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ROLE OF ICH IN HARMONIZING DRUG REGULATION

Greeshma S, Sreekanth Reddy CP, Jyoshtna Devi K, Jayachandra Reddy P

Department of Drug Regulatory Affairs,
Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati-517605, Andhra Pradesh, India.

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.

Key words: European Community, ICH, Patient population.

INTRODUCTION

Drug regulatory agencies share the common goal of allowing safe and effective drugs to reach the market. Despite this, drug regulators have acted in isolation in developing standards for evaluating the quality, safety and efficacy of drugs [1]. Accordingly, the detailed technical requirements of drug testing standards have varied significantly from country to country. As a result of this, new drugs poised for international marketing have been subject to multiple and duplicate testing [2]. The time and costs associated with this multiple testing and unnecessary regulation have been overwhelming. This results in higher prices, delays in treatment and the unavailability of some drugs in some markets [3]. Harmonization of the scientific requirements of pharmaceutical regulatory schemes worldwide will reduce duplication of tests and speed the approval of drugs throughout the world and the aim is to describe role of ICH in drug regulations, in order to understand how they affect the quality and availability of Medicines [4].

History of ICH

The International Council for Harmonization (ICH), formerly the International Conference on Harmonization (ICH) held the inaugural Assembly meetings on 23 October 2015 establishing ICH as an international association, a legal entity under Swiss law. This step built upon a 25-year track record of successful delivery of harmonized guidelines for global pharmaceutical development as well as their regulation, and a longer standing recognition of the need to harmonize [5].

The Need to Harmonize

The realization that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. However in many cases the realization was driven by tragedies, such as that with thalidomide in Europe in the 1960s [6].

For most countries, whether or not they had initiated product registration controls earlier, the 1960s

*Corresponding Author **Greeshma S** E mail: greeshmasamanthula51527@gmail.com

and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. The industry, at the time, was becoming more international and seeking new global markets; however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally [7].

The urgent need to rationalize and harmonize regulation was impelled by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.

Initiation of ICH

Harmonization of regulatory requirements was pioneered by the EC, Europe, in the 1980s, as the EC, Europe moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible. At the same time there were discussions between Europe, Japan and the US on possibilities for harmonization. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialize. Soon afterwards, the authorities approached International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonization, and ICH was conceived [8].

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 but the meeting also discussed the wider implications and terms of reference of ICH. At the first ICH Steering Committee meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonization would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorizing new medicinal products.

The Evolution of ICH

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). As ICH started into a new millennium, the need to expand communication and dissemination of information on ICH Guidelines with non-ICH regions became a key focus. Attention was also directed throughout the second decade towards facilitating the implementation of ICH Guidelines in ICH's own regions and maintaining already existing ICH Guidelines as science and technology continued to evolve [9].

Now in its third decade of activity, ICH's attention is directed towards extending the benefits of harmonization beyond the founding ICH regions. A significant step was taken in 2015 to facilitate this which saw ICH undergoing a series of organizational changes. These changes constituted a number of reforms including: increasing international outreach; changing ICH's governance structure; disseminating more information on ICH processes to a wider number of stakeholders; and establishing ICH as a legal entity to provide for a more stable operating structure [10].

The resulting ICH association establishes an Assembly as the over-arching governing body with the aim of focusing global pharmaceutical regulatory harmonization works in one venue that allows pharmaceutical regulatory authorities and notably concerned industry organizations to be more actively involved in ICH's harmonization work [11].

Assembly

The ICH Assembly brings together all Members and Observers of the ICH Association as the overarching governing body of ICH. It adopts decisions in particular on matters such as on the Articles of Association, admission of new Members & Observers and adoption of ICH Guidelines. The ICH Assembly meets biannually and its agendas as well as reports are made available on the ICH website summarizing the main decisions taken at each meeting.

Auditors

Assembly has appointed an auditing firm as Auditors. The Auditors are appointed for a period of two years and may be re-appointed. The responsibility of the Auditors is to audit the financial statements of the Association upon conclusion of each Fiscal Year. They should ensure that the accounting of the Association complies with Swiss law and generally accepted Swiss accounting principles.

