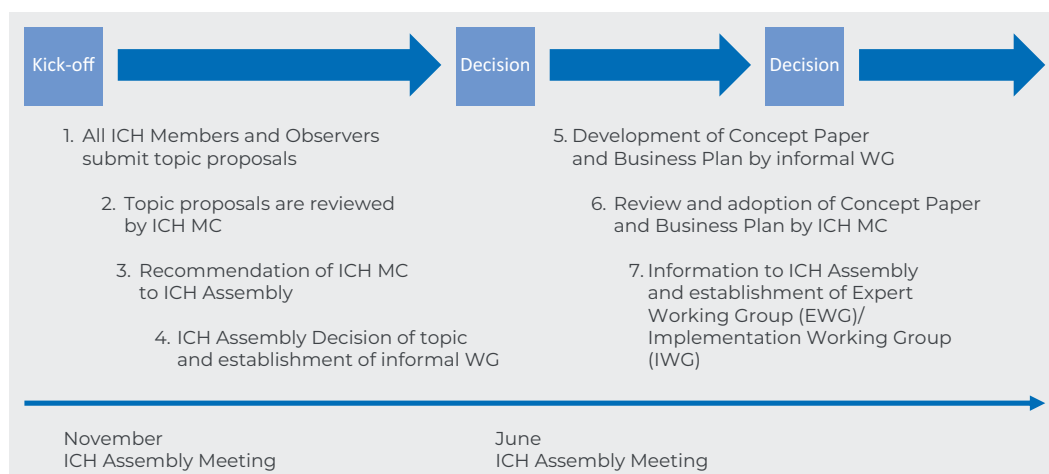
Milton Bonelli

- EC, Europe Representative and Technical Coordinator
- Scientific Advice Officer, EMA

SELECTION OF NEW TOPICS

FIGURE 6

Steps in the process to select new topics for harmonisation:



The selection of new topics represents the start of the technical harmonisation process, the “raison d’être” of the ICH organisation. New guideline topic proposals are considered in the context of the ICH work plan once per year, with deadline for submission of proposals defined during each November biannual meeting of the ICH Assembly.

A topic proposal can be submitted by any ICH Member or ICH Observer. Proposals can articulate harmonisation actions related to a novel scientific area or propose a revision of existing ICH Guidelines in isolation or be based on one, or more, of the deliverables included in an ICH Reflection Paper. The ICH MC reviews any topic proposals received and prioritises proposals that are to be recommended for endorsement by the ICH Assembly during each June meeting – based on an outline of the (to-be) Concept Paper.

The ICH Assembly decides during its June

meeting to either endorse or reject a topic proposal recommended by the ICH MC. In principle, the agreement of all Members of the ICH Assembly is necessary for initiating any ICH harmonisation activities. However, in exceptional cases when ICH Assembly consensus cannot be achieved, the Assembly Rules of Procedure foresee the possibility of proceeding to voting and the possibility of endorsing a new topic proposal by majority. In the case of voting, only the ICH Regulatory Members have the right to vote on the selection of topics for harmonisation. The Regulatory Members of the ICH Association (ICH regulators) are required in good faith to consider the opinions expressed by the Members representing industry and others. To date, all topics were endorsed to start by consensus.

If a new topic proposal and Concept Paper outline are endorsed by the ICH Assembly, an informal WG is established to develop the full Concept Paper and a Business Plan,

if requested. In general, the ICH MC oversees all operations of an informal WG, also ensuring that the right expertise is included in its membership. ICH Members and Observers are invited to express their interest within a three-week period. The ICH MC then reviews the expert nomination requests and confirms the WG Membership.

A Concept Paper is developed by the informal WG. It provides further context and details on the agreed proposal, describing the perceived problem and the issues to be resolved by a harmonisation project. The Concept Paper should ideally be completed within two months (60 days) following the endorsement of the topic proposal by the ICH Assembly to allow for approval at an ICH MC teleconference. The ICH MC works with the informal WG to ensure that a Concept Paper is developed in line with the topic proposal and

Concept Paper outline endorsed by the ICH Assembly. The final Concept Paper is then submitted to the ICH MC for endorsement and the ICH Assembly is notified once a final Concept Paper is endorsed.

A Business Plan should be developed in parallel with the Concept Paper and is intended to complement it by expanding on the costs and benefits of harmonising a topic and on regulatory feasibility. The Business Plan is submitted by the informal WG for review and approval by the ICH MC no later than 30 days following endorsement of the Concept Paper by the ICH MC. The Business Plan submitted to the ICH MC is reviewed for either feedback to or revision by the WG, or approval by the ICH MC. The ICH MC reports the decision to approve the Business Plan to the ICH Assembly.



Joan Blair
• FDA, United States Representative
• Senior Advisor, International Affairs, Center for Biologics Evaluation and Research (CBER), FDA, United States



Lenita Lindström-Gommers
• ICH Assembly Chair (EC, Europe)
• Senior Expert, Unit B4 – Medical products: quality, safety, innovation, Directorate General for Health and Food Safety, EC, Europe

KEYS TO ICH'S SUCCESS YOU WON'T FIND IN RULES OR PROCEDURES

Why has ICH been so successful over the years in achieving harmonisation? What is the secret formula? How do the ICH EWGs actually manage to bring a Concept Paper to a fully-fledged guideline and how do they go about building consensus? While many factors have been cited over the years, some may be less obvious and deserve mention.

Evolution and flexibility to meet changing circumstances

Many would point to the detailed procedures and managed process for which ICH is renown as any reading of the substantial body of operating procedures would attest. Perhaps equally important to this success, however, is what could be considered the antithesis of a structured process: flexibility. Despite what some may perceive as a procedurally constrained organisation, ICH has proven to be agile over the years, flexing and adapting when called for in a given situation. Indeed, the modifications to the procedures themselves reflects that very adaptation. An extraordinary example of this agility and adaptability is the major reform where ICH “reinvented” itself in 2015 to adapt to the new global realities of pharmaceutical

development. ICH became an independent, Swiss non-profit organisation and expanded participation, increased transparency, reinforced its public health mission and strengthened the strategic focus of its work. All this while the harmonisation work was ongoing. Fortunately, the continuous growth of the ICH Association since then, with the biannual ICH meetings drawing some 500 participants, has not slowed down the guideline development process, which has though been impacted by COVID-19.

Broadening perspectives to meet evolving needs

Over time, ICH recognised the need to augment expertise in certain topics and introduced creative approaches to meeting that need. This has included inviting non-ICH experts on an ad hoc basis to the deliberations of an EWG; by holding public workshops to inform the work of a group and undertaking engagement with stakeholders critical to the modernisation and broader use of ICH Guidelines.

Talented individuals – with the right skillset

The impressive capability of the individual experts and representatives to exercise

Mike Ward

- Former Health Canada, Canada Representative
- Former WHO Representative

real-time negotiation skills cannot be overstated. ICH places a high value on its face-to-face work, conducted in biannual week-long meetings (in non-COVID times) which builds trust among experts in the WGs. Reaching consensus requires that individuals have a mastery of both technical content and a sensibility of how best to avoid or overcome a roadblock on a given issue on-site. This can translate into sidebar conversations after hours between individual parties to clarify misunderstandings, a timely coffee break to allow for caucusing within parties, or recognising and respecting a party's domestic constraints and finding a path around them. This is fundamental as ICH is a diverse, multilateral forum where the participants come from different backgrounds and therefore the importance of understanding cultural differences is crucial. Importantly, there is a willingness on the part of participants to work in good faith to strive for consensus, rather than holding steadfast to a position and where the Rapporteurs or leads of the WGs try to keep the focus on the key concepts of the guidelines.

