Pharmaceuticals Policy and Law 18 (2016) 79–89
DOI 10.3233/PPL-160434
IOS Press

The International Council for Harmonisation: Positioning for the future with its recent reform and over 25 years of harmonisation work

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The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, also known as "ICH", is a key international harmonisation initiative founded by the drug regulatory authorities and industry associations from the European Union, Japan and the United States of America. The main objective of ICH is to promote public health globally through the development and implementation of harmonised guidelines and standards. With its recent reform, ICH became an Association under Swiss law, and set the stage to broaden its membership to regulatory authorities and international pharmaceutical industry associations beyond the three founding regions. Building on greater than 25 years of harmonisation work, ICH is now well-positioned to grow into a truly global venue for the development of guidelines and standards to facilitate the registration of human medicines across the world.

Keywords: Pharmaceutical, regulation, harmonisation, guidelines, standards

1. Introduction

Pharmaceutical drugs are an essential component of modern human medicine, and are developed for a variety of purposes ranging from diagnosis, prevention, treatment or the management of disease. Pharmaceuticals are developed to meet stringent regulations set by regulatory authorities in different countries, primarily to ensure that the public has access to medicines that are safe, effective and of high quality.

Over the past two decades, the pharmaceutical industry has become increasingly international, with research and development (R&D) shifting to emerging markets outside of Europe, Japan and the United States (U.S.), in search of better economies of scale [1,2]. The pharmaceutical industry aims to market its products as widely as possible, to provide broad access to medicines while optimizing the returns on

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investment. One of the advantages of globalization is capacity-building in emerging markets and greater access to high quality, safe, and effective medicines by different people across the globe. Greater returns on investment from globalization should lead to re-investment in research and innovation to continue work towards important future discoveries in human medicine.

Guidelines and standards are developed to help interpret the regulatory requirements and assist the pharmaceutical industry in meeting those requirements. Historically, different regulatory authorities have developed their own technical guidelines and standards, often resulting in divergent requirements across regions, which impact on the costs of R&D and delay access to new medicines. More recently, efforts by regulatory authorities and industry associations have emerged to work collaboratively to increase harmonisation of requirements and reduce duplication of efforts by industry when aiming to market their products in different countries. ICH is the main international initiative dedicated to developing harmonised guidelines and standards to facilitate the registration of human pharmaceuticals globally.

2. The origins of the International Council for Harmonisation (ICH)

The harmonisation of regulatory requirements was pioneered by the European Community in the 1980s, as it moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time, there were bilateral discussions between Europe, Japan and the U.S. on possibilities for harmonisation. It was, however, at the World Health Organisation (WHO) International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived.

The ICH was launched in April 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels. ICH emerged as a tri-partite effort involving the European Community (now the European Union), the U.S. Food and Drug Administration (U.S. FDA), and the Japanese regulatory authorities (Ministry of Health, Labour and Welfare (MHLW), and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA)) along with the industry associations representing these three regions, namely, EFPIA, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Japan Pharmaceutical Manufacturers Association (JPMA). At the first ICH Steering Committee meeting, it was decided that the topics selected for harmonisation would be divided into Safety, Quality, and Efficacy, to reflect the three criteria that form the basis for the regulatory authorisation of new medicinal products. ICH has since held bi-annual face-to-face meetings of its Steering Committee and various working groups working

on guidelines and standards, resulting in the publication of a myriad of harmonised guidelines for implementation across the participating regions and beyond.

Although ICH began as a tripartite effort, there have been several observers since its inception, including Health Canada, the WHO, and Swissmedic (previously representing the European Free Trade Association (EFTA)). Over the years, additional regulatory authorities and regional harmonisation initiatives have joined ICH as observers, making it a truly global venue for harmonisation work.

3. The objectives of ICH

The primary objective of ICH is to promote public health. The aim is to contribute to a more timely introduction of new medicines and continued availability of approved medicines to patients, by minimising the use of animal testing and preventing unnecessary duplication of clinical trials in humans, without compromising safety and effectiveness, as well as contributing to the development, registration and manufacturing of safe, effective and high quality medicines in an efficient and cost-effective manner.

ICH is a non-profit organization and does not pursue any commercial purposes. The work of ICH is accomplished through formal procedures and working groups involving the participation of experts nominated by the participating regulatory authorities and industry associations. The experts represent different perspectives, which combined, bring a wealth of knowledge and experience for the efficient development of guidelines and standards.