ICH Management Committee

The ICH Management Committee (MC) is the body that oversees operational aspects of ICH on behalf of all Members, including administrative and financial matters and oversight of the Working Groups (WGs). The MC is responsible for submitting recommendations or proposals to the Assembly in preparation of Assembly discussions [12]. To date, the ICH MC has representatives from the six Founding Members (EC, Europe / EFPIA / FDA, US / JPMA / MHLW/PMDA, Japan / PhRMA), Standing Regulatory Members (Health Canada, Canada / Swiss medic, Switzerland) as well as Standing Observers (IFPMA, WHO).

MedDRA Management Committee

The MedDRA Management Committee (MC) has responsibility for direction of MedDRA, an ICH standardized dictionary of medical terminology. The MedDRA MC is composed of the EC, Europe / EFPIA / MHLW/PMDA, Japan / JPMA / FDA, US / PhRMA, the

Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, Canada and WHO (as Observer).

Secretariat

The Secretariat is located in Geneva, Switzerland. The ICH Secretariat is responsible for day-to-day management of ICH, coordinating ICH activities as well as providing support to the Assembly, the ICH Management Committee and its Working Groups. The ICH Secretariat also provides support for the ICH MedDRA Management Committee.

Coordinators

Fundamental to the smooth running of ICH has been the designation of an ICH Coordinator per ICH Member to act as the main contact point with the ICH Secretariat. Coordinators ensure proper distribution of ICH documents to the appropriate persons from their organisation and are responsible for the follow up on actions within their respective organisation within assigned deadlines. They also assist communication between the ICH Management Committee and/or Assembly and the ICH Working Groups as needed.

Working Groups

An ICH Working Group (WG) is established for each technical topic selected for harmonization.

There are several different types of ICH working group:

- EWG: Expert Working Group is charged with developing a harmonized guideline that meets the objectives in the Concept Paper and Business Plan.
- IWG: Implementation Working Group is tasked with developing Q&As to facilitate implementation of existing guidelines.
- Informal Working Group: Is formed prior to any official ICH harmonization 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.

ICH Members and Observers appoint experts to participate in the WGs in line with the applicable procedures in the Assembly Rules of Procedure and EWG/IWG Standard Operating Procedures. A Rapporteur from one of the Members is designated by the Assembly to lead the scientific discussions of the WG. The Management Committee oversees the work of the WGs on an ongoing basis, while the Assembly receives reports on each WG's progress at the time of its biannual face-to-face meetings.

Formal ICH Procedure

The Formal ICH Procedure is a step-wise procedure consisting of 5 steps.

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 ICH Management Committee, the EWG will also meet face-to-face at the time of the biannual Assembly meetings. Interim reports on the progress of the draft are made to the Assembly on a regular basis. When consensus on the draft is reached within the EWG, the technical experts of 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 Assembly to request adoption under Step 2 of the ICH process.

Step 2a: Confirmation of consensus on the Technical Document

Step 2a is reached when the Assembly 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.

Step 2b: Adoption of draft Guideline by Regulatory Members

On the basis of the Technical Document, the ICH Regulatory Members will take the actions they deem necessary to develop the draft Guideline.

Step 2b is reached when the Regulatory Members endorse the draft Guideline.

Step 3: Regulatory consultation and Discussion

Step 3 occurs in three distinct stages: regulatory consultation, discussion and finalization 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 ICH regions. 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.

Stage III - Finalization 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 ICH Regulatory Members. The Step 3 Expert Draft Guideline with regulatory EWG signatures is submitted to the Regulatory Members of the Assembly to request adoption as Step 4 of the ICH process.

Step 4: Adoption of an ICH Harmonized Guideline

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

The Step 4 Final Document is adopted by the ICH Regulatory Members of the ICH Assembly as an ICH Harmonized Guideline at Step 4of the ICH process.

Step 5: Implementation

Having reached Step 4, the harmonized 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 ICH regions.

Q&A Procedure

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

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 Assembly 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 ICH Assembly of a Concept Paper. For revisions a Business Plan is not necessary. An Expert Working Group (EWG) 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 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 and Q3D Guidelines 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.

Maintenance Procedure for Q3C Guideline Impurities: Residual Solvents and Q3D Guideline for Elemental Impurities

The Maintenance Procedure for Q3C/Q3D is followed when there is a proposal of a "permitted daily exposure" (PDE) for a new solvent/elemental impurity or a revised PDE for an already classified solvent/elemental impurity. The procedure is similar to the Formal ICH Procedure in that it follows the 5 ICH steps.

