

A Review on Impact of ICH and its Harmonisation on Human Health Care and Pharmaceuticals

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ABSTRACT

Harmonisation of regulatory requirements was initiated by the European Community (EC), in the 1980s, the EC moved towards the development of a single market for pharmaceuticals. At the same time there were bilateral discussions between Europe, Japan and the US on possibilities for harmonisation. ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States. ICH guideline gives special concern for the patient population; large-scale human clinical trials lasting up to one year can begin in the absence of completed carcinogenicity studies in rodents. ICH regulatory authorities are among the first to evaluate new chemical entities and new products obtained from biotechnology. ICH provides various guidelines which are categorised into four category, Quality guidelines, safety guidelines, efficacy guidelines and multidisciplinary guidelines. These guideline give special concern for the patient population, large-scale human clinical trials lasting up to one year can begin in the absence of completed carcinogenicity studies in rodents. The major aim of ICH To achieve greater harmonization in the interpretation and application of technical guidelines for the registration of new active substances or products obtained by biotechnology by its members; to improve the efficiency of global drug development; to reduce redundant studies; and to improve pharmacovigilance activities and quality assurance.

Keywords: Clinical trial, ICH, impact, guidelines, steering committee (SC)

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INTRODUCTION

At the first ICH Steering Committee (SC) meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorising new medicinal products [1].

The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference and terms of reference of ICH.

First decade saw significant progress in the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for

Regulatory Activities) and the CTD (Common Technical Document).

For two decades the ICH process has achieved much success. This success is attributed not only to a process of scientific consensus developed between industry and regulatory experts, but also to the commitment of the regulatory parties to implement the ICH Tripartite Harmonised Guidelines and recommendations.

Throughout the second decade the development of ICH Guidelines continued, but with more attention given to the need to maintain already existing Guidelines as science and technology continued to evolve. Entering into its third decade of activity, ICH's attention is directed towards extending the benefits of harmonisation beyond the ICH regions.

Mission

- ICH reduced the duplication of testing carried out during the research and development of new human medicines. ICH's mission is to achieve greater harmonisation in the interpretation and application of technical guidelines and its requirements for pharmaceutical product registration [2].
- ICH is a unique undertaking that brings together the drug regulatory authorities

and the pharmaceutical industry of Europe, Japan and the United States.

- Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness.

Organisation

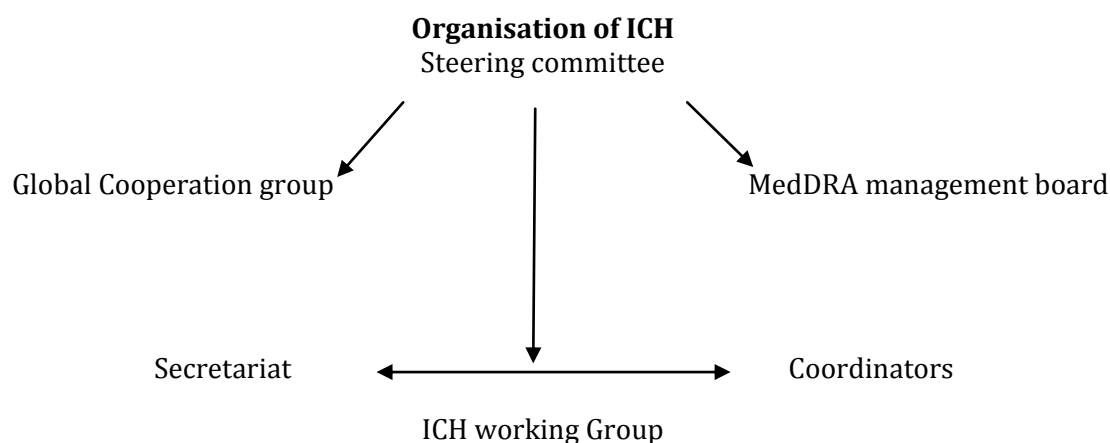


Figure 1 Various organisations of ICH

Steering committee

The ICH Steering Committee (SC) is the governing body that oversees the harmonisation activities. Since its establishment in 1990, each of its six co-sponsors (EU, EFPIA, MHLW, JPMA, FDA, PhRMA) has had two seats on the SC. Other parties have a significant interest in ICH and have been invited to nominate Observers to the SC. The three Observers are the World Health Organization (WHO), Health Canada and the European Free Trade Association (EFTA). The IFPMA participates as a non-voting member of the SC [3].

