International Journal of Pharmaceuticals and Health care Research (IJPHR)
IJPHR |Vol.12 | Issue 4 | Oct - Dec -2024
www.ijphr.com
DOI : https://doi.org/10.61096/ijphr.v12.iss4.2024.306-316
ISSN: 2306-6091

Review

Role Of ICH In Harmonising Drug Reulations

A. Sree Deepthi*[1], V. Lavanya [1], K. Devamani[1]

Department Of Regulatory Affairs, Princeton College Of Pharmacy, Narapally, Ghatkesar, Telangana

*Author for Correspondence: A. Sree Deepthi
Email: pcopaac2007@gmail.com

Published on: 11 Nov 2024

Published by:
DrSriram Publications

Abstract

The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. 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. 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.

Keywords: ICH, united states, pharmaceutical industry, EC

INTRODUCTION

The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.[1] ICH stands for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". ICH's logo has been designed with a view to representing the letters "I", "C", "H" in a manner which embodies the letters in an abstract human form. The principle colour of the logo is blue, a colour often synonymous with healthcare, and which adds an air of vitality and wellbeing to the depicted abstract figure. Purple was chosen as being complementary to blue.

Mission

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical Guidelines and requirements for pharmaceutical product registration. Harmonisation is achieved through the development of ICH Guidelines.

History

Since ICH's inception in 1990, the ICH process has gradually evolved. ICH's first decade saw significant progress in the development of 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). During 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;

- Expand communication and dissemination of information on ICH Guidelines with
- other regions; Facilitate the implementation of ICH Guidelines in the ICH regions;
- Coordinate with other organisations, particularly for the development of electronic
- standards.

In its third decade of activity, ICH's attention is directed towards extending the benefits of harmonisation beyond the ICH regions. Training, as well as active participation of other regions in Guideline development is seen as key in this effort.

Organisation

ICH Steering Committee and its sub-groups

Fig 1: ICH structure

The ICH structure consists of the ICH Steering Committee (SC), ICH Coordinators, ICH Secretariat and ICH Working Groups. The ICH MedDRA Management Board is a subcommittee of the ICH SC (Figure 1). In June 2013, the Global Cooperation Group (GCG) format was modified. A recast "GCG session" was incorporated into a standing agenda item of the ICH SC agenda entitled Global Cooperation (GC). Other countries (Regional Harmonisation Initiatives (RHIs) and individual Drug Regulatory Authorities and Department of Health (DRAs/DoH) are invited to participate in the GC session of the ICH SC meeting. The ICH SC and its MedDRA sub-committee are comprised of representatives from all ICH Parties which are described as follows:

Regulatory ICH Parties:

- Europe: the ICH Regulatory Party is represented by the European Commission (EC) andthe European Medicines Agency (EMA);
- Japan: The ICH Regulatory Party is the Ministry of Health, Labor and Welfare (MHLW)and the Pharmaceuticals and Medical Devices Agency (PMDA);
- USA: The ICH Regulatory Party is the Food and Drug Administration (FDA);
- Canada: The ICH Regulatory Party is the Health Products and Food Branch (HPFB);
- Switzerland: The ICH Regulatory Party is the Swissmedic.

Industry ICH Parties

- Europe: the European Federation of Pharmaceutical Industries and Associations (EFPIA);
- Japan: The Japan Pharmaceutical Manufacturers Association (JPMA);
- USA: the Pharmaceutical Research and Manufacturers of America (PhRMA).

- WHO, the ICH Observer, has been associated with the ICH process from the beginning to act as a link with countries and regions beyond ICH. WHO is a non-voting member who is part of the ICH SC.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) which has been closely involved with ICH since its inception participates also as a non-voting member.