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 Members of the EWG, and are approved by the ICH Assembly. Each new version of the M2 Recommendations is designated by a different version number. The Topics selected for harmonization were divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorizing new medicinal products. As of now, forty five guidelines have been harmonized between the three regions. ICH guidelines are divided into four main categories:

quality, safety, efficacy and multidisciplinary.

Quality Guidelines

Harmonization achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Twelve different guidelines fall under the category of quality. The guidelines cover various issues including stability, analytical validation, impurities, pharmacopoeias, biotechnology products, specifications and GMP.

Q1A(R2) - Stability Testing of New Drug Substances and Products

Q1B - Stability Testing: Photo stability Testing of New Drug Substances and Products

Q1C - Stability Testing for New Dosage Forms

Q1D - Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E - Evaluation for Stability Data

Q1F - Stability Data Package for Registration Applications in Climatic Zones III and IV

Q2(R1) - Validation of Analytical Procedures: Text and Methodology

Q3A(R2) - Impurities In New Drug Substances

Q3B(R2) - Impurities in New Drug Products
Q3C(R7) - Impurities: Guideline for Residual Solvents
Q3D – Guideline for Elemental Impurities
Q4 - Pharmacopoeia
Q4A - Pharmacopoeial Harmonization
Q4B - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
Q4B Annex 4A(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Microbial Enumerations Tests
Q4B Annex 4B(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Test for Specified Micro-Organisms
Q4B Annex 4C(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
Q4B Annex 1(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash
Q4B Annex 2(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Extractable Volume of Parenteral Preparations
Q4B Annex 3(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Particulate Contamination: Sub Visible Particles
Q4B Annex 5(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Disintegration Test
Q4B Annex 6(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Uniformity of Dosage Units
Q4B Annex 7(R2) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Dissolution Test
Q4B Annex 8(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Sterility Test
Q4B Annex 9(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Tablet Friability
Q4B Annex 10(R1) - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Polyacrylamide Gel Electrophoresis
Q4B Annex 11 - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Capillary Electrophoresis
Q4B Annex 12 - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Analytical Sieving
Q4B Annex 13 - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bulk Density and Tapped Density of Powders
Q4B Annex 14 - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Bacterial Endotoxins Test
Q4B - Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
Q5A(R1) - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Q5B - Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of r-DNA Derived Protein Products
Q5C - Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
Q5D - Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
Q6A - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
Q7 - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Q8(R2) - Pharmaceutical Development
Q9 - Quality Risk Management
Q10 - Pharmaceutical Quality System
Q11 - Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

There are eleven guidelines covered in the Safety section. This section deals with detailed scientific issues including: carcinogenicity, genotoxic, toxicokinetic (including reproductive toxicity testing), and pharmacokinetics and immunotoxicology studies.

S1 - Rodent Carcinogenicity Studies for Human Pharmaceuticals
S1A - Need for Carcinogenicity Studies of Pharmaceuticals
S1B - Testing for Carcinogenicity of Pharmaceuticals
S1C(R2) - Dose Selection for Carcinogenicity Studies of Pharmaceuticals
S2(R1) - Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
S3A - Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
S3A - Q&AsQuestions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Micro sampling

S3B - Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
S4 - Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)
S5(R2) - Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
S5(R3) - Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals
S6(R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
S7A - Safety Pharmacology Studies for Human Pharmaceuticals
S7B - The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
S8 - Immunotoxicity Studies for Human Pharmaceuticals
S9 - Nonclinical Evaluation for Anticancer Pharmaceuticals
S10 - Photo safety Evaluation of Pharmaceuticals
S11 - Nonclinical Safety Testing in Support of Development of Pediatric Medicines

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.

The Efficacy section covers nineteen guidelines. The guidelines addressed in this section are a combination of technical and administrative issues. Technical issues include: the effectiveness of long-term treatment for non-life treating conditions and dose response information. Administrative issues include: clinical safety data management and standards for successful expedited reporting, maintenance of ICH guidelines, structure and content of clinical safety reports and ethnic factors in the acceptability of foreign clinical data.

