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ICH

(INTERNATIONAL COUNCIL FOR HARMONISATION)

Nupur B. Thite, Pradnya J. Raut, Shivani K. Mokate
Student,
Department of Pharmaceutics,
SCSSS's Sitabai Thite College of Pharmacy, Shirur, Pune, India

Abstract:

The international council for harmonization (ICH) is the regulatory requirement to confirm the quality safety and efficacy (QSE) of drugs. It brings a union of drug regulatory experts and Pharma business partners from a few countries such as the European union, Japan, and the United States for harmonisation of technical requirements for drugs in humans. The major aim of ICH is to achieve greater harmonisation in the interpretation and application of technical guidelines for the registration of new active substances obtained by biotechnology by its members; to improve the efficacy of global drug development; to reduce redundant studies; to improve pharmacovigilance activity and quality assurance.

Keywords:

- ICH regulatory guideline
- Pharmacoepial harmonisation
- PSUR (Periodic safety update report)
- Good manufacturing practices
- Regulatory bodies
- Organization of ICH

Introduction:

ICH stands for the international council for harmonization of technical requirements for the registration of pharmaceuticals for human use

The ICH logo has been designed with a view to representing the letters "I" "C" "H" in a manner that embodies the letter in an abstract human form. The principal colour of the logo is blue, a colour often synonymous with healthcare, which adds an air of validity and well-being to the depicted abstract figure. purple has been chosen as being complementary to blue.

ICH mission:

ICH'S mission is to make recommendations towards the achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

Organization:

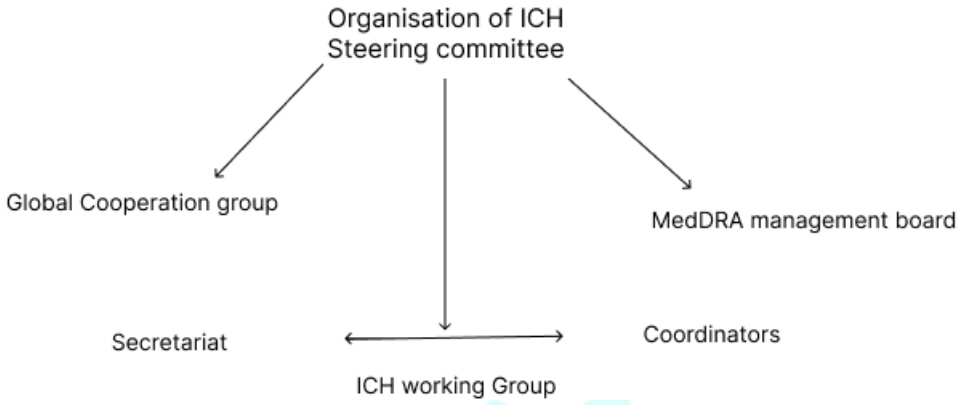

Figure 1 Various organisations of ICH

ICH steering committee and its subcommittee are comprised of a representative of 6 parties that represent the regulatory body and research-based industry in the European Union Japan and the USA.

Region	Regulatory body	Research-based industry
Japan	**MHLW**-Ministry of health, labour, and welfare	**JPMA**- Japan pharmaceutical manufacturers association
Europe	**EU-** European Union	**EFPIA**- European federation of pharmaceutical industry and associations
USA	**FDA**- Food and drug administration	**PhRMA**- Pharmaceutical research and associations of America

Steering committee:

The ICH steering committee is the governing body that oversees the harmonization activities. Its co-sponsors (EU, EFPMA, MHLW, JPMA, FDA, and PhRMA) have two steering committee seats. 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 steering committee.

- WHO (World Health Organization)
- Health Canada
- EFTA (European Free Trade Association)
- IFPMA (international federation of pharmaceutical manufacturers and association)
- PhRMA (pharmaceutical research and manufacturers of America)
- EU (European Union)
- EFPIA (European federation of pharmaceutical industries and association
- MHLW (Ministry of health, labour and welfare)
- JPMA (Japan pharmaceutical manufacturers and association)
- FDA (U.S Food and Drug Administration

Global Cooperation Group:

The global Cooperation group was originally formed as a subcommittee of the ICH steering committee in response to a growing interest in ICH guidelines. A few years later recognizing the need to engage actively with other harmonization initiatives, representatives from five Regional Harmonisation Initiatives (RHI) were invited to participate in Global cooperation discussion, namely APEC, ASEAN, EAC, GCC, PANDRH, and SADC.