Fig 2: ICH SC composition

b. ICH Expert Working Groups (EWGs) / Implementation Working Groups (IWGs) Each of the ICH Parties (EU, MHLW/PMDA, FDA, Health Canada, Swissmedic, EFPIA, JPMA, PhRMA) and the ICH Observer (WHO) nominate official representatives to each ICH Working Group. The official membership of EWG/IWG shall be comprised of one Topic Leader and one Deputy Topic Leader for ICH Parties and one representative per ICH Observer. Experts are nominated by the ICH regional Coordinators. Experts from Regional Harmonisation Initiatives (RHIs), Drug Regulatory Authorities (DRAs) and Department of Health (DoH) participating in ICH activities are invited to nominate one expert to participate in all ICH Working Groups (WGs). Depending on the topic under harmonisation, other experts may also be invited by the ICH SC to nominate one representative to participate in WGs: if approved by the SC, one expert can be invited from: ICH Regional Pharmacopeias and ICH Interested Parties (World Self-Medication Industry - WSMI, International Generic Pharmaceutical Alliance - IGPA, Biotechnology Industry, International Pharmaceutical Excipients Council – IPEC, Active Pharmaceutical Ingredient Industry – API and Pharmaceutical Inspection Co-operation Scheme – PIC/s).

Work products

Guidelines*:* ICH has developed over 60 harmonised Guidelines aiming at eliminating duplication in the development and registration process, so that a single set of studies can be generated to demonstrate the quality, safety and efficacy of a new medicinal product.

ICH has also developed Questions and Answers (Q&As) when additional guidance and advice were considered necessary to help the interpretation of some harmonised Guidelines.

CTD*:* The Common Technical Document (CTD) describes the common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.

eCTD: The electronic Common Technical Document (eCTD) has been developed for the electronic submission of the Common Technical Document from applicant to regulator, in order to facilitate international electronic communication through the provision of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

MedDRA: The Medical Dictionary for Regulatory Activities (MedDRA) terminology has also been developed under the auspices of ICH.

Consideration documents: The Consideration documents have been developed by discussion groups i.e., Gene Therapy Discussion Group, and ICH & Women Discussion Group to report specific scientific considerations.

Strategy on Training and Capacity Building

The ICH SC recognises the importance of training in helping to facilitate the implementation of ICH Guidelines both in its own regions and beyond.

ICH regions: The need for oversight on training with respect to ICH Guidelines is generally left to each region's discretion, except for MedDRA, where the ICH MedDRA Management Board oversees the provision of training

to MedDRA subscribers worldwide. The SC acknowledges that from time to time there is benefit in coordinating training activities so as to ensure consistency in the manner in which Guidelines are implemented, particularly where new and complex concepts are introduced.

Other ICH regions: There is an increasing interest from countries beyond ICH regions in the utilisation of ICH Guidelines, and as a consequence, training and capacity-building have become a key focus of the ICH Global Cooperation session of the SC meeting.

Process of harmonization

The ICH SC is responsible for the governance of ICH. This includes deciding on the adoption of every ICH project, whether a new topic, maintenance of an existing Guideline, or a specific implementation work. Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required. Any ICH Party or the ICH Observer is welcomed to submit a proposal for a new ICH activity. ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure.

Formal ICH Procedure

A formal ICH 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. At the same time, a Rapporteur (and co-Rapporteur) is officially designated by the SC and a Regulatory Chair is officially designated the by the regulatory parties of the SC. 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 Guideline.

Step 1: Consensus building: The process of consensus building begins when the ICH SC adopts a Concept Paper as a new topic. Step 1 is initiated when the EWG begins the preparation of 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 webconferences. 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 technical document are made to the SC on a regular basis. When consensus is reached among EWG members from all ICH Parties, the EWG will sign the Step 1 Experts sign-off sheet. The Step 1 Technical Document with EWG signatures is then submitted to the ICH SC to request adoption under Step 2a of the ICH process.

Step 2a: Confirmation of consensus on the Technical Document: Step 2a is reached when the ICH 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. The consensus text approved by the experts under Step 1 is signed-off by the SC as the Step 2a Final Technical Document.