E1 - The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions
E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B(R3) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2B(R3) - IWGImplementation: Electronic Transmission of Individual Case Safety Reports
E2C(R2) - Periodic Benefit-Risk Evaluation Report
E2D - Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
E2E - Pharmacovigilance Planning
E2F - Development Safety Update Report
E3 - Structure and Content of Clinical Study Reports
E4 - Dose-Response Information to Support Drug Registration
E5(R1) - Ethnic Factors in the Acceptability of Foreign Clinical Data
E6(R2) - Good Clinical Practice (GCP)
E7 - Studies in Support of Special Populations: Geriatrics
E8 - General Considerations for Clinical Trials
E9 - Statistical Principles for Clinical Trials
E10 - Choice of Control Group and Related Issues in Clinical Trials
E11 - Clinical Investigation of Medicinal Products in the Pediatric Population
E11(R1) - Addendum: Clinical Investigation of Medicinal Products in the Paediatric Population
E11A - Paediatric Extrapolation
E12 - Principles for Clinical Evaluation of New Antihypertensive Drugs
E14 - The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
E16 - Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions
E17 - General principles for planning and design of Multi-Regional Clinical Trials
E18 - Genomic Sampling and Management of Genomic Data
E19 - Optimisation of Safety Data Collection

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

The Multidisciplinary section covers ten topics that do not traditionally fit into one of the three sections discussed above. Many of the subjects in this section are actually tools that helped ICH to create medical terminology dictionary and a common marketing application for new pharmaceutical products. The multidisciplinary section covers eight guidelines.

M1 - MedDRA Terminology
M2 - Electronic Standards
M3(R2) - Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
M4 - Common Technical Document
M5 - Data Elements and Standards for Drug Dictionaries
M6 - Virus and Gene Therapy Vector Shedding and Transmission
M7(R1) - Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
M8 - Electronic Common Technical Document (eCTD)
M9 - Bio pharmaceutics Classification System-based Bio waivers
M10 - Bio analytical Method Validation

Why International Council for 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.

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.

Potential Benefits from Pharmaceutical Harmonization

There are numerous potential benefits to the pharmaceutical industry that could result from harmonization.

a) Timesaving

Perhaps the strongest impact of harmonization will be the resultant saving of time. Inconsistent national standards create lag time between product development and distribution thereby increasing industry costs including loss of sales, loss of revenue from a decrease in effective patient life, loss of working capital, and loss of staff costs for processing multiple applications. Such timesaving's will provide earlier access to innovative therapies. This will help save more lives and will also be more profitable to companies.

b) A Reduction in the Cost of Drug Development

Harmonization will allow drug companies to avoid duplicative tests in states that are parties to the ICH agreement. Furthermore, it will simplify preparation of application dossiers and will lessen the costs associated with guiding drugs through the process of regulatory review for each country's market. This will provide companies with great cost savings. These savings in costs will be beneficial for the drug companies and consumers. Companies will be able to shift these cost savings into more research and development of new drugs. Consumers will benefit from the development of new drugs. Furthermore, as the cost of drug approval declines, more pharmaceutical companies may enter the market, which will increase competition among drug companies and could result in a decline in drug prices. In addition, it will allow smaller drug companies to enter the market. Multinational companies bear extremely large expenses in learning the various regulations of each market in which they operate. "This capital-intensive process eliminates small drug companies" from the development of new drugs.

c) Improvement of World Health

Harmonization will ideally make the world safer, and thereby reduce the spread of disease within and between nations. Health concerns of nations are interrelated. Most developing countries use a certification scheme, which allows use of the drug if it has been approved for use in the nation that developed it. Hence, they are relying on the regulatory processes of the developed countries. The certification scheme is problematic when drugs are received from nations whose regulatory process is too lax (because dangerous and ineffective drugs could be marketed). If pharmaceutical regulation is harmonized such that the regulatory processes of developed nations ensure the efficacy and safety of drugs, the developing nations will be better off.

Furthermore, harmonization will hopefully eliminate repetitive testing and requirements such that effective treatment will be able to reach developing nations with less delay. While improving health in the Third World is in and of itself a benefit of harmonization, it is also beneficial in that it may reduce the spread of disease between nations. When inferior and inefficacious

drugs are used by a nation, this could very well have an impact on the entire world. "For instance, antibiotics on developing countries are frequently used in inadequate dosages and for too short a treatment period, resulting in inadequate treatment for the local population and creating drug-resistant strains of bacteria. These bacterial become impossible to treat as they invariably spread throughout the world." The health of nations is also interrelated when one considers the health care implications for citizens of the developed world who travel abroad. Moreover, pharmaceutical harmonization will improve information transfer between countries on public health issues.