Role of the Rapporteur and the Regulatory Chair

The impact of an ICH Guideline is significant as the work output will set global requirements for drug development. This can at times lead to intense discussions between experts. The Rapporteur's ability to ensure that all voices are heard, proposals and positions are well-understood, facilitate good group dynamics, maintain impartiality, articulate points of difference and work towards resolution of contentious issues can greatly influence the success of a WG in attaining stated goals and respecting timelines. This role has now, since the ICH reform, been supported by the establishment of a Regulatory Chair whose function is to ensure adherence to ICH procedures, timelines and the agreed upon objectives of the WG. The Regulatory Chair alleviates the Rapporteur from the procedural aspects allowing the Rapporteur to focus on the scientific consensus-building. Good communication skills are also important in clearly reporting to the ICH MC and ICH Assembly on progress, issues and proposed strategies to resolve and responding to sometimes difficult questions. This can additionally require an element of education, reducing complex concepts and the ramifications of work

into language that can be understood by non-specialists.

Diversity

The diversity of backgrounds, views and perspectives is a key strength of ICH and helps to ensure that the final work products take into consideration the broad spectrum of experience and knowledge that helped shape them. This in turn contributes to high quality guidelines that are fit for purpose, have the buy in of regulators and the regulated parties alike, reflect the global dimension of drug regulation and are implementable. At the same time, it is important that differences in language and culture, which could introduce different interpretations of terms and even concepts, are understood to avoid disharmony in the application of ICH Guidelines across all the geographies that now span the ICH membership. Nevertheless, the main challenge is often how to "translate" the technical aspects for the non-experts as the experts seem indeed at times to speak their own "language".

Caucuses

In the evenings during the ICH meeting week, ICH Members and Observers get together in their own or in joint caucus-meetings. The purpose of those meetings is to share information about the ongoing developments in the various WGs and to see whether the work is on track. If there are issues in a given WG, the ICH MC representatives may subsequently approach their counterparts in the ICH MC, such as the ICH Member that holds the position of Regulatory Chair or Rapporteur in that WG. This usually allows overcoming misunderstandings or disagreements, which may ultimately be brought to the full ICH MC. Caucus meetings contribute to the consensus-building process and also allow for useful interactions between the individual experts and their respective ICH MC representatives during the very intense "ICH weeks".

The ICH Secretariat

A well-functioning secretariat is key to a smooth and efficient operation. Throughout the 30-year history of ICH, the handful of individuals who constituted the Secretariat have been instrumental in contributing to the success of the harmonisation initiative. The myriad of tasks undertaken by the Secretariat – the "guardian of the articles,

rules and procedures” – and the quiet efficiency by which they are executed have enabled experts and decision-makers to focus on their work. The Secretariat has been invaluable in helping organise meetings, document decisions, monitor progress, facilitate remote work, assist in contracts with third parties, maintain

the ICH website, welcome newcomers and advise experts and management on procedural matters. We are all indebted to Secretariat for their professionalism, commitment and contribution to the harmonisation process and ensuring continuity of the ICH activities.

THEME 2 - HOW ARE ICH GUIDELINES IMPLEMENTED AND HOW IS IMPLEMENTATION MEASURED?



**Ana Carolina Moreira
Marino Araujo**
• ANVISA, Brazil
Representative and
Coordinator
• General Manager of
Inspections and Law
Enforcement, ANVISA,
Brazil

IMPLEMENTATION FROM THE PERSPECTIVE OF A NEW REGULATORY MEMBER

Regulatory authorities interested in becoming an ICH Member should apply fulfilling the eligibility criteria determined for ICH Regulatory Member, including information of the degree of implementation of ICH Guidelines in their jurisdiction. It is expected that the Authority has implemented the ICH Q1, ICH Q7 and ICH E6 Guidelines (also referred as “Tier 1” Guidelines).

After approval of membership, specific plans with identified milestones and time-frames for implementation of the priority ICH Guidelines within the next five years should be submitted. The priority ICH Guidelines are ICH E2A, ICH E2B, ICH E2D, ICH M4 and ICH M1 (also referred as “Tier 2”). For the remaining ICH Guidelines (also referred as “Tier 3”) the implementation is expected in the near term and as soon as possible.

The use of appropriate tools and methods during implementation are necessary to ensure that the regulatory outcome is effective, transparent, inclusive, sustained and that adequate adherence to the guideline is achieved.

New Regulatory Members should self-assess their existing legislative framework comparing with the requirements in ICH Guidelines to identify if the national and/or regional guideline fully implements ICH Guideline or if there are gaps indicating the need for revision or development of new legislation.

To do so, training and the correct understanding of ICH Guidelines are crucial to guarantee adequate implementation.

ICH training programmes as well as ICH Q&A documents are essential tools not only for regulators but also for local industry. Industry trade associations also play an important role contributing with training events to raise awareness of ICH Guidelines in the region.

The elaboration of a work plan with specific milestones for implementing each guideline will assist the implementation process, prioritising the Tier 2 Guidelines, and defining a step wise approach.

Regulatory authorities may vary in their capability of implementation considering resources (human and financial) capacity to conduct changes in legislation, adhering to Good Regulatory Practices, internal impact in IT systems, impact in workflows, adequate training of the experts involved in the assessment of pharmaceuticals as well as the involvement of local industry. All these aspects are relevant for an adequate implementation and adherence of the ICH Guidelines.

Participation on ongoing WGs promotes better understanding of the guideline, provides opportunity to begin internal discussions during the process of harmonisation that will facilitate future implementation by new ICH Regulatory Members.

Regional public consultation is advised during the ICH process of harmonisation (*Step 3*) and has a relevant aspect specially for new Members considering that local trade associations do not have a direct participation in ICH, as well as Academia and other impacted stakeholders. Regional public consultations provide inclusiveness

by permitting contributions to the draft ICH Guidelines and encourages engagement.

Regional consultation is also important during the local guideline elaboration, especially for non-English speaking countries, to identify any translation problems and improve clarity. In this step stakeholders can also inform challenges for immediate implementation and proposed a step wise approach since new members have not yet implemented all ICH Guidelines.

The implementation of ICH Guidelines by new ICH Regulatory Members provides a harmonised regulatory environment that can improve faster access to new drugs as well as contributes that the products marketed within the jurisdictions meet the same international quality, safety and efficacy criteria adopted by ICH.

<https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf>
www.ich.org/page/articles-procedures



Hironobu Hiyoshi
• JPMA Representative
• Chair, Drug Evaluation Committee, JPMA

IMPLEMENTATION SEEN FROM THE INDUSTRY PERSPECTIVE

For the pharmaceutical industry to fully benefit from ICH Guidelines, it is important that all ICH Regulatory Members adequately implement and adhere to all ICH Guidelines in a consistent manner. After an ICH Guideline is adopted by the ICH Assembly, each ICH Regulatory Member implements the final guideline by directly referring to the original ICH Guideline or translating it into a local language in accordance with the applicable local/regional rules. This milestone is identical to the achievement of *Step 5* defined by ICH. For an ICH Guideline to be adequately implemented, the addition or omission of requirements should be avoided as it would significantly undermine the purpose or effectiveness of the ICH Guideline. Meanwhile, the local guideline may be justified to incorporate additional information beyond those defined in an ICH Guideline in certain circumstances, such as when the ICH Guideline is high-level and does not provide sufficient guidance to the industry when it is utilised in practice.

Once an ICH Guideline has been adequately implemented by an ICH Regulatory Member, the regulatory authority is encouraged to consistently adhere to all identified relevant elements, concepts and principles of the ICH Guideline in its practice.

Achievement of adherence in each jurisdiction leads to a stable regulatory environment and increased sustainability and predictability by confirming ideal global harmonisation of the ICH Guideline on a practical and operational level. The industry

supports successful and adequate ICH Guideline implementation and adherence through close collaboration with the regulator at the local level. Cooperating with local industry associations, the ICH Industry Members also support adequate guideline implementation by new ICH Regulatory Members.