Step 2b: Adoption of the draft Guideline: On the basis of the technical document, the Regulatory ICH Parties will take the actions they deem necessary to develop the "draft Guideline". The consensus text is signed-off by the SC Regulatory ICH Parties as Step 2b Draft Guideline.

Step 3: Regulatory consultation and Discussion: Step 3 occurs in three distinct stages:

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 ICH 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, in the USA it is published as draft guidance in the Federal Register and in Canada it is posted on the Health Canada website to solicit comments. Regulatory authorities and industry associations in other 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. If the Rapporteur was from an industry party, until Step 2b a new Rapporteur from a regulatory party is appointed, preferably from the same region as the previous Rapporteur. The same procedure described in Step 1 is used to address the consultation results.

Stage III: Finalisation of Step 3 Experts Draft Guideline: When, after due consideration of the consultation results by the EWG, consensus is reached amongst the experts from the ICH Parties on a revised version of the Guideline, the Step 3 Experts Draft Guideline is signed by the EWG experts of the Regulatory ICH Parties. The Step 3 document with regulatory EWG signatures is submitted to the SC to request adoption at Step 4 of the ICH process.

Step 4: Adoption of an ICH Harmonised Guideline: Step 4 is reached when the ICH SC agrees, on the basis of the report from the Regulatory Chair and the Rapporteur of the EWG, that there is sufficient consensus on the draft guideline. Step 4 is reached when the document is signed-off by the SC Regulatory ICH Parties as an ICH harmonised Guideline.

Step 5: Implementation: Having reached Step 4, the harmonised Guideline moves immediately to the final step of the process that is the regulatory implementation or Step 5. Step 5 is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the EU, Japan, USA, Canada and Switzerland.

The Q&As Procedure

The Q&As procedure is followed when additional guidance is considered necessary to help the interpretation of certain ICH harmonised Guidelines and ensure a smooth and consistent implementation in the ICH regions and beyond. The procedure is initiated with the endorsement by the SC of a Concept Paper (a Business Plan may be required in certain cases). An IWG is nominated to work on a draft Q&A document. The group makes a recommendation to the SC on whether the document would require a public consultation (Step 3 of the ICH process) based on the level of information provided by the answers. The document then follows the normal path of a Step 2b/Step 4 document as per the Formal ICH Procedure.

The 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 in the case of Q4B) to the Guideline. The procedure is initiated with the endorsement by the SC of a Concept Paper. For revisions a Business Plan is not necessary. An EWG with membership as specified by the Concept Paper is subsequently established. 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 has been developed, upon reaching Step 4 the Addendum is added to the existing Guideline.

The Maintenance Procedure

The Maintenance Procedure is currently applicable only for changes to the Q3C Guideline on 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.

ICH meetings

The ICH SC meets on a biannual basis during a week which has the participation of other regulatory members (RHIs and DRAs/DoH) and which also includes meetings of the ICH MedDRA Management Board. Also occurring on the ICH week is the International Pharmaceuticals Regulatory Forum (IPRF), which has participation from both ICH regulators and other regulatory members of the GC. These meetings run in parallel of meetings of ICH technical working groups. Any ICH technical working group face-to-face meeting is subject to decision by the ICH SC. With a view to keeping down organisational and logistical costs of the ICH Process, WGs should meet face-to-face only when necessary and justified in their work plan and when sufficient discussion materials are available.

Table 1: In order for face-to-face meetings to be considered official, all ICH Parties need to be represented in all parallel meetings, at least by one delegate

Saturday	Sunday	Monday		Tuesday	Wednesday	Thursday
ICH MedDRA Management Board		IPRF	IPRF	ICH Steering Committee	ICH Steering Committee	
ICH Technical Working Groups						

ICH week normally adheres to the same schedule of meetings, commencing on Saturday with the ICH MedDRA Management Board meeting and finishing on Thursday with the ICH SC meeting. These meetings run in parallel of meetings of ICH technical working groups. Onsite, the ICH Secretariat and the Host organiser provide

administrative support to all participants to ensure the smooth running of all meetings (e.g., daily update of meeting schedule, document sign-off, presentation printing).