d) Advance International Trade Such that the U.S. will Can Export More

Statistics indicate that U.S. drug companies cannot remain profitable by marketing their products exclusively within in the U.S. Because of the long approval process in the U.S. and the notoriously strict regulatory climate, U.S. pharmaceutical companies have increasingly been performing clinical trials and original product introductions in foreign markets. Because the consumer market in the EU is now larger than the consumer market in the U.S. and because the approval process is generally considered to be faster in the EU, this provides large incentives for U.S. firms to relocate their operations overseas if harmonization fails. Under a harmonized system, the U.S. export position will improve. U.S. drug companies will perform tests at the IND stage, and then will be able to submit a common data package to each of the regulatory participants. Once the foreign regulatory authorities approve the new drugs, the drug companies will be able to export the drugs from the U.S.

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 (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 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.

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.

Barriers to Achievement of the Goals of the ICH

There remain some considerable barriers that need to be overcome before the harmonization of international pharmaceutical regulations can truly be achieved.

1. Lack of Central Enforcement Authority

The primary barrier to harmonization facing the EMEA and the ICH as a whole is the lack of a central enforcement authority empowered to impose its actions on the other countries. Individual countries' legislatures continue to have ultimate control of implementation. "Without enforcement procedures built into the central system to assure compliance, member's countries retain a potential "veto" which in turn jeopardizes the entire system." This is particularly applicable to the U.S. where there is strong ambivalence, both by the legislature and FDA. A lack of enforcement procedures also means that the FDA will go on inspecting foreign manufacturers for compliance with Good Manufacturing Practice and Good Clinical Practice Standards. "Ideally, enforcement would allow a central body to audit practices by all manufacturers and provide independent assurance that ICH adopted standards will be maintained without the need for inspection by each country's own regulatory agency."

2. U.S. Ambivalence

While supporting the ICH in theory, the FDA's approach to implementing ICH guidelines "has failed to meet the standards for openness and balanced representation that are necessary for ready acceptance of the ICH standards." "By its own admission, the FDA is pursuing harmonization as a secondary effort while maintaining its primary effort of domestic drug control." Several observers have commented that the U.S.'s idea of harmonization is that its regulations should apply. Two points of concern seem to underlie FDA's ambivalence towards harmonization. One worry is that the FDA, which is normally accustomed to having a great deal of control, will be subjugated to the will of the international community. Congress, which ultimately shapes a great deal of FDA policy, "is wary of the potential negative effects of ceding a large measure of control to a foreign entity." The second point underlying U.S. ambivalence is the FDA's fear of compromise of safety and efficacy standards and the FDA's general distrust of foreign data. The U.S., not at ease with relying on what it may sense is unconfirmed and uncontrolled foreign clinical and manufacturing practices, may perhaps continue to develop Memoranda of Understanding (MOU). MOUs are one of the ways the FDA is attempting to continue oversight of the drugs used by the American populace. MOUs allow the FDA to impress its more stringent standards on foreign countries and also serve to grant authorization for foreign inspections. "Effectively this adds another layer of inspection which potentially slows the overall process through unnecessary redundancy. This result negates the purpose of harmonization.

3. Constitutional Difficulty

One obstacle within the United States confronting the movement towards international harmonization is the Constitutional difficulty with delegating decision-making

authority to a foreign government. The no delegation doctrine limits the ability of Congress to delegate to administrative agencies the legislative powers vested in it by Article 1 of the Constitution. However, the Supreme Court has rarely ever invalidated on Article 1 grounds acts of Congress which delegated authority to the President or any administrative agency. The Supreme Court has, however, set limits on Congress's ability to delegate authority beyond the bounds of the federal government. Despite the fact that the Supreme Court has never explicitly addressed the issue of delegation to foreign powers, constitutional concerns may apply to an agreement that allowed a foreign regulatory body to bind the FDA to a particular decision. For example, some scholars have argued that Article 43 of the United Nations Charter, which authorizes the UN Security Council to carry out an agreement whereby U.S. forces would serve under foreign command, might violate Congress's Article 1 power to declare war. Case law suggests that the non-delegation doctrine could be overcome as long as the FDA retained the final authority to object particular new drugs.

