

# International Conference on Harmonization: Recent Reforms as a Driver of Global Regulatory Harmonization and Innovation in Medical Products

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Eight years ago, this journal published “The Value and Benefits of the International Conference on Harmonization to Drug Regulatory Authorities: Advancing Harmonization for Better Public Health”<sup>1</sup> to mark the 20th anniversary of the International Council on Harmonization (ICH). Much has happened since following the reform of ICH, which culminated in 2015 with the establishment of ICH as an international nonprofit association. This entailed a transformation of the collaboration between a limited number of parties in an informal setting into a formal international organization with its own legal entity. The reform was a time-consuming exercise preceded by in-depth and complex discussions, where different options had to be considered and different interests balanced while ICH continued its normal harmonization work within the existing framework. However, the mission of ICH remained unchanged: advancing harmonization for better health. This article describes what triggered the reform and the work that paved the way for reaching the end result.

## INTERNATIONAL COUNCIL ON HARMONIZATION IN ITS FIRST 20 YEARS

The International Council on Harmonization (ICH) was launched in 1990 to bring together the pharmaceutical regulatory authorities of Europe (European Union), Japan, and the United States along with experts from the research-based pharmaceutical industry in these three regions to agree on common scientific and technical standards toward product authorization. The European Union (European Communities in those days) already had some experience in harmonizing regulatory requirements as part of its work to prepare for the creation of the single market. Around the same time, there were some discussions between Europe, Japan, and the United States on the possibilities of harmonization. Finally, the European Commission took the initiative to establish ICH together with the Ministry of Health, Labour and Welfare of Japan (MHLW), the US Food and Drug Administration (FDA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Pharmaceutical Research and Manufacturers of America (PhRMA), and Japan Pharmaceutical Manufacturers Association (JPMA). The European Free Trade Association (EFTA), represented by Swissmedic at the time, and Health Canada were observers in ICH, and the World Health Organization (WHO) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA),

representing the research-based pharmaceutical industry, became standing observers.

After its establishment in 1990, ICH operated on a relatively informal basis with a Steering Committee composed of the three founding regulatory authorities and founding industry associations serving as its governing body and taking decisions on a consensus basis. The actual work of developing ICH guidelines took place in Working Groups composed of experts from the ICH members and observers. After initially meeting only once a year as a large conference (hence, the initial name of ICH, the International Conference for Harmonization), the ICH meetings transitioned to be held biannually with the Steering Committee meeting at the same time and location as the Working Groups. The meeting venues would rotate between the regions of the founding members, Europe, Japan, and the United States. In addition, all ICH activities were being supported by a permanent ICH secretariat run by IFPMA in Geneva, Switzerland.

In 1999, the Global Cooperation Group (GCG) was set up to engage with other regulatory authorities, and later with regional harmonization initiatives, which had shown an interest in ICH activities. The GCG met on the margins of the ICH biannual meetings and served to promote better understanding of ICH guidelines with a primary focus on training.

The mission of ICH established in 1990 was, and remains, to promote public health. This is accomplished through greater

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harmonization in the development, interpretation, and application of technical guidelines and requirements for pharmaceutical product registration. The harmonization of these regulatory standards is considered to offer direct benefit to both regulatory authorities and to regulated industry. ICH guidelines are often credited with the prevention of duplication of clinical trials in humans and more consistent protection of human subjects in clinical trials. Some ICH guidelines work to minimize the use of animal studies without compromising the safety and effectiveness of medicines, and others have contributed to streamlining the regulatory assessment process for new applications for the authorization of medicines and helping reduce the development times and resources needed for global development.

The ICH has, over the years, developed >60 guidelines setting global standards for the quality, efficacy, and safety of medicinal products, as well as multidisciplinary standards to address electronic document submissions to help modernize the development of medicinal products and the regulatory review. One of the most notable contributions is provided by the ICH guideline on Good Clinical Practice (GCP) to ensure human subject protection and clinical data quality and integrity. Developed in the mid-1990s, this guideline has played a key role in enabling continued growth in the use of multiregional clinical trials of investigational new medicinal products, including guidance related to site training, responsibilities, and expectations of investigators, sponsors, and Institutional Review Boards, supporting earlier submission of new applications to regulators in multiple regions.

Another high-impact guideline specifies the structure and contents of a Common Technical Document<sup>2</sup> and the electronic version<sup>3</sup> for submission of marketing applications to regulatory authorities. The development and adoption of the harmonized Common Technical Document has revolutionized application submissions, enabling sponsors to replace multiple different formats with a single technical dossier that can be submitted to all regions that have adopted the standard, enabling near-simultaneous submission for new review of medicinal products, potential approval, and earlier access for patients around the world.