In between meetings

ICH SC

Ahead of the ICH week, the ICH Secretariat organises teleconferences with the ICH SC, Coordinators, MedDRA Management Board and Global Cooperation members to prepare for their respective meetings and raise any issues to be addressed at the meetings. At its teleconference, the SC should reach agreement on which Working Groups will meet at the faceto-face meeting. Between face-to-face meetings ICH EWGs/IWGs are encouraged to make use of modern communication technologies (e-mail, webconferences, teleconferences, etc.) to progress draft Guidelines. In order for teleconferences/webconferences to be considered official, all ICH Parties need to be represented, at least by one delegate. Working groups could also meet outside the regular ICH SC weeks. These Interim face-to-face meetings have to be endorsed by the ICH SC and take place exceptionally only when there is an absolute necessity in order for the topic to meet its assigned objectives in time. ICH Coordinators designated by each of the ICH co-sponsors and Focal Points nominated by RHI/DRA/DoH representatives, play a fundamental role in smooth running of ICH.

Their role includes to act as the main contact point with the ICH Secretariat and to ensure that any ICH documents are distributed to the appropriate persons within the area of their responsibility (e.g., meeting announcement, registration forms). In addition to providing support to the ICH SC, the ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the SC as well as coordination of preparations for Working Group meetings.[2]

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, unlessthere 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 (nonrodents) 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.

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

Harmonise up or down? Most countriesinvolved 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

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
- 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.

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.[3]

DISCUSSIONS

The Value and Benefits of ICH to Drug Regulatory Authorities-Advancing Harmonization for Better Health

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), launched 20 years ago, is an unparalleled undertaking. ICH brings together the drug regulatory authorities of Europe, Japan, and the United States, along with the pharmaceutical

trade associations from these three regions, to discuss scientific and technical aspects of product registration. It is ICH's mission to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.

In 2000, the 10th Anniversary of ICH, Dr. Caroline Nutley Loew of the Pharmaceutical Research and Manufacturers of America (PhRMA) wrote a report, The Value and Benefits of ICH to Industry, which detailed ICH's creation, procedures, and guideline development in the areas of safety, efficacy, and quality. Dr. Loew's report anticipated that the Common Technical Document (CTD) would revolutionize the submission procedures for industry's regulatory staff. Dr. Loew characterized the CTD as "offering potential benefits to industry far greater than any other single ICH topic," and predicted the CTD would afford significant savings in time and resources as complex multiple submissions were replaced by a single technical dossier submitted in the three ICH regions—facilitating simultaneous submission, approval, and launch of new drugs. In calling the CTD "a topic whose value to industry cannot be underestimated," Dr. Loew noted that with full incorporation of the CTD and the electronic CTD (eCTD), ICH could turn its sights to disseminating guideline information to non ICH countries, yielding additional benefits to both regulators and industry.

Ten years later and in anticipation of ICH's 20th Anniversary, the value and benefits of ICH to regulators have been realized. Moreover, implementation of the CTD in 2003 promoted the involvement of drug regulatory authorities (DRAs) not initially part of ICH, thereby extending ICH's harmonized approach. The development of the Global Cooperation Group, which includes representatives from five regional harmonization initiatives and the newly established Regulators Forum, created to promote participation by non-ICH countries interested in implementing ICH's strategies, have also helped incorporate the CTD into regulatory processes, creating a common regulatory language that promotes faster access to life-saving treatments to patients beyond ICH regions. In recognition of the increasingly global face of drug development, ICH recently updated its logo to emphasize the benefits of harmonization for better global health.