4. Cultural and demographic differences between the Three ICH Regions

a) Differing Attitudes toward Health and Medicine

There seems to be a general unwillingness of Americans to accept any level of risk regarding pharmaceutical products and, that American attitudes about risk are different from those of other countries. "A study be Sheila Jasanoff revealed variances between citizens of Britain and the United Sates in their attitudes toward four different types of environmental risk. Jasanoff found that in Britain, scientists and other decision makers are certain to recognize a risk only when there is persuasive evidence of actual harm... whereas in the United States a risk may also be acknowledged where there is a no direct proof of injury to the public. This cultural diversity of attitude may be compounded in the realm of personal illness—especially terminal disease—where the very notion of 'risk' becomes indeterminate and subjective." Another matter in which attitudes differ in the three regions is in the area of informed consent. This is an obstacle to the development of pharmaceutical standards, particularly in the conduct of clinical trials. The U.S. seems to put a stronger emphasis on informed consent than do Japan and the Europe. Japanese physicians have what Americans view as a 'paternalistic' attitude towards informed consent. For example, it is often the case that many patients are not told that they are being placed on an experimental drug. The EU tends to favour medical progress over fully informed consent. They tend to lie somewhere in the middle of the spectrum between the U.S. and Japan. Additionally, western manufacturers have refrained from conducting clinical trials in Japan because of their belief that doctors there are frequently unwilling to follow protocols precisely. "In Japan, when administering a pharmaceutical, the doctor may decide on his own to mix it with dried herbs and roots from the local area to increase its effectiveness." Identifiable cultural differences also exist with respect to moral attitudes about certain drug products (e.g., the European 'abortion' drug RU-486, or pharmaceuticals developed form the use of fetal tissue research). There also may be differing attitudes toward intensive animal testing.

b) Different Physiological Reactions to Drugs

An additional barrier to the acceptance of one another's foreign data arises from cultural and demographic differences between the U.S., Europe, and Japan. Certain medical evidence suggests that different racial and ethnic groups have various reactions to pharmaceutical products, such that a drug that is safe and effective in one population groups might be less so in other racial or ethnic groups. If it is the case that differences exist in the way different ethnic groups react to certain drugs, then a research protocol which excludes groups may miss not only the side effects of that particular drug, but may result in a significant positive effect being missed altogether. Additionally, there are culturally driven ethnic factors that play a crucial role in the determination of drug equivalence as well as efficacy. These factors include diet, smoking habits, use of alcohol, exposure to pollution, amount of daily sunshine, socioeconomic status, and compliance with prescription drug regimens.

5. Political barriers

Several authors have noted the close relationship of drug regulatory activities and public policy in any given country. Surrendering this control to a central agency would prove essentially unworkable for many states, which view regulation of drugs as synonymous with national sovereignty. In large part, this has led to the structuring of the ICH without any central enforcement capabilities.

6. Patent Laws

"There is strong evidence that the vitality of any modern health care system is directly dependent upon a strong intellectual property regime." Presently, there is a great dissonance in patent laws around the world. Furthermore, there appears to be little potential for harmonization of patent laws. The chief impediment in the sphere of patents is the United States resistance to implementation of a "first to file" system for patent recognition. In contrast to the "first to file system," which is the de facto international standard, the United States uses the "first to invent" system. While it is acknowledged that a change by the U.S. to the first to file system would necessitate statutory amendment of a system supported by 200 years of case law in the U.S., most U.S. companies doing business internationally are currently working under the "first to file" system with no difficulty.

7. Mission creep

Another impediment to harmonization of pharmaceutical regulation is "mission creep." "Mission creep" is an expansion of original objectives to include less focused and less realistic goals. Recognition of a significant need for international collaboration has led some to advocate a sort of "mission creep." For example,

Peter Southerland, former European Community Commissioner for Ireland, has urged the European Federation of Pharmaceutical Industries' Association to be more aggressive in demanding that non-drug health care technology and treatments be subjected to the same level of regulatory scrutiny as the pharmaceutical industry. Standards for such varied things as lawnmowers and electromagnetic radiation, which are beyond the scope of the ICH, are being developed under the general umbrella of the Mutual Recognition Agreement. Although consumer safety is the common theme for these products as it is for with drugs, the means and methods of defining and assuring it differ vastly, thus limiting the potential for optimal determination of issues specific to drugs.