The development and maintenance of the Medical Dictionary for Regulatory Activities (MedDRA)<sup>4</sup> offers another example of ICH value. MedDRA is a highly specific standardized dictionary of medical terminology available to all subscribers for use in the registration, documentation, and safety monitoring of medical products before and after a product has been authorized for marketing. Originally developed by the UK's Medicines Agency and transferred to ICH, MedDRA has been translated into 10 languages and continues to increase in importance as a global standard, with >5,000 subscribing organizations worldwide.

The value of ICH guidelines laying down scientific and technical requirements can largely be attributed to the ICH approach to guideline work. ICH works by involving both regulators and industry parties in the detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process. The work to be accomplished was clearly outlined and closely managed by a senior governance body (the ICH Steering Committee), and the work to draft these technical guidelines was conducted by experts with comparable

levels of expertise in a given topic area drawn from both regulatory agencies and the pharmaceutical industry. In addition, following the reforms to be described in this article, the final steps of approval and adoption were clarified to be controlled solely by the regulators, with a corresponding commitment to implement any approved guidelines within their region.

#### **DEVELOPMENTS SINCE 2010: WHY WAS A REFORM OF ICH INITIATED?**

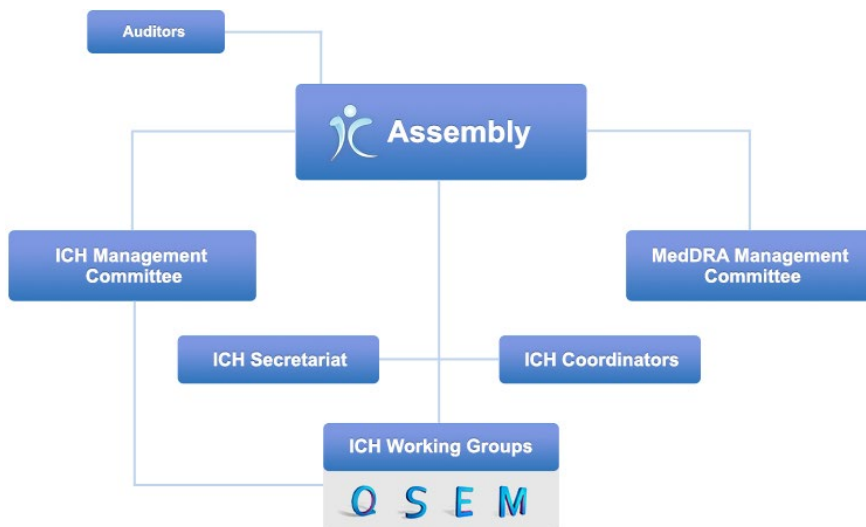
Although the ICH structure and operations had remained essentially unchanged since its creation in 1990, the global environment had significantly evolved, and other non-ICH national and regional economies had grown rapidly and were emerging players in the pharmaceutical sector. In addition, public demands for the assurance of government integrity and transparency had increased in several developed regions, in response to high-profile safety issues, concerns about the growing influence of “big pharma” and other developments. Reflecting these considerations, for example, in 2010, the European Commission conveyed concerns about the current role of industry in this international initiative that had become a de facto developer of international standards for pharmaceuticals for human use.

Although this concern regarding clear lines of control for the regulators in all guideline work was initially met with some reservation in the Steering Committee, it was acknowledged as legitimate by the other ICH regulators. There was also a shared interest among all ICH parties in global outreach by opening up membership in ICH and establishing a more fairly distributed stable approach to funding. In addition, other considerations (e.g., the need for increased transparency appropriate to a modern organization operating in the public sphere) were recognized. After the concept of such a change had been embraced by all involved, the ICH Steering Committee was prompted to engage in a comprehensive reform effort while being mindful of those key factors that had contributed to the success of ICH. The concern was to avoid that the overhaul of ICH would render the organization less effective and significantly slow down the guideline development process with the risk that the ICH guidelines would no longer reflect cutting-edge scientific developments. In addition to the foregoing considerations, the Steering Committee identified several goals for a reformed ICH. These included the following: (i) establishing one major and preferred venue to focus global regulatory harmonization work for pharmaceuticals that would be accessible to all regulatory stakeholders that are committed to align with the highest global standards, (ii) creating a venue that would allow all these stakeholders the opportunity for input to the harmonization work and (iii) maintaining the efficiency and effective management of harmonization operations that had been key to ICH success and effectiveness throughout its past.