The work at ICH is complemented by other international regulatory harmonisation and collaboration initiatives such as the International Pharmaceutical Regulators Forum (IPRF), the International Generic Drug Regulators Programme (IGDRP), and the International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA in particular provides executive-level strategic leadership and direction for a range of areas that are common to many regulatory authorities' missions. These initiatives promote collaboration among regulatory authorities and provide an additional context for discussion of scientific issues that may either not be ready for work at ICH, or may be out of scope for ICH but nonetheless complementary for international harmonisation.

4. The recent reform of ICH

ICH was, until recently, known as the International *Conference* on Harmonisation. However, as of October 23, 2015, it became an Association under Swiss Law upon the finalization of the Articles of Association [3]. With this change, ICH became the International *Council* on Harmonisation, changed its governance structure (see Fig. 1) and funding model, and opened its doors to new members to widen the

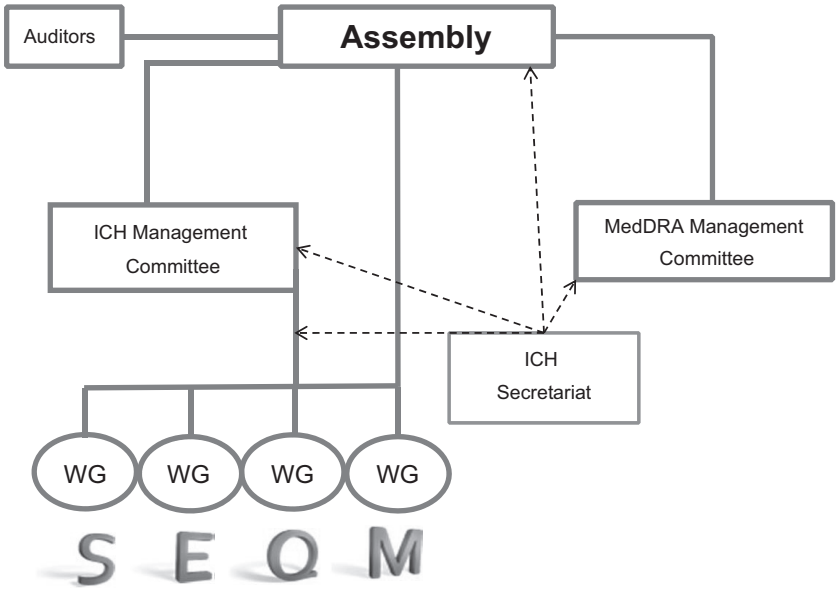

Fig. 1. Governance structure of the new ICH. WG = working group; S = Safety topic; E = Efficacy topic; Q = Quality topic; M = Multidisciplinary topic.

global reach of ICH. An important objective of the reform was also to increase the transparency of ICH activities.

Building on the 25 years of experience of the ICH Steering Committee, the new governance structure includes an Assembly and a Management Committee. The Assembly is the overarching body of the Association composed of all members (Table 1) and observers (Table 2) that takes decisions regarding governance aspects such as the Articles of Association, Rules of Procedure, admission of new members, adoption of new ICH topics, adoption of ICH guidelines, and setting membership fees. The U.S. FDA, European Commission and the Japanese MHLW and PMDA are the regulatory founding members of ICH, whereas the industry founding members are EFPIA, JPMA, and PhRMA. With the reform, Health Canada and Swissmedic were accepted as standing regulatory members of the ICH Assembly, in recognition of their contribution to ICH over the years. Furthermore, at the Assembly meeting held in Lisbon, Portugal, in June of 2016, two new industry members were accepted, specifically, the International Generic and Biosimilar Medicines Association (IGBA) and the World Self-Medication Industry (WSMI).

The Assembly uses a consensus-based approach for all decisions; however, if consensus is not reached on an issue, the decision is taken by a vote of the members, with each member having one vote.

The Management Committee is the body that oversees the operational aspects on behalf of all the members of the Association and has responsibility primarily for ad-

Table 1
Current members of the ICH assembly and role in the management committee*

Name	Membership status	Management committee role
European Commission (EC)	Founding Regulatory Member	Permanent Member
Ministry of Health, Labour and Welfare (MHLW) of Japan, also represented by the Pharmaceuticals and Medical Devices Agency (PMDA)	Founding Regulatory Member	Permanent Member
U.S. Food and Drug Administration (U.S. FDA)	Founding Regulatory Member	Permanent Member
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Founding Industry Member	Permanent Member
Japan Pharmaceutical Manufacturers Association (JPMA)	Founding Industry Member	Permanent Member
Pharmaceutical Research and Manufacturers of America (PhRMA)	Founding Industry Member	Permanent Member
Swissmedic	Standing Regulatory Member	Permanent Member
Health Canada	Standing Regulatory Member	Permanent Member
International Generics and Biosimilar Medicines Association (IGBA)	Industry Member *(as of June 2016)*	Not currently participating
World Self-Medication Industry (WSMI)	Industry Member *(as of June 2016)*	Not currently participating