The progress of implementation and adherence of ICH Guidelines by each ICH Regulatory Member is monitored and confirmed by the ICH Assembly. By leveraging multiple monitoring methods, ICH can measure the status of implementation and adherence of ICH Guidelines in a more objective and accurate manner, which in turn provides better transparency to the ICH operation. All ICH Regulatory Members provide updates on their status of implementation of each ICH Guideline by presenting a relevant document describing the implementation of the corresponding ICH Guideline. This also provides an opportunity for the ICH Regulatory Members to share their experience, explain challenges and solutions, and develop best practices in relation to the implementation of ICH Guidelines.

In addition, both the implementation and adherence of ICH Guidelines have been assessed through an ICH survey, which was developed by the ICH MC and conducted by an independent third party. The ICH survey confirms the status of implementation and adherence of ICH Guidelines in each country or region by collecting information from both the regulator and the industry. In the survey, the industry provides its experience-based



Michelle Limoli

- FDA, United States Representative and Technical Coordinator; ICH Training Subcommittee Co-Lead
- Senior International Health Science Adviser, CBER, FDA, United States



Masafumi Yokota

- JPMA Representative; ICH Training Subcommittee Co-Lead
- Chair, ICH Project Committee of JPMA

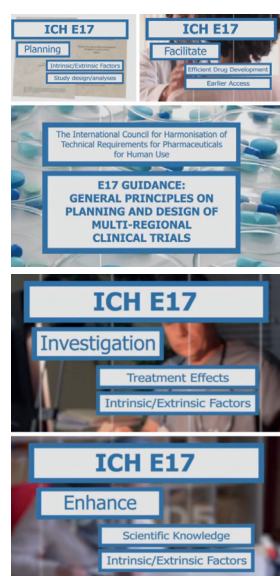


FIGURE 7
Example of ICH training video – highlighting “what is ICH E17 Guideline” for broad stakeholders involving in Multi-Regional Clinical Trials

perceptions on each ICH Guideline implementation in each jurisdiction. When the survey identifies gaps, they can be filled by trainings and/or further communication

between the regulator and the industry, which will help strengthen global harmonisation of the ICH Guidelines.

THE ROLE OF TRAINING IN THE IMPLEMENTATION OF GUIDELINES

To achieve globally harmonised implementation of ICH Guidelines, ICH is working on ensuring that high-quality training is available to address the scientific and regulatory principles outlined in the guidelines. Training materials developed by, and/or with, ICH, such as *Step 4* WG presentations and WG training materials, can be accessed with the respective ICH Guideline as they become available.

To facilitate the training on the ICH Guidelines globally, ICH has three strategic pillars of training modalities:

- 1) ICH Recognised Training Programmes, which are discrete training events organised by training providers,
- 2) accredited non-profit training organisations/institutions as ICH Training Associates,
- 3) ICH Regulatory Training with ICH funding. While ICH Guidelines are developed as a single global document, the end of its value chain is consistent implementation and intent of the ICH WGs.

Thus, training to achieve appropriate implementation, whether globally, regionally, or locally, has grown in importance as a critical ICH activity.

- 1) **ICH Recognised Training Programmes:** Following a successful pilot in 2017, the ICH MC’s Training Subcommittee has been working with selected training providers to organise and deliver high-quality ICH-recognised face-to-face and online training programmes based on pre-set criteria.
- 2) **ICH Training Associates:** In 2019, ICH launched an initiative to engage appropriate accredited non-profit training organisations/institutions as Training Associates, with a Call for Expressions of Interest made to solicit interest from eligible organisations. The goal of identifying such Associates is to assist

ICH in its efforts to address the training needs of its Regulatory and Industry Members and Observers in a strategic manner.

- 3) **ICH Regulatory Training with ICH funding:** ICH provides funding to support training programmes on ICH Guidelines organised by ICH Regulatory Members and ICH Regulatory Observers. These regulatory training events, developed to address the needs of interested regulators, are selected through a Call for Expression of Interest by the ICH MC.

In 2020 the ICH launched a new initiative to develop a Training Library on the ICH website, to make it easier for ICH stakeholders broadly to access all training materials, including *Step 4* WG presentations, WG training materials, Training Associate materials, and materials developed by Training Providers. The Training Library also covers web links on the ICH website to translated training materials in local languages, mainly translated by ICH Regulatory Members.

Further, to assist in the understanding of new concepts (such as Multi-Regional Clinical Trials for ICH E17 and Estimand for ICH E9(R1)) and implementation of their respective ICH Guidelines, ICH has expanded its training tools to utilise introductory and more in-depth videos (Fig 7).

Overall, as individual ICH Guidelines become more scientifically and technically sophisticated, and the portfolio of ICH Guidelines expands, training on ICH Guidelines through various modalities and tools will become even more critical in ensuring their implementation.



Jerry Stewart

- Former PhRMA Representative; ICH Implementation Co-Lead
- Vice President, Head of Global Regulatory Policy & Intelligence, Pfizer

IMPLEMENTATION MEASURED

According to the ICH Articles of Association, the Regulatory Members of ICH are expected to implement ICH Guidelines. In the ICH Assembly Rules of Procedure, it is stated that there should be a process for the Assembly to monitor the progress of international harmonisation and coordinate efforts providing current state of play of the implementation and adherence to the ICH Guidelines.

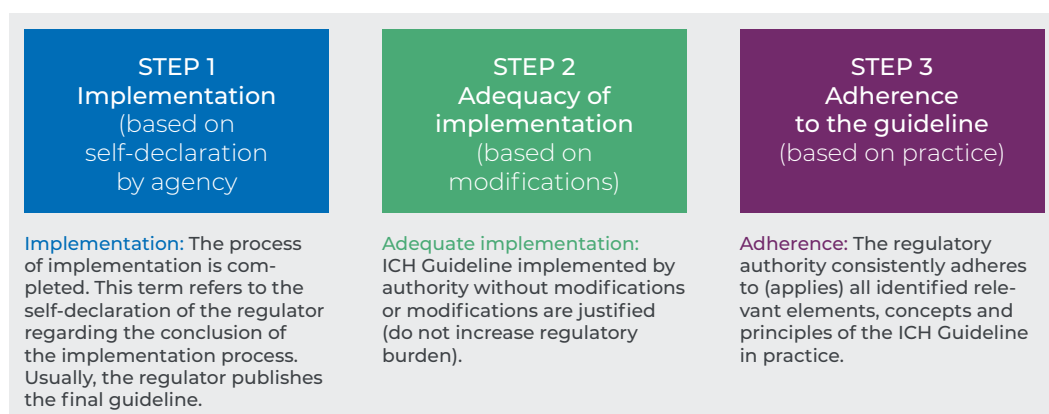
In 2017, the ICH MC supported the ICH Founding Industry Members to conduct a pilot study, Phase 1, to obtain feedback from companies on their perspective and perception of the implementation to the ICH Guidelines. An independent third party, the Centre for Innovation in Regulatory Science (CIRS), developed and conducted a proof-of-concept survey of PhRMA/EFPIA/JPMA company members on the Tier 1 and 2 ICH Guidelines. The Phase 1 study results demonstrated that a survey could be undertaken across companies, where the response rate

was excellent indicating strong interest in the project.

Therefore, in 2018, ICH contracted with CIRS to undertake a follow-on study to assess the adequacy of implementation and adherence to ICH Guidelines. CIRS was selected because of its longstanding work with regulators and industry on advancing regulatory science and harmonisation. This next study, named Phase 2a, was to build on the outcomes and lessons learned from Phase 1. Under the direction of the ICH MC's Implementation Subcommittee, CIRS developed an online questionnaire/data collection tool and definitions around the stages of implementation.

The following diagram outlines the process by which ICH regulatory authorities implement the technical guidelines over time, including the respective definitions used in the survey.