Shift in Emphasis

Substantial benefits to DRAs resulted when ICH shifted emphasis from the input of information by industry to the output of information by regulators. This transition was made possible by the development of a common submission format—the CTD— which greatly influenced regulatory review processes, ultimately leading to a harmonized electronic submission and e-review initiatives, which, in turn, have enabled implementation of good review practices. These activities are having a global effect on information review and sharing among drug regulatory authorities.

Originally, ICH focused on input by industry—the technical submission requirements for pharmaceuticals for human use. Harmonizing the differences in these requirements through ICH guidelines helped industry reduce development times and save resources. To extend the benefits of harmonization, industry proposed assembling the building blocks of information intended for inclusion in a submission into a consistent harmonized format, referred to as the CTD, which would relieve pharmaceutical companies of the time, workforce, and financial burdens of assembling a submission for one DRA and then having to reformat it for another. This new consistent format also greatly benefited the U.S. Food and Drug Administration (FDA), enabling the agency to establish templates for each of the review disciplines while promoting more consistent review practices and processes.

Prior to the advent of the CTD, regulatory reviewers received an application from one company and spent a year or more engaged in its review. When the review was completed, reviewers received the next application—most likely in a different format—and had to learn the structure of the new application. As a result, review staff were constantly on a learning curve when new assignments were received — time they could have better used reviewing the information as opposed to simply trying to find it.

When industry proposed the CTD in 1996, ICH regulators were hesitant to change their submission formats, believing it would be too disruptive to the review process. They needed convincing that harmonizing the submission format had value. Regulators asked industry to do a feasibility study. That study, conducted in May 1996, evaluated the time it took to convert an FDA new drug application into an European Medicines Agency (EMA) submission, and the reverse. It also evaluated the number and types of staff needed to carry out the conversion of the submission formats. Regulators quickly saw the potential value of harmonizing submission formats

Regulatory Benefits

The CTD has also made the exchange of information among drug regulatory authorities easier. For a number of years, FDA and the EMA have had a confidentiality arrangement in place allowing the sharing of confidential information, greatly increasing interactions between the two agencies. Now that submissions are received in the same format and, generally, at the same time, these interactions have become more efficient, facilitating discussions of common concerns as submissions are evaluated.

Last, and perhaps most important, the CTD has facilitated electronic submissions (the eCTD). In the past, drug applications were voluminous, delivered to FDA by the truckload due to the sheer amount of paper involved. When the agency first transitioned to electronic submissions, an application was on a compact disc or hard drive. Although this certainly helped with transportation and storage issues, it did not necessarily enhance the review process. FDA has now implemented the FDA Electronic Submission Gateway, which allows a new drug application (NDA) to be sent electronically, essentially very much like e-mail. After being assessed for completeness, a submission is immediately and fully accessible on the reviewer's desktop. This innovation has alleviated the need for industry to create and assemble the many pieces of paper that constituted a traditional paper-based product application, organize the application, box thousands of pages, load the boxes on a truck, and deliver them to FDA— all before a reviewer could even begin the assessment process.

The eCTD has proved critical to improving application submission efficiencies as well as reviewer efficiency. Besides delivering submission material to the reviewer in an expedited manner, the eCTD format has made it easier to develop standardized reviewer e-templates and review tools for each of the review disciplines.
Another benefit of a harmonized format has been the ease of developing and implementing harmonized good review practices. What is evaluated in a review is closely tied to the requested data. As a result, there is considerable similarity between ICH guidance to industry and what we consider good review practices. Because ICH regions have harmonized much of the information submitted for marketing authorization, ICH regulators could easily begin moving toward similar review practices.

In general, good review practices promote transparency and consistency, both of which are very important if industry and the public are to understand how regulatory authorities carry out their responsibilities. This is especially important because of the complexity of the disciplines and specialties involved in the review process. We needed a consistent approach to evaluating submissions and reaching conclusions, and the CTD and eCTD have helped to achieve these goals.