*The new ICH Assembly and Management Committee were founded on October 23, 2015. Founding and Standing Regulatory Members, as well as Founding Industry Members, have been Permanent Members of the Management Committee as of the inauguration date of October 23, 2015. Each Permanent Member has appointed two representatives to the Management Committee. New members may be eligible in the future to nominate two representatives to the Management Committee, which may be appointed by election at the Assembly.

ministrative and financial matters. The reform introduced a funding model that relies less on industry-sourced funding. Under the previous ICH structure, the operations of ICH were supported by a Secretariat funded by ICH industry members and housed within the IFPMA. The funding of the venue for the bi-annual face-to-face meetings was primarily supported by the industry association of the hosting region. However, under the new ICH structure, the funding of ICH activities, including bi-annual face-to-face meetings of the ICH Assembly and the activities of the ICH Secretariat, are now provided by membership fees paid by its members.

The Management Committee is currently composed of two permanent representatives from each of the three founding regulatory members, the three founding industry members and the two standing regulatory members (Table 1), for a total of sixteen permanent representatives. IGBA and WSMI recently joined ICH, and may be eligible to nominate for election by the Assembly up to two representatives in the future, provided the party will meet the conditions defined by the Articles of Association (such as regular participation in all ICH meetings during the previous four years). In the future, it is expected that the Management Committee will have an

Table 2
Current observers of ICH

Southern African Development Community (SADC)
Gulf Cooperation Council (GCC)
Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
Pan American Network for Drug Regulatory Harmonization (PANDRH)
Asia-Pacific Economic Cooperation (APEC)
Association of Southeast Asian Nations (ASEAN)
Biotechnology Innovation Organisation (BIO)
Central Drugs Standard Control Organization (CDSCO, India)
Council for International Organizations of Medical Sciences (CIOMS)
Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
East African Community (EAC)
European Directorate for the Quality of Medicines & HealthCare (EDQM)
Health Sciences Authority (HSA, Singapore)
International Pharmaceutical Excipient Council (IPEC)
Ministry of Food and Drug Safety (MFDS, South Korea)
Roszdravnadzor (Russia)
Food and Drug Administration (TFDA, Chinese Taipei)
Therapeutic Goods Administration (TGA, Australia)
United States Pharmacopeia (USP)

additional up to twelve elected representatives who will be elected from amongst the new regulatory and industry members expected to join ICH.

4.1. Membership requirements for new members

The Articles of Association set out the requirements for entities interested in applying for membership at ICH. A pharmaceutical regulatory authority may be eligible to be a member if it has attended at least three ICH meetings during the previous two consecutive years, and has appointed experts in at least two working groups. The regulatory authority is also expected to have implemented the Q1: Stability Testing, Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients and E6: Good Clinical Practice guidelines in its jurisdiction.

New industry members are required to be a global pharmaceutical industry association representing a global constituency (i.e., with members from several countries in at least three continents). The industry association or its members must be regulated or affected by all or some ICH guidelines, have been an observer of the Association or interested party as defined prior to the establishment of the Association, and have appointed experts in at least two working groups.

4.2. Rights and duties of regulatory and industry members

Regulatory members have the right to attend Assembly meetings and vote in the Assembly. While the founding regulatory members have a duty to appoint members in every working group, the standing and other regulatory members may appoint experts to working groups of their choosing. Regulatory members have exclusive

voting rights related to selection of new topics, and adoption, amendment or withdrawal of ICH guidelines. New regulatory members may wish to participate in the Management Committee, in which case, the regulatory member may propose two representatives for election by the Assembly, provided the party meets the conditions defined by the Articles of Association. All regulatory members are expected to implement ICH guidelines.

Industry members have the right to attend Assembly meetings and vote in the Assembly with the exception of decisions on selection of topics for ICH guidelines, and adoption, amendment or withdrawal of ICH guidelines. New industry members may propose two representatives for the Management Committee, for election by the Assembly, provided the party meets the conditions defined by the Articles of Association. Industry members may appoint experts to those working groups that are developing guidelines applicable to the industry member or its affiliates.

Industry members should actively support and encourage the compliance with the ICH guidelines applicable to the industry member or its affiliates. While the founding industry members are likely to appoint experts in every working group, the new industry members are expected to appoint experts in at least one working group that is developing an ICH guideline relevant to the industry member.

4.3. Observers of ICH

In recognition of the historical contribution of the WHO and the IFPMA, these organizations have been accepted as standing observers under the new ICH, in accordance with the Articles of Association. They may attend the Assembly and Management Committee meetings without any voting rights. They may also appoint experts to working groups.