FIGURE 8
Guidelines implementation steps



The initial step undertook a gap analysis by obtaining both the authorities' and companies' viewpoint on the implementation and adherence to the ICH Guidelines. The long-term objective was to establish a sustainable ICH-driven mechanism to assess guidelines over time to inform ICH stakeholders on multiple areas.

The overall phase 2a study objectives were to:

- Inform the ICH decision-making related to regulator membership applications

- Provide ICH Members and Observers with additional data for internal considerations
- Identify regulatory training and capacity building needs.

Based on the successful outcome of the phase 2a study, at the ICH 2019 biannual meeting in Singapore, the ICH MC discussed and proposed that a follow-up survey should be conducted in 2020/2021, with results presented at the May/June 2021 biannual meeting. The remit of this study,

referred to as Phase 2b, was principally to assist the ICH MC in determining whether ICH Regulatory Members would meet the eligibility criteria for the ICH MC elections in June 2021 and to also allow participating Regulatory Observers interested in future ICH Member-ship to reference survey findings to confirm their eligibility.

Collectively, the Phase 2a and 2b studies have covered many ICH Guidelines, across all ICH Regulatory Members and selected Regulatory Observers. In each phase, approximately 30 companies participated, comprising global and regional footprints, with both innovative and generic focus.

The overall responses, supported by evidence-based rationale, identified general agreement between regulatory authorities and companies, but with some divergences. These differences were largely supported by justifications and specific examples, whereas gaps and divergences could be used to support training and capacity building efforts across authorities and companies. In general, the survey study results from Phase to Phase have demonstrated progress made by authorities in implementing ICH Guidelines.

Further information on guideline implementation can be found at www.ich.org/page/ich-guideline-implementation

THEME 3 - HOW DO ICH GUIDELINES TRANSFORM THE DEVELOPMENT OF MEDICINES?



Jan Willem van der Laan
• ICH S1B(R1) Regulatory Chair (EC, Europe)
• Senior Pharmacological/Toxicological Assessor, Medicines Evaluation Board, Netherlands



Frank D. Sistare
• ICH S1B(R1) former Rapporteur (PhRMA)
• Contractor, consultant, adjunct professor at the University of North Carolina, United States

CONTRIBUTING TO REPLACEMENT, REDUCTION AND REFINEMENT (3RS) IN ANIMAL TESTING THROUGH HARMONISATION OF INTERNATIONAL SAFETY GUIDELINES

Celebrating the 30th anniversary of ICH reminds us of its start in 1990. In the non-clinical area, reduction of animal testing was an important goal of harmonising scientific and technical aspects of pharmaceutical development safety guidelines from the very beginning (Ohno, 2013, see note 1). Current practice at that time was for regulatory authorities to apply their own rules, e.g. in reproductive toxicity testing, where disharmony was long recognised, so success of ICH in this area was rapidly appreciated (Bass et al, 2013, see note 1).

Carcinogenicity testing was started to harmonise approaches and limit exorbitant exposures being requested to reach the Maximum Tolerable Dose. As a way of refinement the 25 area under the curve (AUC) was introduced to avoid distress (ICH S1C). In addition, over a 50% reduction in the numbers of (transgenic) mice being treated for six months were introduced by ICH S1B to provide an alternative to the (at least) 500 wild-type mice being tested for two years (Van der Laan et al, 2013, see note 1).

A multidisciplinary approach improved definition of the need and timing for toxicity data during pharmaceutical development (ICH M3), resulting also in refinement and

reduction of animal use, (e.g. the recognition that acute toxicity data in two animal species are of no regulatory value). A reduction was also reached in the duration of chronic toxicity studies in non-rodents from 12 to nine months.

The area of Biotechnology-derived proteins is covered in ICH S6, where the first version (1997) focused on reduction of the package of animal studies. In the addendum (2011) improvements toward reduction of irrelevant animal studies were made on selection of relevant animal species, the duration of chronic toxicity studies, and a new protocol on reproductive toxicity especially for non-human primates.

In the course of 30 years several other topics were launched, including Safety Pharmacology and Cardiac Safety, which have incorporated a substantial in vitro component (Koerner and, Siegl, 2013). The Immunotoxicity Guideline ICH S8 was important in harmonising that any additional stand-alone immunotoxicity testing was not routinely necessary unless triggered from signals in standard animal toxicology studies (Hastings, 2013, see note 1). In the area of oncology therapeutics is ICH S9, impacting reductions in the package of animal studies both to support clinical trials as well as final marketing



Kumiko Ogawa

- ICH S1B(R1) Expert (MHLW/PMDA, Japan)
- Head of the Department of Pathology, National Institute of Health Sciences, Japan

authorisation. Another important example is ICH S10, Photosafety. This document clearly indicates when non-animal testing including absorption spectrum and in vitro toxicity testing are sufficient and in vivo studies have no added value.

The new legislation on paediatric drugs in the European Union has led to a world-wide reflection on juvenile toxicity testing, and the initiative to have a harmonised ICH Guideline S11, released recently, seeks to limit the need for studies in juvenile animals. In June 2019 a new EWG started with a new ICH S12 Guideline on “Nonclinical Biodistribution Considerations for Gene Therapy Products” to provide recommendations on nonclinical studies that include biodistribution assessment, while minimising the use of animals. In 2015, a revision of ICH S5 Reproductive Toxicity Testing was started, completed in 2020. An important inclusion has been the wording on the qualification of “alternatives”, in vitro and ex vivo assays. It encourages the use of new non-animal approaches in the full regulatory environment, eventually leading to experience to support a reduction of animal use in this respect.

In 2012 a new process was started to reduce use of animals in a process evaluating the prediction of the carcinogenic potential of small molecule pharmaceuticals based upon chronic and other toxicity study outcomes. It was found that pharmacological properties would be of substantial aid in positive as well as in negative prediction. After a Prospective Evaluation Period of 8-9 years a new addendum to ICH S1B has been released at *Step 2* describing an additional testing approach of carcinogenic potential, based upon available data at the end of Phase II. For certain pharmaceuticals carcinogenicity potential can be determined without the need for two-year testing of small molecule pharmaceuticals in rats, just as for biologic medicines.

Note 1:

- In 2013 a book has been published explaining the background of all Safety Guidelines being published till then, highlighting also the 3Rs in detail. JW van der Laan, JJ DeGeorge (eds.) Global approach in Safety Testing, AAPS Advances in the Pharmaceutical Sciences 5, DOI 10.1007/978-1-4614-5950-7_4, © AAPS 2013
- Bass R, Ohno Y, Ulbrich B. Why and How Did Reproduction Toxicity Testing Make its Early Entry into and Rapid Success in ICH.
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Jean-Louis Robert
• ICH Q12 Expert (EC, Europe)
• Chair of the CEP Steering Committee, EDQM



Graham Cook
• ICH Q12 Expert (EFPIA)
• Senior Director, Pfizer Global Supply – Quality Operations

NEW PARADIGM IN PHARMACEUTICAL QUALITY – EVOLUTION OVER 30 YEARS

When ICH started in 1990, the most urgent topic to be addressed was the generation of stability data that would be acceptable in regulatory submissions across the three founding regions (European Union, Japan, United States). Lack of harmonised requirements led to inefficiencies where applicants had to perform a multiplicity of stability studies to meet the expectations of each individual market. This was the start of the journey to develop a series of guidelines that specify technical requirements in several areas including validation of analytical procedures, impurities, specifications, etc. Complementary guidelines for biological medicines and pharmacopoeial harmonisation have also been developed. An important ICH Guideline was the Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH Q7) which was rapidly accepted worldwide.

During discussion on the ICH M4Q Common Technical Document (CTD), a structural guideline to harmonise the submission file for marketing applications, it was agreed to include a pharmaceutical development section. This resulted in the elaboration of a more conceptual guideline on pharmaceutical development (ICH Q8). Together with the quality risk management guideline (ICH Q9), these supported the shift from “testing to specification” to “designing quality into the product” and the use of more formal, risk-based approaches in pharmaceutical development. In parallel, agreement was reached at the 2003 Brussels meeting on the future of quality in ICH:

“Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science.”