In summary, the CTD format influences the content of the review by imposing a consistent order of information and data. This shapes both the conduct of the review and the presentation of the results of the review and promotes good review practices and increased efficiencies. As more countries embrace ICH guidelines and the CTD format, a common regulatory language could evolve that will further promote interactions among drug regulatory authorities

CONCLUSION

Any medicinal agent to be marketed in the United Kingdom has to follow the guidelines and regulations framed by MHRA, a regulatory authority which approves the drug products. The objective of this review article is to highlight information regarding the requirements, the different types of submissions for the registration of a medicinal product in a market in the UK. It also includes all the details about the fee for the application and the time period for the approval of the application after the submission of the application. By knowing the requirements of the MHRA guidelines and regulations, it is easy for a product to get into the
UK market.

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.

Drug regulation is interplay between law and science, as well as among regulators and pharmaceutical companies, with input and influence from patients and healthcare professionals. These stakeholders help to determine the regulatory environment in each of the seven GCC authorities and cannot be neglected in the course of the assessment of each country's regulatory practices. A focused view of the regulatory review process and the quality measures currently used to improve the standard of the assessment procedure is critical to underscore the similarities and differences among the GCC regulatory authorities. However, these similarities and differences cannot be exploited unless they are placed in the context of the GCC harmonized strategic plan.

In general, an effective harmonization strategy requires an effective, coordinated approach, legislation and administration at the country and regional level. Regional cooperation is needed to ensure that regulatory capacity is sufficiently developed to meet the demands of the regulatory environment and to ensure that public health protection is the main purpose of a quality review process, which is a critical step to ensure patients' access to safe and effective medicines.

ACKNOWLEDGEMENT

The Authors are thankful to Sura Pharma Labs, Dilshukhnagar, Hyderabad for providing the necessary facilities for the research work.

REFERENCES

1. https://en.wikipedia.org/wiki/International_Council_on_Harmonisation_of_Technical_Requirements_for Registration_of_Pharmaceuticals_for_Human_Use
2. http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Vision/Introduction_to_ICH_24Jun2014.pdf
3. http://www.rroij.com/open-access/a-review-on-impact-of-ich-and-its-harmonisation-on-human-health-care-and-pharmaceuticals.pdf
4. http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Vision/Value_Benefits_for_Regulatory_2010.pdf
5. http://apps.who.int/medicinedocs/en/d/Jh2977e/4.html
6. http://www.ncbi.nlm.nih.gov/books/NBK174222/
7. file:///C:/Users/SURA%20LAB/Downloads/RF_2012_11_Gulf_Region.pdf
8. http://www.rroij.com/open-access/a-review-on-impact-of-ich-and-its-harmonisation-on-human-health-care-and-pharmaceuticals.pdf
9. http://onlinelibrary.wiley.com/doi/10.1038/clpt.2011.10/abstract
10. Ankit Gupta, Raghav Goel, Suresh Jain, Vipin Saini . A Review on Impact of ICH and its Harmonisation on Human Health Care and Pharmaceuticals. Journal of Pharmaceutical Research & Clinical Practice, 2014; 4(2):41-49 .
11. JA Molzon, A Giaquinto, L Lindstrom,T Tominaga, M Ward, P Doerr, L Huntand,L Rago The Value and Benefits of the International Conference on Harmonisation to Drug Regulatory Authorities: Advancing Harmonization for Better Public Health .*Clinical Pharmacology & Therapeutics* (2011) 89 4, 503–512.
12. Dixon JR Jr .The International Conference on Harmonization Good Clinical Practice guideline.Qual Assur. 1998 ;6(2):65-74.
13. ICH the need to harmonise [Online]. [cited 2014 May 02]; Available from: URL:http://www.ich.org/about/history.html
14. ICH harmonise for better health vision [Online]. [cited 2014 Apr 25]; Available from: URL:http://www.ich.org.about/vision.html
15. ICH steering committee [Online]. [cited 2014 Apr 25]; Available from: URL:http://www.ich.org/about/organisation -of-ich/steering.html.