What followed were in-depth discussions within the Steering Committee to reach agreement on the way forward, including an organizational design and operating model for ICH that would address these goals and concerns. In the process of designing for change, the Steering Committee also aimed to recognize past longstanding leadership experience and commitments to ICH that would be critical to maintaining the key elements of past success as the organization opened to new members with less experience,



**Figure 1** Steps in the International Council on Harmonization (ICH) process for guideline development. Source: ICH, Formal ICH Procedure.



**Figure 2** The International Council on Harmonization (ICH) Association is composed of five bodies: the Assembly, the Management Committee, the MedDRA Management Committee, the ICH Secretariat, and the Auditors. The overarching body is the Assembly, where decisions are adopted, whereas the Management Committee focuses on administrative and financial matters and the MedDRA Management Committee focuses on MedDRA-related activities. The ICH Secretariat is responsible for the day-to-day management of the Association. While not being bodies of the ICH Association, the ICH Working Groups continue, as they did before the reform, the guideline development work, supported by the ICH Coordinators. Source: ICH, Structure of the ICH Association. MedDRA, Medical Dictionary for Regulatory Activities.

including with ICH guidelines. Thus, early in the reform and redesign process, the Steering Committee membership was amended to include Swissmedic and Health Canada.

To address the concern about a clear delineation of regulatory authorities’ control over guideline development, another early step in the reform process involved changes in ICH procedures to strengthen the role of regulators in the selection of new topics for harmonization and in the adoption process of guidelines, whereby the regulators could decide to proceed in case no consensus with industry could be reached. The so-called step 2 in the guideline development process was divided into two well-distinct parts in which the industry and regulator experts adopt the technical document under step 2a, followed by the adoption of the draft guideline as step 2b, in which only the regulatory experts were involved (Figure 1). In addition, Regulatory Chairs were introduced in the expert Working Groups with a view to complementing the role of the Rapporteurs and ensuring the integrity of the process. Finally, transparency was improved, with more information being made available on the ICH website.

Several major components of the ICH redesign address the other above-cited goals and considerations that drove this reform

effort. These addressed the new approach to structure and governance, creation of a new legal entity, a more transparent and equitable approach to financing, the approach to global outreach, and enhancements to transparency around both ICH operations and work products.

**Approach to structure and governance**

The ICH Steering Committee agreed that for the redesigned ICH to both serve as the one major venue and be inclusive of an expanded set of stakeholders in the pharmaceutical sector, decisions should be taken by a body in which all members and observers would be represented and which would have decision-making powers on all important matters. In addition to the Assembly, which is the main decision-making body of the Association, other bodies were set up, such as the Management Committee and the ICH Secretariat (Figure 2). Challenging discussions took place about the division of roles and responsibilities between the different bodies of the redesigned organization and in particular between the Assembly and the Management Committee. The finally agreed design transferred most of the tasks previously handled by the Steering Committee to the ICH Assembly. This included, for

example, deciding on the adoption of ICH guidelines and other important matters, such as admission of new members. Other more operational tasks of the Steering Committee, such as the oversight of Working Groups and the organization of the ICH meetings, were entrusted to the Management Committee.

In planning the redesign, in-depth discussions also evolved around the different categories of Members and Observers and around the rights and obligations that these would have. It was considered that rights and obligations should be linked and that, therefore, more rights should correspond to more obligations and vice versa. The founding members of ICH were thus entrusted the maximum of rights and obligations in the Association as they committed to making the biggest contribution to the Association and taking the ultimate responsibility for ensuring the continuity of ICH activities. This being said, the rights and obligations of other Members were designed in such a way as to make membership in ICH both attractive and meaningful. Another important principle in line with Swiss law-governed nonprofit organizations was that individual members belonging to the same category should have the same rights and obligations.

Early on, there were reflections about the different roles of regulators and industry. Although developing guidelines is a prerogative of regulators, the success of ICH since its establishment shows that the model, as it was set up in 1990, had produced good results. This success is also attributed to the contribution that industry has made to ICH in providing its expertise in the development of the guidelines and in identifying gaps in harmonization between different regions. Therefore, it was agreed that industry should continue to be actively involved in ICH, and the focus was rather on how to optimize the collaboration while ensuring the independence and integrity of the regulators. As a result, the distinct roles of regulators and industry were clearly defined, and the role of regulators strengthened to enhance the credibility and integrity of ICH and its processes.