This was, and remains, an important statement because it reminds us that science (development, knowledge, technical progress, innovation), does not stop at submission for the first marketing authorisation, but continues during the commercial phase. The new paradigm emphasises the development of scientific understanding of a product and manufacturing process throughout the lifecycle, and this provides the basis for continual improvement. This scientific knowledge, together with risk management within the pharmaceutical quality system (ICH Q10), enables the product and process to be updated in line with scientific standards. This new paradigm was embodied in the ICH Q11 Guideline on Development and Manufacture of Drug Substances, and the concepts are also used in draft guidelines currently in progress – continuous manufacturing, and development of analytical procedures.

It became apparent that the management of post-approval changes needed to be facilitated to fully enable the new paradigm, and so the guideline on Pharmaceutical Product Lifecycle Management (ICH Q12) was developed. This guideline provides tools and approaches to perform post-approval changes in a more controlled and predictable way, allowing some flexibility while maintaining regulatory oversight. Pharmaceutical products and processes can be changed more easily to take advantage of scientific understanding and progress and this should benefit patients by helping to mitigate some of the problems associated with difficulties in the supply of certain medicines.

Over the last 30 years, ICH has brought together expertise from regulators and industry from different regions to develop valuable ICH Guidelines that have enabled pharmaceutical innovation and cooperation between regulatory authorities. ICH provides a good basis for better mutual understanding and reliance, which can have a huge impact on driving accelerated regulatory pathways giving patients access to high quality medicines globally.



Fergus Sweeney

- ICH E6(R3) Regulatory Chair (EC, Europe), ICH E8(R1) Expert and ICH E8(R1) former Regulatory Chair (EC, Europe)
- Head, Clinical Studies and Manufacturing Taskforce, EMA



Lisa M. LaVange

- ICH E8(R1) Rapporteur (FDA, United States)
- Professor and Chair, Department of Biostatistics, Gillings School of Global Public Health, Chapel Hill, NC, United States



Mark Levenson

- ICH E8(R1) Expert (FDA, United States)
- Director, Division of Biometrics VII, CDER, FDA, United States

MODERNISING THE DESIGN AND CONDUCT OF CLINICAL STUDIES

Quality Continuum in Design and Conduct – ICH E8 & ICH E6

Clinical trial designs, methodologies and data sources are evolving and diversifying at a rapid pace. Following extensive discussion, the ICH Reflection paper on GCP renovation⁽¹⁾ (2017), addressing the ICH E8 (General Considerations for Clinical Trials) and ICH E6 (Good Clinical Practice) Guidelines, called for quality to be built into the design and conduct of clinical trials and clinical development programmes (Figure 9). These ICH Guideline revisions are intended to provide the substantive guidance and flexibility needed to address the increasing diversity of study types, data sources, innovative methods and technology used in studies whose results support regulatory and other health policy decisions.

Revision of the ICH E8 Guideline started in November 2017 and focuses on designing quality into clinical study protocols and processes, emphasising those elements – critical to quality factors – that are most essential to the protection of study participants and the reliability of results. Proportionate, risk-based, approaches to design (and conduct) are emphasised to ensure focus on the processes and data that really matter. The scope was widened to acknowledge the increasing use of real-world evidence and observational studies, particularly after initial marketing authorisation. The ICH E8(R1) Guideline provides a general introduction to clinical development and study planning and orientation to other ICH Efficacy Guidelines⁽²⁾.

ICH E8 and ICH E6 have a significant impact for study participants and patients who may use the medicine once authorised, and for academia both as sponsors of their own studies and as investigators. As such, broader stakeholder engagement is a key feature of this GCP renovation. This broader engagement was launched at a public workshop on ICH E8 in 2019, where the draft guideline was discussed by a wide range of patient and academic groups. Within the ICH E8(R1) Guideline, patient engagement is now a general principle when designing clinical development plans and sponsors are asked to seek input from stakeholders, such as clinical investigators and potential trial participants, in study design and identification of critical to quality factors.

In April 2020, the ICH MC and Assembly endorsed the multifaceted stakeholder engagement plan for the ICH E6 GCP Guideline revision. Six academic experts nominated from across the ICH regions work with the EWG to provide input from their perspectives as clinical trial sponsors and investigators. This very enriching experience has contributed to the draft ICH E6 GCP principles, published in advance in April 2021 as a transparency measure. Regional workshops and public webinars including patients and academia were also held. Two recent webinars, held in May 2021 involved over 5500 participants worldwide, where the ongoing revision and the draft principles were explained, and patients and academia explained their aspirations for the revision of ICH E6. The ICH E6 revision started in November 2019, with the public consultation planned for 2022 (Figure 10).

The EWG focused initially on the stakeholder engagement plan and the overarching principles. These principles will be accompanied by two Annexes (Figure 11). In drafting the guideline, the EWG took into consideration the rapid acceleration of the use of digital tools and communication, home treatment and other adaptations that have gained importance during the COVID-19 pandemic.

The vision for ICH E6(R3) is for GCP to be flexible to allow for and to encourage innovation, while concentrating resources on what is most important (the critical to quality factors) in safeguarding the protection of trial participants and the reliability of results. The principles set out in ICH E6(R3) will remain relevant as technology and clinical trial design evolve, leveraging and facilitating an increasingly digital ecosystem.

In conclusion, both ICH E8(R1) and ICH E6(R3) emphasise the application of thoughtful process throughout clinical trial design, conduct and analysis. This is about doing things differently, not adding to the status quo – change management will be essential.



Mutsuhiro Ikuma

- ICH E8(R1) Expert (MHLW/PMDA, Japan)
- Senior Scientist, Pharmaceuticals and Medical Devices Agency

FIGURE 9

The quality continuum between the main design concepts of ICH E8 and the clinical trial conduct in ICH E6



FIGURE 10

Development of ICH E6(R3)

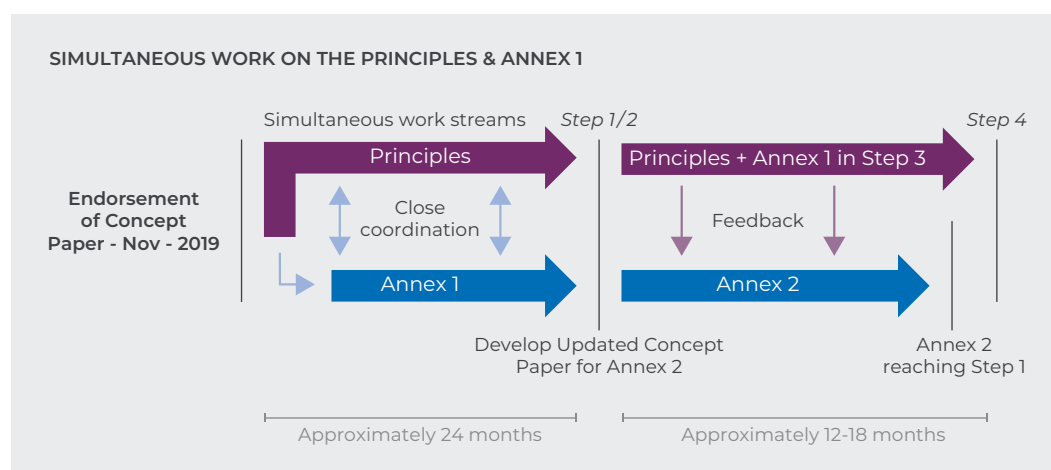
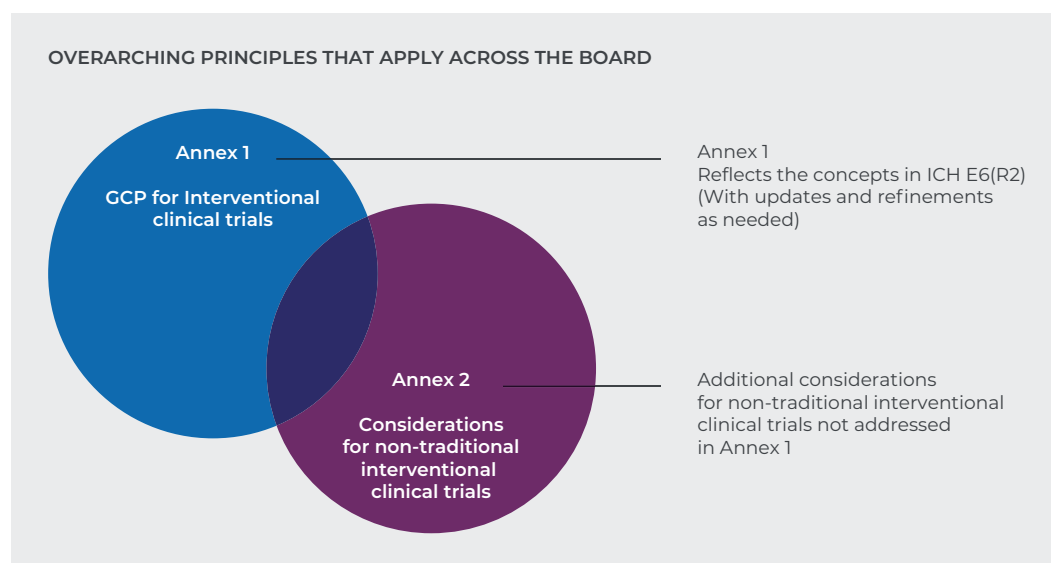