- WHO (World Health Organisation)
- Health Canada
- EFTA (European Free Trade Association)
- IFPMA (International Federation of Pharmaceutical Manufacturers & Associations)
- PhRMA (Pharmaceutical Research and Manufacturers of America)
- EU (European Union)

- EFPIA (European Federation of Pharmaceutical Industries and Associations)
- MHLW (Ministry of Health, Labour and Welfare)
- JPMA (Japan Pharmaceutical Manufacturers Association)
- FDA (US Food and Drug Administration)

Global Cooperation Group

The Global Cooperation Group (GCG) was originally formed as a subcommittee of the ICH Steering Committee in 1999 in response to a growing interest in ICH Guidelines beyond the three ICH regions [4]. A few years later, recognising the need to engage actively with other harmonisation initiatives, representatives from five Regional Harmonisation Initiatives (RHIs) were invited to participate in GCG discussions, namely, APEC, ASEAN, EAC, GCC, PANDRH and SADC. A further expansion of the GCG was agreed in 2007 and regulators were invited from countries with a history of ICH Guideline

implementation and/or where major production and clinical research are done (Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore).

MedDRA Management Board

The MedDRA Management Board, appointed by the ICH Steering Committee, has overall responsibility for direction of MedDRA, an ICH standardised dictionary of medical terminology. The Board oversees the activities of the MedDRA "Maintenance and Support Services Organisation" (MSSO), which serves as the repository, maintainer, developer and distributor of MedDRA. The Management Board is composed of the six ICH Parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, the Health Canada and the WHO (as Observer). The IFPMA acts as a non-voting observer on the Management Board and chairs the Board [5].

Secretariat

The ICH Secretariat is located in Geneva, Switzerland. Its staff member is responsible for day-to-day management of ICH, namely preparations for, and documentation of, meetings of the Steering Committee and its Working Groups. The ICH Secretariat also provides administrative support for the ICH Global Cooperation activities and the ICH MedDRA Management Board [6].

Coordinators

Fundamental to the smooth running of ICH has been the designation, by each of the six co-sponsors, of an ICH Coordinator to act as the main contact point with the ICH Secretariat [7]. Coordinators ensure proper distribution of ICH documents to the appropriate persons from their party (SC members, Topic Leaders, Experts) and are responsible for proper follow up on actions by their respective party within assigned deadlines.

Working Groups

For each of the technical topics which have been selected for harmonisation in the first phase of activities, the SC appointed a Working Group to review the differences in requirements between the three regions and develop scientific consensus required to reconcile those differences. Working groups do not have a fixed "membership"

but each of the six parties have nominated a Topic Leader (and, frequently, a Deputy Topic Leader) as the contact for the topic. The Observers to ICH, the Pharmacopoeia authorities and representatives from the self-medication industry and the generic industry have been invited to participate in various working groups [8].

There are several different types of ICH working groups that can be identified:

- **EWG:** Expert Working Group is charged with developing a harmonised guideline that meets the objectives in the Concept Paper and Business Plan.
- **IWG:** Implementation Working Group is tasked to develop Q&A's to facilitate implementation of existing guidelines.
- **Informal Working Group:** Is formed prior to any official ICH harmonisation activity with the objectives of developing/finalizing a Concept Paper, as well as developing a Business Plan.
- **Discussion Group:** Is a group established to discuss specific scientific considerations or views i.e. Gene Therapy Discussion Group (GTDG), and ICH & Women Discussion Group.

Process of ICH Harmonisation

Formal ICH Procedure

The procedure is initiated with the endorsement by the SC of a Concept Paper and Business Plan. An Expert Working Group (EWG) with membership as specified by the Concept Paper is subsequently established [9].

The EWG works to develop a draft Guideline and bring it through the various steps of the procedure which culminate in *Step 5* and the implementation in the ICH regions of a Harmonised Tripartite Guideline.

Step 1: Consensus building

The EWG works to prepare a consensus draft of the technical document, based on the objectives set out in the Concept Paper. Work is conducted via e-mail, teleconferences and web conferences.

If endorsed by the SC, the EWG will also meet face-to-face at the biannual SC meetings. Interim reports on the progress of the draft are made to the SC on a regular basis.

When consensus on the draft is reached among all six party EWG members, the EWG

will sign the *Step 1* Experts sign-off sheet. The *Step 1* Experts Technical Document with EWG signatures is then submitted to the Steering Committee to request adoption under *Step 2* of the ICH process.

Step 2a: Confirmation of six-party consensus on the Technical Document

Step 2a is reached when the SC agrees, based on the report of the EWG, that there is sufficient scientific consensus on the technical issues for the Technical Document to proceed to the next stage of regulatory consultation. This agreement is confirmed by at least one of the SC members for each of the six ICH parties signing their assent.