MedDRA Management Board:

The MedDRA Management Board appointed by the ICH Steering committee has overall responsibility for the direction of MedDRA, an ICH-standardized dictionary of medical terminology. The board oversees the activity of the MedDRA "Maintenance and support services organization" (MSSO). Which serves as a repository, maintainer, Developer, and Distributer of MedDRA. The Management Board is composed of six ICH parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA).

Secretariat:

The ICH secretariat is located in Geneva, Switzerland. Its staff member is responsible for day to day management of ICH, namely preparation for, and documentation of, meetings of the steering committee and its working group. The ICH secretariat also provides administrative support for the ICH Global cooperation activities and the ICH MedDRA Management Board.

Coordinators:

Fundamental to the smooth running of ICH has been the designation, by each of the six co-sponsors, of ICH coordinator to act as the main content point with the ICH secretariat. Coordinators ensure proper distribution of ICH documents to the appropriate person from their party (SC Member, Topic Leaders, Experts) and are responsible for proper follow-up on actions by their representative party within the assigned deadline.

Working Group:

The steering committee appointed a working group to review the differences in requirements between the three regions and develop the scientific consensus required to reconcile those differences. The Working group does not have a fixed membership but each of the six parties has nominated a Topic Leader (and, frequently, a Deputy Topic Leader) as the contact for the topic.

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

- EWG: The expert working group is charged with developing a harmonized guideline that meets the objective of the concept paper and business plan.
- JWG: The implementation working group is tasked to develop Q and A to facilitate the implementation of existing guidelines.
- Informational working group: Is formed prior to any official ICH harmonization activity with the objective of developing/ finalizing a concept paper, as well as developing a business plan.

- Discussion group: This is a group established to discuss specific scientific considerations or views i.e., Gene therapy Discussion Group (GTDG), and ICH and women Discussion Group.

Steps of formal ICH procedure:

STEP 1: Consensus building

STEP 2: Confirmation of six-party consensus

STEP 3: Regulatory consultation and discussion

STEP 4: Adoption of ICH Harmonised Tripartite Guideline

STEP 5: Implementation

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 by e-mail, telephone, and web conferences. If endorsed by SC, the EWG will also meet face-to-face at the biannual SC meeting. 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 Expert technical document with EWG signature is then submitted to the steering committee to request adoption under step 2 of the ICH process.

STEP 2: Confirmation of six-party consensus on the technical document:

Step 2 is reached when the SC agrees, based on the report of the EWG, that there is sufficient scientific consensus on the technical issue 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 3: Regulatory consultation and discussion

Occurs in three distinct stages:

Regulatory consultation, discussion, and finalisation of the step 3 Expert draft guideline.

Stage 1: Regional regulatory consultation:

The guideline embodying the scientific consensus leaves the ICH process and becomes the subject of normal wide-ranging regulatory consultation in 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 external consultation and in the USA it is published as a draft guidance in the federal register. Regulatory authorities and industry associations in non-ICH regions may also comment on the draft consultation document by providing their comments to the ICH Secretariat.

Stage 2: Discussion of regional consultation comments:

After obtaining all comments from the consultation process, the EWG addresses the comments received and reaches a consensus on the step 3 Experts draft guideline.

Stage 3: Finalisation of step 3 Experts draft guideline:

If after due consideration of the consultation result by the EWG, consultation result by the EWG, the consensus is reached amongst the experts on a revised version of step 2b draft guidelines, the step 3 Experts 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 ass step 4 of the ICH process.

STEP 4: Adoption of an ICH Harmonised tripartite guideline

draft guideline. The step Step 4 is reached when the steering committee agrees that there is sufficient consensus on the 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 harmonised tripartite guideline moves immediately to the final step of the process which is the regulatory implementation. This step is carried out according to the same national/regional regulatory guideline and requirements, in the European Union, Japan, and the USA.