FIGURE 11

ICH E6(R3) GCP Principles and Annexes 1 and 2⁽³⁾



M. Khair ElZarrad

- ICH E6(R3) Rapporteur (FDA, United States)
- Acting Director – Office of Medical Policy, CDER, FDA, United States



Andreas Kirisits

- ICH E8(R1) Regulatory Chair (EC, Europe)
- Senior Clinical Assessor, Austrian Agency for Health and Food Safety

(1) https://admin.ich.org/sites/default/files/2019-04/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf

(2) www.ich.org/page/efficacy-guidelines

(3) In the 2017 ICH GCP Reflection Paper a third annex was anticipated to address standards for observational studies. ICH is now considering a standalone guidance as a better solution to present standards for such data and studies and to enable such work to start earlier if agreed.



Sabine Brosch

- EC, Europe Representative in the MedDRA MC
- Principal Scientific Administrator, Data Analytics and Methods Task Force, EMA



Mark Gray

- ICH M8 Rapporteur (FDA, United States)
- Senior Project Manager, CBER, FDA, United States



Christina Winter

- EFPIA Representative in the MedDRA MC; ICH M1 Rapporteur
- Safety Evaluation and Risk Management, GlaxoSmithKline (GSK), United Kingdom



(1) Chinese, Czech, Dutch, English, French, German, Hungarian, Italian, Japanese, Korean, Portuguese, Brazilian Portuguese, Russian and Spanish

THE DIGITAL AGE AND ELECTRONIC COMMUNICATION OF REGULATORY INFORMATION – MedDRA, ICH E2B, eCTD, ICH M4

Since its early start, ICH was a pioneer in preparing for the digital age focusing on standardisation of formats, terminologies and the electronic exchange of regulatory information in the pharmaceutical sector. The following examples are showcases for ICH initiatives resulting in major efficiency gain, improved data quality and better data analytics capabilities.

The first showcase refers to adverse reaction/event reporting in clinical trials and pharmacovigilance. Considering the large number of participants in a worldwide exchange of safety information, there was a need for an electronic format capable of secure direct database to database transmissions. Such format was developed under the ICH E2B topic dedicated to Individual Case Safety Reports (ICSRs). This work was complemented by a messaging format initially developed by ICH M2 and subsequently technically advanced in collaboration with international standards development organisations such as International Organization for Standardization (ISO) and Health Level Seven (HL7). The ICH E2B ICSR standard is now implemented globally. In 2020 more than 1.8 million case reports were processed in the European Union alone thus facilitating signal detection and safety monitoring of medicines.

Structuring of data also implies the use of a standardised medical terminology. MedDRA, the Medical Dictionary for Regulatory Activities, is a standardised medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products. It is used for registration, documentation and safety monitoring of medical products in the pre-and post-authorisation phase. This terminology is highly specific, hierarchical, multiaxial, multilingual, regularly updated, and strictly maintained. MedDRA is currently available in 14 languages⁽¹⁾ and more translations will follow. Each MedDRA term has an associated numerical code which remains the same irrespective of the language. This multilingual approach allows many users to operate in their native language which promotes accuracy of assigning codes. MedDRA mapping with other terminologies is ongoing; e.g. a bidirectional MedDRA/SNOMED mapping was released recently. ICH launched MedDRA over 20 years ago and is currently being

used by over 6,600 organisations in more than 125 countries. MedDRA is also an important component of ICH M4, the Common Technical Document (CTD). The agreement to assemble all Quality, Safety and Efficacy information in a common format has revolutionised the regulatory review processes, led to harmonised electronic submission and enabled diversity of solutions and implementation of good review practices.

The CTD is organised into five modules. Module 1 is region specific and Modules 2-5 are the harmonised modules for all regions. The ICH M4 Guidelines provide the common format for the preparation of a well-structured CTD for Modules 2-5. Module 2 contains the summary of quality information, the nonclinical overview and clinical overview, as well as the nonclinical written and tabulated summaries, and clinical summary.

The detailed supporting information is in the last three modules. Module 3 contains the structure and format for providing Chemistry, Manufacturing and Controls information. Module 4 delineates the structure and format for nonclinical study reports and data, and Module 5 describes the structure and format of clinical study reports and data in the dossier. The Electronic Common Technical Document (eCTD) allows for the electronic submission of the dossier from applicant to regulator taking into consideration the creation, review, lifecycle dossier and content management, and electronic submission archiving. The eCTD specification is based on the structure and level of detail specified in the ICH M4 CTD Guidelines and was used to define the eCTD technical structure and content to provide a harmonised technical solution for implementing the CTD.

Looking toward the future, ICH M8 is implementing the next version of the eCTD that enhances lifecycle dossier and content management and provides flexibility to address future CTD updates.

The success of the eCTD as a global standard is demonstrated by the number of countries that accept eCTD submissions. For many countries and regions the eCTD is the only electronic submission format accepted and is mandatory in several countries and regions.