The focus on regulators was because they are expected to implement ICH guidelines that contribute to global harmonization. Considerable time was, therefore, devoted to determining the eligibility criteria for regulatory members in terms of requirements for the implementation of ICH guidelines. The criteria for joining ICH as a member should not be set too high with the risk that few regulators would meet them, but they should, on the other hand, not be too low either given that ICH membership is considered to bring with it integrity and recognition. In-depth reflections followed on the membership eligibility criteria for regulatory authorities and, finally, agreement was reached on a fixed number of key ICH guidelines that a regulatory authority would need to have implemented, including some requirements in terms of future implementation, to qualify for membership in ICH. Once having become a member, the regulatory authority would be expected to implement the remaining ICH guidelines. It was also decided that members should have more rights than observers, thus making membership attractive, especially for regulatory authorities.

Decision making would continue to be on a consensus basis, but it was recognized that this may be challenging in a larger setting with more members and, therefore, voting rules were put in place

should consensus not be reached. Every member would have one vote, with some exception for industry members with respect to guideline developments, and certain important decisions would require the support of the founding regulatory members.

### Creation of a legal entity for ICH

Because ICH initially was not a legal entity, IFPMA was acting as a trustee of ICH in some areas and had, as such, signed various contracts on behalf of ICH, notably relating to MedDRA. This was not an optimal arrangement for any of the parties and not in line with the aim of making ICH more independent from the industry. Moreover, the expansion of membership in ICH called for moving away from the previous informal collaboration into a formal structure with clear rules.

It was agreed from the outset that the key focus of the reform was introducing a change in the governance of ICH, which would also entail the creation of a legal entity. In addition to enabling ICH to sign contracts on its own and, thus, dismantle the trusteeship with IFPMA, a formalized structure with well-defined rules would facilitate the running of the activities in an expanded setting with more members. After having explored different options, it was agreed to establish ICH as a nonprofit association under Swiss law. Swiss law provided sufficient flexibility for such associations, and there were several examples of other international organizations, such as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), which were established in Switzerland; moreover, the ICH Secretariat was located there.

Setting up ICH as a legal entity meant that there was a need for Articles of Association<sup>5</sup> outlining the composition and roles of the various bodies of the Association and the rights and obligations of the members and observers. The structure and governance considerations and decisions directly informed the drafting of the Articles. To provide further clarity on ICH operations, the Articles of Association have been complemented by Rules of Procedures.<sup>6</sup>

The legal entity was established on October 23, 2015, as a nonprofit international association under Swiss law. Subsequently, the trusteeship with IFPMA has been terminated and assets previously held by IFPMA, including some contracts that had been signed by IFPMA on behalf of ICH, were transferred to the ICH Association. With the creation of the legal entity, ICH had become a fully independent organization.

### Financing of ICH activities

Before these reforms, the three founding industry members would finance a significant part of ICH activities, notably the ICH secretariat and the organization of the ICH meetings. This financing model was not sustainable in the longer term. Also, costs were expected to increase as ICH opened up its membership to other parties. An alternative funding model had to be found, and it was agreed that the best way forward would be to introduce membership fees to be paid on an annual basis by all members. The establishment of a new legal entity, a nonprofit association, also enabled the regulatory parties to contribute substantially and more equitably to the funding of ICH.

Bearing in mind that the level of rights should correspond to the level of obligations, it was agreed that the fee for founding

members should be higher than for the others member categories. The new ICH members were consulted on different options and, finally, a fee model consisting of three grids was introduced (one for the founding members, another for the standing members, and a third for new members), which was payable for the first time in 2018. There is no one-off fee for joining the ICH Association.

### Approach to global outreach

It was clear from the outset that membership in ICH should primarily be open to a wider community of regulatory authorities and international pharmaceutical industry organizations that fulfilled the eligibility criteria. The generic pharmaceutical industry, in particular, expressed a strong interest in joining ICH as a member. To qualify for membership under the current eligibility criteria, a pharmaceutical industry organization must demonstrate that it is not only regulated or affected by ICH guidelines but also that it is truly global. The way to membership for any interested party would normally be through observership. However, for some regulatory authorities and pharmaceutical industry organizations that had previously participated in ICH meetings and had appointed experts in Working Groups, it was made possible, provided certain conditions were met, to become a member directly without first being an observer.