Step 2b: Adoption of draft Guideline by Regulatory Parties

On the basis of the Technical Document, the three ICH regulatory parties will take the actions they deem necessary to develop the draft Guideline.

Step 3: Regulatory consultation and Discussion

Step 3 occurs in three distinct stages: regulatory consultation, discussion and finalisation of the *Step 3* Expert Draft Guideline.

Stage I: Regional regulatory consultation: The Guideline embodying the scientific consensus leaves the ICH process and becomes the subject of normal wide-ranging regulatory consultation in the three regions. In the EU it is published as a draft CHMP Guideline, in Japan it is translated and issued by MHLW for internal and external consultation and in the USA it is published as draft guidance in the Federal Register.

Regulatory authorities and industry associations in non-ICH regions may also comment on the draft consultation documents by providing their comments to the ICH Secretariat.

Stage II: Discussion of regional consultation comments: After obtaining all comments from the consultation process, the EWG works to address the comments received and reach consensus on what is called the *Step 3* Experts Draft Guideline.

Stage III: Finalisation of Step 3 Experts Draft Guideline: If, after due consideration of the consultation results by the EWG, consensus is reached amongst the experts on a revised version of the *Step 2b* draft

Guideline, the *Step 3* Expert Draft Guideline is signed by the experts of the three ICH regulatory parties.

The *Step 3* Expert Draft Guideline with regulatory EWG signatures is submitted to the Steering Committee to request adoption as *Step 4* of the ICH process.

Step 4: Adoption of an ICH Harmonised Tripartite Guideline

Step 4 is reached when the Steering Committee agrees that there is sufficient consensus on the draft Guideline.

The *Step 4* Final Document is signed-off by the SC signatories for the regulatory parties of ICH as an ICH Harmonised Tripartite Guideline at *Step 4* of the ICH process.

Step 5: Implementation

Having reached *Step 4* the harmonised tripartite Guideline moves immediately to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the European Union, Japan and the USA.

Q & A Procedure

The Q&A Procedure is followed when additional guidance is considered necessary to help the interpretation of certain ICH harmonised tripartite guidelines and ensure a smooth and consistent implementation in the ICH regions and beyond.

The additional guidance is usually developed in the form of Questions and Answers "Q&As". The procedure is initiated with the endorsement by the SC of a Concept Paper. In the case of major implementation activities, the Steering Committee may also consider the need for Business Plan. An Implementation Working Group (IWG) with membership as specified by the Concept Paper is subsequently established [10].

The Q&A Procedure is driven by questions/issues raised by stakeholders, which serve as the basis for the development of model questions for which standard answers are developed. To assist the process, stakeholders are often invited via the ICH website to submit their questions on a specific guideline.

The IWG works to reach consensus on a draft Q&A document and makes a

recommendation to the SC on whether the document should be a *Step 2b* draft Document published for consultation or a *Step 4* final Document published as final without consultation. This recommendation is based on the level of information provided by the answers.

The document then follows the normal path of a *Step 2/Step 4* Document as per the Formal ICH Procedure.

Revision Procedure

The Revision Procedure is followed either in cases where the scientific/technical content of an existing ICH Guideline is no longer up-to-date or valid, or in cases where there is new information to be added with no amendments to the existing ICH Guideline necessary. In the case of the latter, the new information can be added in the form of an Addendum or an Annex to the Guideline in question.

The procedure is initiated with the endorsement by the SC of a Concept Paper. For revisions a Business Plan is not necessary. An Expert Working Group (EWG) with membership as specified by the Concept Paper is subsequently established [11].

The Revision Procedure is almost identical to the Formal ICH Procedure i.e. 5 ICH Steps. The only difference is that the final outcome is a revised version of an existing guideline, rather than a new guideline.

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

Maintenance Procedure

The Maintenance Procedure is currently applicable only for changes to the Q3C Guideline Impurities: Residual Solvents and M2 Recommendations. In each case the procedure is used when there is new information to be added or the scientific/technical content is out-of-date or no longer valid [12].

Maintenance Procedure for Q3C Guideline Impurities: Residual Solvents

The Maintenance Procedure for Q3C is followed when there is a proposal of a "permitted daily exposure" (PDE) for a new solvent or a revised PDE for an already classified solvent. The procedure was harmonised by all six parties in Brussels on February 2002 and is similar to the Formal ICH Procedure in that it follows the 5 ICH steps [13-14].

Updates to the Addenda of the Q3C guidelines are considered as revisions to the Q3C guideline and are designated by the letter R.