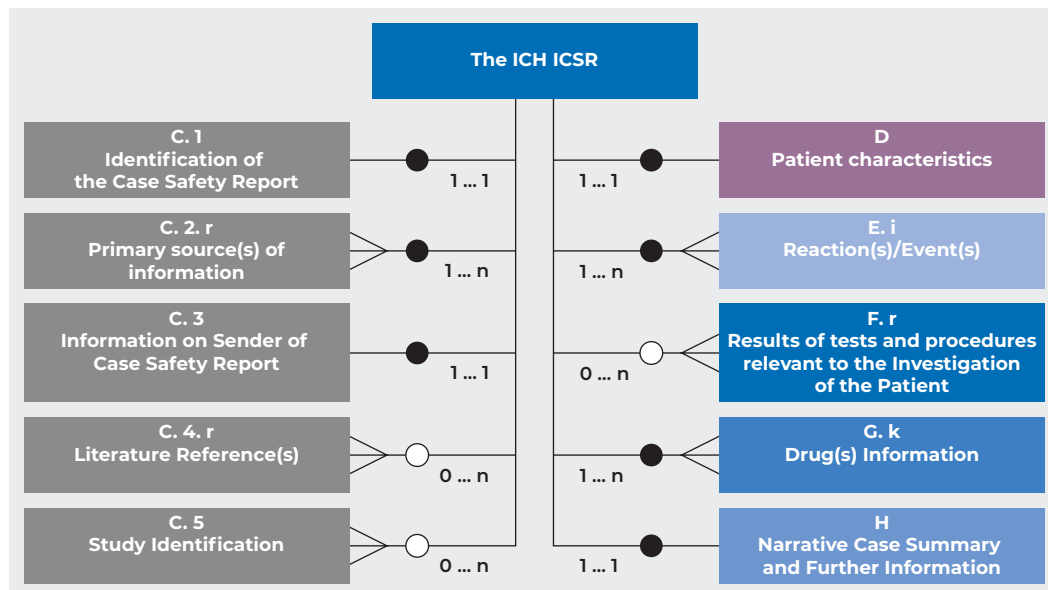


FIGURE 12
The ICH ICSR Structure

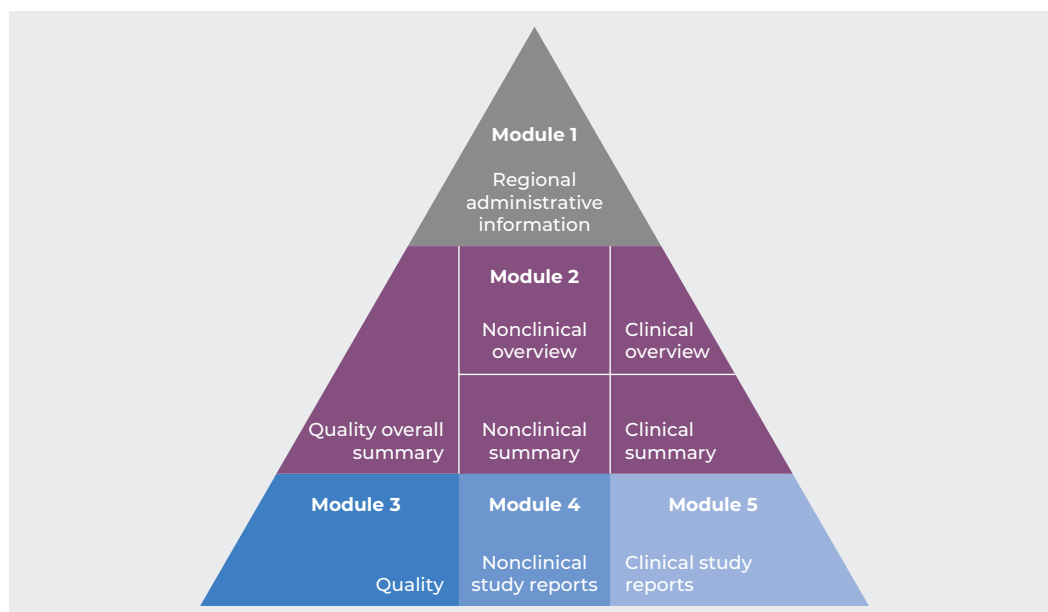
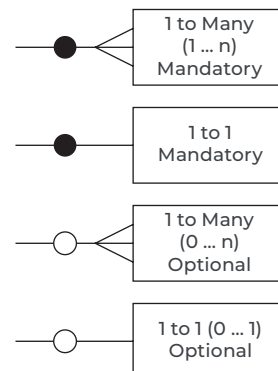


FIGURE 13
The Common Technical Document (CTD)

Not part of the CTD

Module 1

The CTD

Module 2

Module 3

Module 4

Module 5

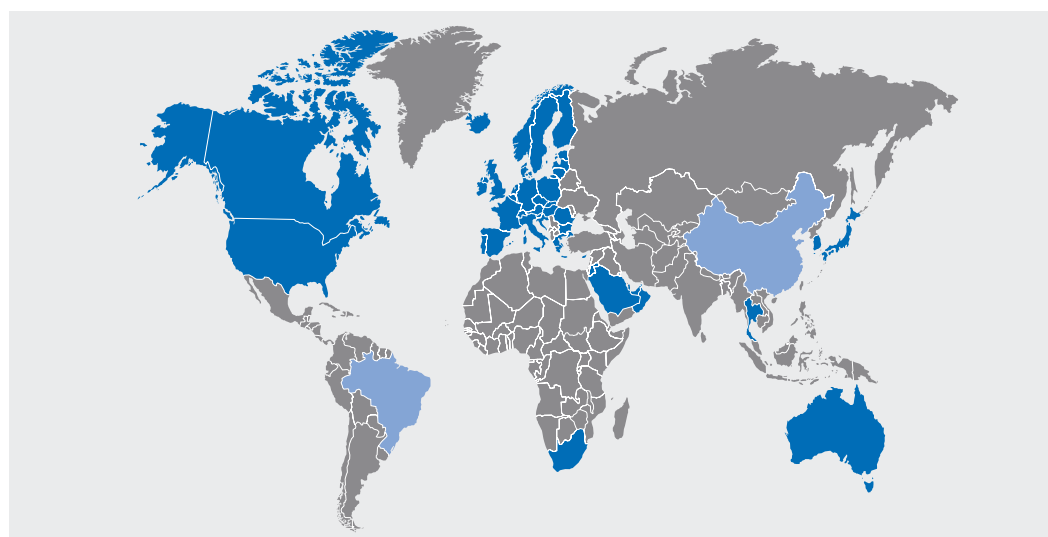


FIGURE 14
ICH eCTD

THEME 4 - HOW IS ICH INTERACTING WITH EXTERNAL STAKEHOLDERS?



Agnès Saint Raymond
• EC, Europe
• Head of Division,
International Affairs,
EMA

ICH AND ICMRA

ICH may seem remote from ICMRA but there are in fact many commonalities to these two organisations. ICMRA is a voluntary coalition of heads of regulatory authorities created, much more recently than ICH, in 2013. The heads of regulatory authorities for human medicines who have joined use the forum to share common challenges and strive to find together common solutions, at a strategic level. One of the benefits of ICMRA is to offer a safe harbour for strategic discussions. When a topic is identified as requiring further development, it is managed as a project to be led by one volunteering authority supported by a couple of others. The deliverables are reflection papers, statements or, for example, agreeing on a process to share innovation findings emerging from horizon scanning if the findings are likely to have a regulatory impact. A deep dive with typical examples then allows to identify legal or regulatory challenges, and the need for new expertise. Such a deep dive was done for a gene-edited product. To avoid the risk of duplication, additionally, ICMRA may identify the most appropriate operational group to follow and transform the strategic reflection into a guideline, process or system interoperability. Recently ICMRA worked on Interoperable systems for Track and Trace, with a clear reference to Data standards developed by ICH. Strategic convergence is one of the goals to reduce unnecessary differences in a globalised pharmaceutical environment. This is very close to the objectives of ICH.

ICH has a clear operational goal, with main outcomes as harmonisation through guidelines and a very successful history of delivering. ICH has another strength in that it involves pharmaceutical industry associations as peers in the discussion. ICMRA includes regulators only, with WHO as observer. This is intentional but requires dissemination of its outcomes. There is however clear complementarity in the scope of activities. ICMRA does identify, at strategic level, the areas where harmonisation is necessary and then hand over to ICH, or IPRP, for consideration by these entities to prioritise the topic and ensure that it is integrated in the body of existing guidance.

ICMRA has identified areas such as supply chain and completed some strategic

reflections on Good Manufacturing Practice (GMP) which were then handed to ICH and PIC/S. It is currently engaging in Pharmaceutical Quality Knowledge Management Systems at strategic level with a similar proposal at ICH which should lead to guidelines' revision or creation in Quality and GMP inspections. Another area covers the use of Real World Evidence (RWE) for regulatory purpose. While there are many parallel initiatives on RWE there is no coordination and obvious duplication. Bringing a topic to ICH requires a certain level of maturity so it can be transformed into a new or integrated into an existing guideline. ICMRA does not have the wide representation of ICH but its membership is increasing. Of note, neither ICH nor ICMRA involves patients as members and this requires reflection especially when it comes to guidance. ICMRA informality contrasts with the well-structured ICH, its processes, membership and Secretariat. The lack of formality makes ICMRA agile and responsive. For example, ICMRA reacted immediately on COVID-19-related issues and was able to ensure two main benefits: active dissemination of information towards regulatory authorities which do not normally have this level of access, and agreeing and drafting in real time some regulatory requirements for pharmaceutical companies on trials, therapeutics and vaccine efficacy and safety in COVID-19.