ICH GUIDELINES:

GUIDELINE	SUBPART	AREA COVERED
Q1 Stability	Q1 A	Stability testing of new drug substances and product
	Q1 B	Photostability testing of new drug substances and product
	Q1 C	Stability testing for new dosage forms
	Q1 D	Breaking and matrixing designs for stability testing of new drug substances and products.
	Q1 E	Evaluation of stability data.
Q2		Validation of analytical procedures
Q3 Impurities	Q3 A	Impurities in new drugs substances
	Q3 B	Impurities in new drug products
	Q3 C	Guidelines for residual solvents
	Q3 D	Guidelines for elemental impurities.
Q4 Pharmacopoeias	Q4 A	Pharmacopoeial harmonization
	Q4 B	Evaluation and recommendation of pharmacopoeial texts for use in ICH regions.

Q5 Quality of biotechnological products	Q5 A	Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
	Q5 B	Analysis of expression construct in cells used for production of r-DNA derived protein products.
	Q5 C	Stability testing of biotechnological/ biological products
	Q5 D	Derivation and characterization of cell substrates used for production of biotechnological/biological products
	Q5 E	Comparability of biotechnological/biological products subjects to change in their manufacturing process.

Why International Conference on Harmonisation:

Trade Battle: Trade investigation plays an important role in formation of ICH. US, Japan, being trade talks that included discussion of opening up the Japanese market for US pharmaceutical. In response, the European commission strengthen its resolve to establish a single EU standard for drug approvals in order to be competitive with Japan and US international trade negotiation. The international federation of pharmaceutical manufactures association responded to these competing trade initiatives by organizing meeting between EU, Japan, US.

Faster approvals: 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 regulation 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 cost and reduce the time to get drug 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 patient, so the quicker the drug can get to market, the longer the exclusive sale period.

ICH is advantageous for the brand-name pharmaceutical companies: To bring drug 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 drug.
- Ensure similar application processes for drug approval in all countries.
- Ensure that research finding from one member country will be accepted by all other countries (with some exception for special populations)

All of those measure would help to bring drugs more quickly. Important is to protection of public health, and new medicines that have been thoroughly tested for safety of and that meet the real human need. If the ICH process leads to compromise in safety standard through a rush to harmonise to the lowest of existing standard, there is good reason to be concerned.

ICH impact on safety guideline during clinical trials:

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

Testing for cancer risk and adverse drug event Animal testing is carried out to make sure a new drug is safe for eventual human use. The ICH wants to minimized the number of such tests because of financial concerns (reducing pre-market testing requirement helps spend the process of getting drug to market) and controversy over the use of animals. However, without a suitable replacement reducing animal testing could expose Canadian to significant cancer risk or toxic effect.

- 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 performed on two different rodent species (usually the rat and the mouse). Studies have shown that result from two animal species are better predictor than from one alone (although testing on rodents does not guaranty degree of safety, as with thalidomide).
- Clinical trials on humans are only supposed to being after on experimental drug passes all the animal safety checks.

ICH Impact on post marketing safety data:

Once new drug is approved for use, government must still monitor their safety. Sometime side effects do not show up in a research group but become obvious when drug is used in larger populations. Interactions with other medicines are not uncommon and can't always be assessed in pre marketing research trials. Similarly, a drug can have adverse effect in particular population who were excluded from pre marketing trials.

There are some areas of concern about the ICH delebering in these area

- Harmonised up or down? Most countries involved in the ICH requirement companies to file "periodic Safety update Reports" (PSUR) for new drugs. (Canada does not although it is currently reviewing this.) The US currently requires PSURs every four month during the first 3 year after a drug goes to market. The UE and Japan required PSURs only every 6 month. Waiting for 6 month to find out that a newly marketed drug is having more harmful effect than anticipated is too long. The ICH is still debating this standard, but should harmonise these requirement upward to the US standard to protect public health, in these intense, Canada shoul US model.
- Companies are required to report increases in the frequently of adverse drug reaction. However, no rules are in place to make sure companies monitor how often adverse drug reaction occur or at what point adverse drug reaction occur or at what point they must report as increased frequency; this is unacceptable since significant increases in the occurrence of known adverse drug reaction (ADR) have not been reported in timely manner by companies. The ICH should provide a clear cut, enforceable standard for changes in ADR occurrence that would trigger point.

The ICH guideline 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.
- 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; 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 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 . 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.

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