Maintenance Procedure for M2 Recommendations

Due to the information technology (IT) nature of the M2 EWG's work on Electronic Standards for the Transfer of Regulatory Information (ESTRI), some of their activities result in Recommendations. These Recommendations do not undergo the formal ICH step process, so as to allow for flexible change as both science, and technologies evolve. They are agreed in the EWG, signed by all parties of the EWG, and are approved and signed off by the ICH Steering Committee.

Why International Conference on Harmonisation (ICH)

Trade battles: Trade initiatives played a key role in the formation of the ICH. In the mid and late 1980s, the US and Japan began trade talks that included discussion of opening up the Japanese market for US pharmaceuticals. In response, the European Commission strengthened its resolve to establish a single EU standard for drug approvals in order to be competitive with Japan and the US in international trade negotiations. The International Federation of Pharmaceutical Manufacturers' Associations responded to these competing trade initiatives by organising meetings between the EU, Japan and the US [15].

Faster approval: The driving force behind ICH is the pharmaceutical industry. Prior to ICH, a multinational company was required to conduct a variety of studies and follow different government regulations in order to get its new product approved for patient use in different countries. The industry was interested in streamlining this process in

order to reduce development costs and reduce the time to get drugs to market. These changes would allow trade name pharmaceutical companies to reap greater profits from a drug because a shorter part of the patent protection period is spent in the pre-marketing phase. The patent clock begins ticking from the time that companies file an application for patent, so the quicker the drug can get to market, the longer the exclusive sales period.

ICH is advantageous for the brand-name pharmaceutical companies: To bring drugs to market as quickly and inexpensively as possible, and in as many countries as possible, the pharmaceutical industry needs the ICH to:

- Agree on one set of scientific rules for running clinical trials;
- Reduce the number of research animals and human test subjects necessary for testing (thus reducing expenses);
- Establish one set of standards for the manufacturing process of new drugs;
- Ensure similar application processes for drug approval in all countries;
- Ensure that research findings from one member country will be accepted by all other countries (with some exceptions for special populations).

All of those measures would help to bring drugs to market more quickly. No one would disagree with doing away with unnecessary and uninformative duplication of research. However, when it comes to cutting corners and shortening timelines, it's another matter. For most of the public, speed of approval is not the major consideration. More important is protection of public health, and new medicines that have been thoroughly tested for safety and that meet real human needs. If the ICH process leads to compromises in safety standards through a rush to "harmonise" to the lowest of existing standards, there is good reason to be concerned.

ICH impact on Safety Guidelines during Clinical Trials

The ICH has challenged the necessity of particular safety checks on new drugs.

Testing for Cancer Risks and Adverse Drug Events Animal testing is carried out to make sure a new drug is safe for eventual human use. The ICH wants to minimise the

number of such tests because of financial concerns (reducing pre-market testing requirements helps speed the process of getting drugs to market) and controversy over the use of animals. However, without a suitable replacement, reducing animal testing could expose Canadians to significant cancer risks or toxic side effects:

- *Two long-term animal* studies are usually used to ensure that a new drug is not carcinogenic and does not cause other serious harmful effects.
- Historically, cancer-risk testing is performed on *two different* rodent species (usually the rat and the mouse). Studies have shown that results from two animal species are better predictors than from one alone (although testing on rodents does not guarantee drug safety, as with thalidomide).
- Clinical trials on humans are only supposed to begin *after* an experimental drug passes all of the animal safety checks.

Despite the above,

- An ICH guideline recommends that, unless there is a special concern for the patient population, large-scale human clinical trials lasting up to one year can begin in the absence of completed carcinogenicity studies in rodents. In other words, trial participants could be exposed to an unknown cancer risk. It is unethical to expose trial participants to an unknown cancer risk when waiting six months to one year longer would add the results of animal trials.
- Although its own data on reducing standards was inconclusive, the ICH now recommends that only one long-term rodent cancer study needs to be conducted, plus one other short or medium-term study. This eliminates the safety of two long-term studies on two different rodents.

Health Canada should not adopt any ICH guidelines that reduce long-term testing, or testing of two rodent species, unless there is reliable scientific evidence that another model is *equally* valid.

Testing for Repeat Dose Problems In another phase of testing, animals (non-rodents) are exposed to large or repeat doses of an experimental medication to ensure that the drug does not become toxic

above certain levels. Before the ICH, the US required 12 months of such testing, while in European countries only 6-month toxicity testing has been required prior to marketing approval. When it set out to harmonise these two systems, the ICH concluded that it was not advisable to reduce the repeat dose testing to 6 months because the US Food and Drug Administration proved that some cases of toxicity only showed up by 12 months. To protect the consumer, the ICH should have adopted a 12-month standard. Instead, an ICH Expert Working Group concluded that a study of 9 months duration should be long enough to detect toxicity. Equally problematic was that it didn't even impose nine months as a minimum standard, but rather as a maximum one.