Other entities have shown an interest in the work of ICH over the years, given the impact on international harmonisation. Under the previous ICH structure, the Global Cooperation Group was created in 1999 as a subcommittee of the ICH Steering Committee in order to make information available to any non-ICH party such as interested regulatory authorities, regional harmonisation initiatives, or pharmaceutical companies that requested the information. The non-ICH parties observed the open sessions of the old ICH Steering Committee, and many of these parties have now become official observers under the new ICH (Table 2), in accordance with the Articles of Association. The Articles of Association further define categories of observers, specifically, regulatory authorities, regional harmonisation initiatives, international pharmaceutical industry organizations and other international organizations with an interest in pharmaceuticals. Observers of the new ICH should have a contribution and benefit to ICH, and may attend the Assembly meetings without any voting rights.

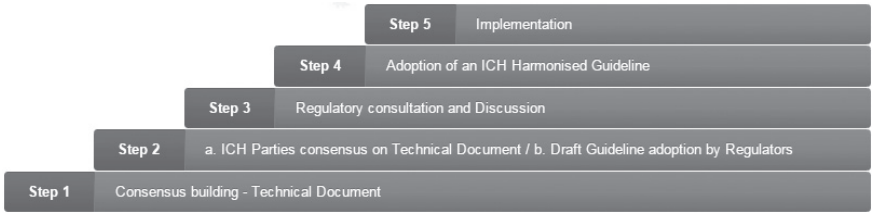

Fig. 2. Steps in the ICH guideline development process.

5. ICH guideline development process

Once a new topic is selected for harmonisation, and a concept paper and business plan are approved by the Assembly, an expert working group is formed to begin drafting the guideline. Each member of ICH appoints up to two experts to the working group. A rapporteur and a regulatory chair are chosen to help draft the technical document and guide the work in accordance with the concept paper and business plan. The expert working group works remotely via periodic teleconferences and meets face-to-face during the bi-annual ICH meetings, when necessary. The guideline-development process moves through a step-wise process as shown by Fig. 2.

The expert working group develops and maintains a workplan, including timelines for completion of each step of the work. Once Step 2b is reached (draft guideline is agreeable to the regulatory members of ICH), each regulatory member proceeds with Step 3 and carries out consultations in their region. The consultation period may range from 30 days up to 6 months, depending on the topic and regional consultation requirements. The timelines for reaching Step 5 (implementation) vary depending on the guideline and complexity of the topic, whether the output is a revised guideline versus a brand new guideline, or whether additional regulatory changes are required prior to implementation in a country or region.

Following the development of a guideline, an implementation working group may be organised to develop tools to facilitate the implementation of the guideline. Tools can include a Questions and Answers document, a slide deck, or other document as deemed necessary.

6. ICH achievements

ICH has delivered benefits to regulators and industry alike. Although industry benefits from harmonised global requirements that reduce duplication of efforts, regulatory authorities also benefit significantly from the exchange of knowledge, worksharing, and the efficiencies gained with the ICH process. The guideline development process at ICH is based on science, driven by consensus, and is effectively managed to provide deliverables under strict timelines. In general, the ICH process requires

Table 3
Summary of harmonised regulatory guidelines*

Safety guidelines	
– S1A – S1C: Carcinogenicity studies	– S6: Biotechnology products
– S2: Genotoxicity studies	– S7A – S7B: Pharmacology studies
– S3A – S3B: Toxicokinetics and Pharmacokinetics	– S8: Immunotoxicology studies
– S4: Toxicity testing	– S9: Nonclinical evaluation for anticancer pharmaceuticals
– S5: Reproductive toxicology	– S10: Photosafety evaluation
Efficacy Guidelines	
– E1: Clinical safety for drugs used in long-term treatment	– E9: Statistical principles for clinical trials
– E2A – E2F: Pharmacovigilance	– E10: Choice of control group in clinical trials
– E3: Clinical study reports	– E11: Clinical trials in pediatric population
– E4: Dose-response studies	– E12: Clinical evaluation by therapeutic category
– E5: Ethnic factors	– E14: Clinical evaluation of QT
– E6: Good clinical practice	– E15: Definitions in pharmacogenetics/ pharmacogenomics
– E7: Clinical trials in geriatric population	
– E8: General considerations for clinical trials	– E16: Qualification of genomic biomarkers
Quality Guidelines	
– Q1A – Q1F: Stability	– Q7: Good manufacturing practice for active pharmaceutical ingredients
– Q2: Analytical validation	
– Q3A – Q3D: Impurities	– Q8: Pharmaceutical development
– Q4 – Q4B: Pharmacopoeias	– Q9: Quality risk management
– Q5A – Q5E: Quality of biotechnological products	– Q10: Pharmaceutical quality system
– Q6A – Q6B: Specifications	– Q11: Development and manufacture of drug substances
Multidisciplinary Guidelines	
– M1: MedDRA terminology	– M5: Data elements and standards for drug dictionaries
– M2: Electronic standards	
– M3: Nonclinical safety studies	– M6: Genotoxic impurities
– M4: Common technical document	– M7: Electronic common technical document