In addition to the pharmaceutical industry, there was also some consideration of the value in allowing other international organizations active in the pharmaceutical sector as observers in ICH. Moreover, the wish to be inclusive needed to be balanced against ensuring a smooth functioning of the Association. Indeed, soon after setting up the ICH Association, there were increasing numbers of applications for observership from many different types of international organizations, which subsequently led to the revision of the rules with a view to tightening the eligibility criteria.

### Improved transparency

There is no doubt that expectations for transparency and disclosure had changed dramatically over the years since ICH first began. The perceptions and expectations are often linked to norms and policies in different cultures and, thus, the approaches to transparency differed significantly between regions. Nonetheless, improving the transparency of ICH's activities and its decision making was thus one of the cornerstones of the reform. Over the past several years, more information has been made available to the public on the ICH website, such as meeting records, minutes, and agendas, with the exception of documents containing commercial or sensitive information that is considered confidential. It is recognized that improving transparency is increasing the public trust in ICH. Additional communication efforts are being pursued, notably through the organization of meetings with stakeholders and the use of social media. Recently, the names of the experts participating in the Working Groups have also been disclosed on the ICH website.

### Transformational guidelines to support innovation

ICH attention to modernization has not been limited to key organizational and administrative reforms. Coincidentally, ICH began and continues to pursue transformational work in several

areas, including the following examples of efficacy guidelines that are enabling truly global deployment of innovative approaches in drug development.

Recognizing that clinical trials had evolved substantially, with increasing globalization, study complexity, and technological capabilities, the E6 guideline on GCP was revised to facilitate innovative approaches to clinical trials, including quality risk management and quality-by-design processes, risk-based monitoring, and use of technological tools to ensure robust conduct, oversight, and reporting.

Given the increasing number of multiregional clinical trials (MRCTs) widely conducted in ICH and non-ICH regions, and the lack of harmonized guidance, ICH developed the E17 guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials, to promote conducting MRCT more appropriately and efficiently while minimizing conflicting opinions from regulatory bodies. E17 addresses issues, including design, planning, and conduct of MRCTs; ethnic factors; dose determination; controlling for concomitant medicines in each country; population definition and sample size estimation; and other critically important issues.

To address important advances in pediatric drug development since publishing the original E11 guideline, ICH developed the revised E11(R1), which acknowledges regional regulatory differences but addresses critical technical issues, including the timing of pediatric development milestone agreements to satisfy multiple regulatory authorities, age classification, and pediatric subsets (including neonates), ethical considerations, and advances in clinical trial and statistical designs especially relevant to pediatric populations, encouraging developers to consider nonconventional designs whenever appropriate.

### HAS THE REFORM BEEN A SUCCESS?

ICH set about reforms with the goal of establishing one major venue for harmonization, allowing broad stakeholder input while maintaining efficient work group operations. Three years on, these reforms already show success. The considerable interest in ICH from regulatory authorities and international organizations is evident in the numbers: As of June 2018, the ICH Association was composed of 16 members and 27 observers, twice as many members as there were at the onset of the reformed ICH in 2015. In terms of governance, the role of the regulators has been strengthened in the guideline development process, which was one of the key objectives of the reform. Transparency has been significantly improved, and the funding of ICH is put on a stable basis. In 2017, the meeting in Montreal, Canada, also marked the first time an ICH meeting was organized outside the founding ICH regions of Europe, Japan, and the United States. One of the last steps of the reform was the appointment of new members to the ICH Management Committee at the meeting in June 2018 in Kobe, Japan.

At the same time that the organization has expanded its membership, the identification and uptake of new guideline topics has been robust and the expert Working Group activity has been impressive. This indication of success has also made it clear that there are still challenges that need to be addressed. One relates to the increasing

size of the Working Groups after the expansion of ICH and the need to ensure that the Working Groups remain of a manageable size. ICH is also making efforts to ensure a uniform implementation of the ICH guidelines by all the regulatory members, which is important for enhancing global harmonization. At the same time, ICH is launching important new harmonization activities, such as a revision of existing guidelines on GCP, which has a wide impact because these guidelines are the referenced global standard.

Thanks to the joint efforts of the parties involved, an in-depth reform of ICH has been achieved. This far-reaching modernization has adapted the collaboration to the challenges of the 21st century and formally established ICH as the leading organization for global pharmaceutical regulatory harmonization and one that brings together in a transparent manner key regulatory authorities and industry stakeholders. ICH guidelines are already known for their high standards, and it is the firm belief that ICH will continue its successful path and make an important contribution to the protection of public health.

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#### DISCLAIMER

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