An industry representative acknowledged that science was heavily influenced by political considerations in reaching this guideline:

Patient safety must be rigorously protected. The ICH, and Health Canada, should ensure that a standard of 12 months toxicity testing be required.

ICH Impact on Post Marketing Safety Data

Once new drugs are approved for use, governments must still monitor their safety. Sometimes side effects don't show up in a research group of 3,000 volunteers, but become obvious when drugs are used in larger populations. Interactions with other medicines are not uncommon and can't always be assessed in a pre-marketing research trial because patients taking other medications are excluded from these trials. Similarly, a drug can have adverse effects in particular populations who were excluded from pre-marketing trials. This is why it is crucial to follow a new drug after it has been approved for use [16].

There are some areas of concern about the ICH deliberations in this area.

- Harmonise up or down? Most countries involved in the ICH require companies to file "Periodic Safety Update Reports" (PSURs) for new drugs. (Canada does not, although it is currently reviewing this.) The US currently requires PSURs every four months during the first 3 years after a drug goes to market. The EU and Japan

require PSURs only every 6 months. Waiting for 6 months to find out that a newly-marketed drug is having more harmful effects than anticipated is too long. The ICH is still debating this standard, but should harmonise these requirements upwards to the US standard to protect public health. In this instance, Canada should follow the US model.

- Companies are required to report increases in the frequency of adverse drug reactions. However, no rules are in place to make sure companies monitor how often adverse drug reactions occur or at what point they must report an increased frequency; this is left to the discretion of the company. This is unacceptable since significant increases in the occurrence of known Adverse Drug Reactions (ADRs) have not been reported in a timely manner by companies. The ICH should provide a clear-cut, enforceable standard for changes in ADRs occurrence that would trigger reports [17].

The ICH's guidelines on PSURs cover how and when companies report to regulatory agencies. But such requirements have limited impact unless government regulatory agencies require:

- mandatory, active follow-up of drugs once marketed,
- a rigorous system of reporting by health professionals if their patients experience an adverse reaction,
- clear instructions to physicians about what to report,
- mechanisms for allowing consumers to make direct reports,
- Assurances that the information will get out quickly to the public and health professionals in a manner that will maximise the response to these alerts.

ICH harmonisation for better health

- Regulatory harmonisation offers many benefits to both regulatory authorities and the pharmaceutical industry, and has a positive impact for the protection of public health [18].
- Through the development of harmonised guidelines ICH works to: streamline the regulatory assessment process for new drug applications; reduce the development times and resources needed for drug development; prevent

duplication of clinical trials in humans; and minimise the use of animal testing without compromising safety and effectiveness.

- ICH's work to harmonise requirements in the drug registration process promotes quicker access to medicines for patients.
- ICH has evolved since its inception to respond to the increasingly global face of drug development, and through its ICH Global Cooperation Group works so that the benefits of international harmonisation for better global health can be realised worldwide.

The Future of ICH

ICH has completed an important phase. Key guidelines are now being implemented in the areas of Efficacy, Quality and Safety in the three ICH regions. The organization has established a maintenance procedure to ensure that the guidelines continue to reflect the latest scientific developments and best practice. These maintenance activities are essential to the future of ICH, and to ensure that harmonization continues. Several more ambitious guidelines are under development, such as Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients (APIs), Pharmacopoeias Harmonization. The Common Technical Document and its electronic counterpart will be available in less than two years, both set to change procedures for regulatory dossier submission significantly. The organization has recognized the importance of making available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines [19].

Other topics that may now come to the fore are those such as the Harmonization of Regulatory Review Procedures. While the guidelines set a common standard for development, there is no commonality in review. By promoting greater interaction between the competent authorities, such that there is more transparency in the review process, it is a reasonable hope that a common standard of review will be achieved. Such a development is something

that the industry should actively encourage through the ICH forum, as the benefits would be significant.

DISCUSSION

Finally, ICH looks to the future. It has established a structure to maintain the guidelines, and at the same time is looking to make available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines. From an industry perspective globalization is arguably the most important issue it faces, and the ability of these guidelines to effect intra-company globalization is a facet of ICH that cannot be ignored. This is already happening within companies. Its value has not been quantified; however, the companies able to embrace these principles today will be the world leaders tomorrow. Companies who fail to see the value of harmonization—the value that is already being felt by the scientists carrying out the development, and the value that is yet to be realized in the full drug development cycle—will be left at the starting line of the industry's globalization race.

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