*To download any of the ICH guidelines, visit the ICH website at www.ich.org. Information on accessing MedDRA is available on the ICH and MedDRA websites at www.ich.org and www.meddra.org.

a significantly lower level of resources from any one single regulatory authority to develop guidelines and standards compared to the resources required for regulatory authorities to carry out this work independently. Ultimately, however, harmonised requirements facilitate the development and registration of human medicines across the globe, which is intended to benefit patients the most.

Since 1990, over 60 guidelines and standards have been developed in a variety of topics and implemented across the regions participating in ICH. Table 3 lists the topics for which guidelines have been developed to-date. In particular, the Medical Dictionary for Regulatory Activities (MedDRA), the common technical document (CTD), and the electronic common technical document (eCTD) are important achievements.

MedDRA is a highly specific standardized dictionary of medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medicinal products both before and after a product has been authorized for sale. MedDRA

is currently available in 11 languages, and is open to anyone who would like to use it, with free access to all regulators, as well as to doctors and academics involved in non-commercial activities. A MedDRA Maintenance and Support Services Organisation (MSSO) serves as the repository, maintainer, developer and distributor of MedDRA. The activities of the MSSO are overseen by the MedDRA Management Committee. The costs of MedDRA are covered by subscription fees paid by pharmaceutical companies, with fees determined annually on a sliding scale linked to the annual turnover of companies.

The CTD is a standardized format for pharmaceutical companies to present the quality, safety, and efficacy information in the dossier of a new drug filed for review by the regulatory authorities. It was initially developed to facilitate paper filing, but it has evolved into an electronic format. The CTD/eCTD has revolutionized regulatory review processes by harmonising the format of drug submissions and enabling the implementation of good review practices. For industry, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

Several guidelines are currently under revision or development across the four streams of work products, specifically the efficacy, safety, quality, and multidisciplinary streams. Some of the new guidelines under development address topics such as pharmaceutical product lifecycle management (Q12), nonclinical safety testing of pediatric medicines (S11), and multi-regional clinical trials (E17). Revisions are also being undertaken for some guidelines that have not been updated for many years such as the S5: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility, E6: Good Clinical Practice, E9: Statistical Principles for Clinical Trials and E11: Clinical Investigation of Medicinal Products in the Pediatric Population.

7. Stakeholder engagement

An important aspect of the guideline development process at ICH is consultation with the affected stakeholders, spanning the regulatory, academic, and industry realms. ICH members and observers carry out consultation and engagement activities in their regions through presentations at regional conferences (e.g., Develop Innovate Advance (DIA) meetings)), or through consultations organized specifically for obtaining stakeholder input on specific ICH guidelines at Step 3. Consultations are crucial for gauging the feasibility of draft guidelines, seeking input from stakeholders beyond those that participate at ICH, and ensuring the final product will truly advance harmonisation efforts. By welcoming new members and observers, the ICH Association will continue to expand its engagement with a variety of stakeholders.

8. ICH into the future

With its recent reform and 25 years of experience, ICH is indeed poised to grow into a truly global entity that facilitates the harmonisation of technical require-

ments for new and existing medicines. Transparency will remain at its core, with timely communication of information and engagement of stakeholders throughout the guideline and standard development process. ICH is also positioned to support training activities, to facilitate implementation and application of guidelines across multiple regions. ICH is developing a training strategy to promote the common understanding and interpretation of ICH guidelines. This should not only facilitate harmonisation, but also support worksharing among regions into the future, further increasing the efficiencies gained with harmonisation. The ICH website (http://www.ich.org/home.html) will be updated periodically to reflect the governance structure and activities of the new Association, including information on ongoing guideline development, meeting reports, the application process for Observership and Membership, and many other updates expected in the future.

Acknowledgements

The authors would like to thank the ICH Secretariat and representatives of the ICH Management Committee for reviewing the article, and providing many valuable comments.

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[3] Visit the ICH website at www.ICH.org/html for more information and links to supporting documents such as the Articles of Association and Rules of Procedure of the Assembly and of the ICH Management Committee.