After 30 years, ICH has well established processes and expert groups, which ensure thorough joint development by experts from industry and regulatory authorities, appropriate consultation and review of any guideline. The price to pay for such processes is long timelines that are not compatible with Public Health Emergencies. Should ICH work faster? Probably, but we can be certain that it will thoroughly analyse the lessons learned from COVID-19, including those stemming from ICMRA, integrate them into its guidance, particularly the exceptional regulatory agilities or simplifications that should become routine. This collaboration between ICMRA and ICH will save time and resources, while continuing protecting to a high degree the safety and efficacy of medicines, therefore ultimately protecting the patients and the population receiving those medicines.



Samvel Azatyan
• WHO Representative
• Team Lead, Regulatory
Convergence and
Networks, WHO

ROLE OF ICH IN THE WORLD

Specific plans for action to establish ICH began to materialise in 1989 at the 5th International Conference of Drug Regulatory Authorities (ICDRA) organised by WHO in Paris, France, marking the establishment of the first ever global regulatory harmonisation initiative aimed at streamlining the regulation of pharmaceutical products in different regions. For more than 30 years ICH has been instrumental in advancing the development of globally acceptable regulatory standards agreed by international consensus.

Harmonisation of regulatory requirements in the context of ICH has offered tangible benefits to all involved parties, including national (and regional) governments, manufacturers, national regulatory authorities in ICH regions and ultimately the patients and consumers. ICH has been critically important in better management of healthcare resources, thus leading to improved public health outcomes. It has also led to a greater transparency of regulatory processes, reduced regulatory burden, saving of resources (including human and financial), shorter timelines for approval of critically important products, as well as greater incentive to prioritise dossier submissions. Patients in ICH regions have also benefited thanks to quicker access to more affordable medical products of assured quality, safety and efficacy, especially for priority diseases. These developments were consistent with the Global Public Health agenda formulated by the WHO which has a status of a Standing Observer to ICH and has actively participated and contributed in ICH activities, both at the level of management and the technical working groups.

The work of ICH has been stimulating in terms of development and sophistication of regulatory standards globally, including in non-ICH regions and countries. ICH through its GCG and RHIs has satisfied the growing interest in ICH products beyond ICH regions and countries, which offered

new opportunities to ICH itself through establishment of a dialogue, collaboration and opportunity to better understand the needs of other regions. The RHIs participating in ICH have also got the opportunity to better understand ICH Guidelines and processes.

ICH has been very actively offering training opportunities to both ICH and non-ICH regions and countries in implementation of ICH Guidelines. This process has substantially contributed in regulatory capacity building globally and regionally.

ICH has substantially contributed to the development of a “regulatory culture” – initially in the ICH regions, but also globally. Following the ICH reform, it is now open practically to all interested countries, to observe and/or participate in the work of ICH.

Although not formally part of ICH, the “Regulators Forum”, which had been set up in 2008 as a regulators-only forum in the margins of ICH Meetings, and had emerged into the International Pharmaceutical Regulators Forum (IPRF) in 2013, has become an important forum for its members and observers to exchange information on issues of mutual interest and enable regulatory cooperation, by facilitating the implementation of ICH and other internationally harmonised technical standards and guidelines for pharmaceuticals for human use, as well as to promote collaboration and regulatory convergence, and contribute to the coordination of a range of international efforts related to regulation of medicinal products for human use. It now is known as the International Pharmaceutical Regulators Programme – following the consolidation with the International Generic Drug Regulators Programme (IGDRP) in 2017. Till today, IPRP meets in conjunction with ICH, demonstrating the close ties between the two initiatives.

THEME 5 - FUTURE DIRECTIONS

Wassim Nasabeh

- BIO Representative
- Global Head, Regulatory Policy & International Operations, Roche

Milton Bonelli

- EC, Europe Representative and Technical Coordinator
- Scientific Advice Officer, EMA



Richard Moscicki

- Executive Vice President, Science and Regulatory Advocacy and Chief Medical Officer, PhRMA

ICH 2030... AND BEYOND: A PRAGMATIC VISION

In contemplating the future of ICH, it is important to reflect first on the core elements and values that made the organisation what it is today. In the first three decades since its inception, ICH has developed over 60 guidelines, led training initiatives to support implementation, and established itself as the premier international organisation enabling global regulatory harmonisation. This was done through the development of harmonised science-based regulatory standards, which guide clinical development, safety assessment, control, manufacture and supply of quality pharmaceuticals. These guidelines quickly became the gold standard in defining proper risk-benefit analysis, streamlining the drug development and registration processes, and ensuring that appropriate efficacy, safety and quality standards are maintained and enhanced in line with advancing scientific developments. Initially, ICH focused largely within its three founding regions of the United States, European Union and Japan. However, major reforms were enacted in 2015 enabling the organisation to adapt to the global nature of drug development, thereby expanding its membership and influence across all continents and establishing ICH Guidelines as the basis for global regulatory convergence.

So, what is next for ICH? And what does it need to do to thrive in the next decade while promoting its mission of increasing patients' access to medicines? Firstly, ICH Guidelines should enable more streamlined drug development of both innovative and generic/biosimilar medicines with the goal of near simultaneous development and review in different regions. ICH will also need to evolve to keep pace with the rapidly evolving technological, digital and scientific transformations across the healthcare continuum. Additionally, there will be an increasingly critical need to ensure agility and efficiency in the ICH Guideline development process in view of its expanding membership and its impact on timely decision-making. Finally, in addition to guideline development, ICH should consider the broader regulatory

ecosystem – such as capacity building and implementation – to advance its mission to support increased efficiency in drug development and patient access to medicines.

As ICH launches into its next decade, the Association should consider the following enablers as it advances its future strategy:

- Driving efficiency in the overall ICH ways of working to streamline guideline development timelines and associated processes thereby allowing for expanded capacity within the organisation
- Working toward greater regulatory alignment of technical and scientific requirements and a harmonised approach to the implementation of ICH Guidelines to facilitate more efficient drug development and simultaneous review
- Taking a proactive approach to engage in the evolving scientific development of new computational biology and therapeutic modalities, and continued innovation in toxicology, pre-clinical and clinical trial methods so that regulatory harmonisation becomes an enabler for leveraging scientific advances
- Continued maturation of advanced analytics to innovate and assure scientific rigor across the pre-clinical, clinical and manufacturing pillars
- Embracing the digital revolution along medicines lifecycle to enable real-time structured data exchange, facilitating global efficiencies in application review procedures, and ultimately electronic, dynamic labelling aimed at patients
- Promote methods addressing the needs of specific populations such as pregnant/lactating women, children/neonates and the elderly and enhance meaningful representation of diverse ethnicities as participants in clinical trials to help provide information about drug response and measures of safety and efficacy in such populations

- Building strategic integrated alliances and work plans with related international organisations (e.g. ICMRA, WHO, IPRP, PIC/S), driving seamless integration between guideline development and harmonised implementation and enabling longer term alignment of regulatory practices and procedures

This is a tall order with goals not easy to achieve, but ICH is well practiced in charting an innovative journey in the service of public health. Doing this will ensure that ICH will continue to excel in the service of patients and populations worldwide.

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ICH Secretariat
Route de Pré-Bois, 20
P.O Box 1894
1215 Geneva - Switzerland

admin@ich.org
www.ich.org