8. Global protection of human subjects

There are no international treaties governing experimentation on humans. The trend toward greater acceptance of foreign data and the efforts to harmonize drug regulations can only lead to more research being conducted abroad. To what extent can the countries involved be assured that this research is being conducted ethically? National regulations have very little extra-territorial effect and there are no international treated governing experimentation on humans.

9. Harmonizing Upward v. Harmonizing Downward

An additional problem faced by both the EU and the ICH as a whole is that nations with the most rigorous standards are pushing to "harmonize upward" whereas nations with the least stringent standards are pushing to "harmonize downwards." Both a "race to the top" and a "race to the bottom" would result in an unfavourable outcome. A "race to the bottom" forgoes health and safety standards in favour of freer movement of goods, whereas a "race to the top" would appear to defeat the very objectives of harmonization—reducing the cost of drug development, speeding the process from development to market, and making drugs available to the consumer.

THE IMPACT OF REGULATORY COOPERATION

1. ICH Accomplishments

Despite the significant barriers to harmonization, numerous accomplishments have been made under the auspices of the ICH. The principal achievement of the conference is the willingness of all three regulatory agencies to commit publicly to harmonization principles. The FDA's presence at the conference was particularly striking because of their reluctance in the past to accept foreign data. The collaborative spirit of the agencies was further evidenced through their agreement to a "de facto moratorium" on the introduction of new clinical testing standards. They viewed the development of potentially inconsistent tests as contrary to harmonization. In addition to this political achievement, there have also been many technical accomplishments. To date, fifty guidelines have been harmonized between the three regions. Moreover, they have also developed several products and services to facilitate the harmonization process. These services are designed to help the member parties' manufacturers comply with ICH guidelines and to increase clarity of the guidelines. The main products and services developed thus far are the Common Technical Document (CTD), MedDRA, the Electronics Standards for the Transfer of Regulatory Information and Data (ESTRI), and the Global Cooperation Group (GCG). As well as discussing these products, this section will highlight some of the important guidelines that have been harmonized.

a) The Common Technical Document

At the fourth ICH conference in July of 1997, the three parties agreed to take on the development of a common technical document (CTD). By mid-2001, the CTD application was produced. The development of the CTD is considered to be the ICH's most significant achievement thus far. "It is described as a harmonized core 'information package' of [clinical, pharmacology/toxicology, and quality] technical data' that can be submitted in the same format and with the same content to obtain marketing authorization in any of the three ICH regions—the United States, the European Union, and Japan." All three regions have implemented a "transition period" from July 2001 to July 2003, during which companies will have the option of submitting marketing authorization applications for any new drugs in either the conventional regional format or the new CTD format. Once the transition period ends in July 2003, the EU and Japan will require that marketing authorization applications be filed in the CTD format and the U.S. will highly recommend that the CTD format be used.

b) MedDRA

In order to make harmonization feasible, the ICH realized that they needed to eliminate regulatory communication barriers. The ICH Steering Committee and EWGs created MedDRA, a medical terminology vocabulary that would allow the EU, Japan, and the U.S. to use one medical language. "The multiple dictionaries that were used prior to the creation of MedDRA were often incompatible with one another and lead to communication problems when manufacturers reported their information to multiple regulatory agencies."

c) Electronic Standards for the Transfer of Regulatory Information and Data

Because the three founding parties of the ICH are spread across the world, high-speed technology and the Internet are the most efficient means for information exchange and application processing. The ICH Steering Committee delegated an EWG to manage the development of an electronic system for informational exchange between manufacturers and regulatory authorities. The Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI) "covers the evaluation of encryption technologies, physical media (floppy disks and CD-ROMS), network messaging, message formats and electronic document transfers." In 1996, the EWG selected software to handle ICH needs, and since 1997, members of the ICH have been using the software to transfer drug reports.

d) The Global Cooperation Group

From the onset of the initiative, members of the ICH have made an effort to uphold a transparent system of

practice that would maintain all ICH guidelines and documents open to manufacturers and authorities of all countries. In an attempt to guarantee smooth communication with non-ICH members, the ICH created the Global Cooperation Group (GCG) to serve as an information liaison between ICH member parties and non-ICH member parties. Additionally, the GCG produced a set of principles to be followed when handling requests from non-member parties.

e) Good Clinical Practice Guidance

Another considerable accomplishment of the ICH was the adoption of an ICH harmonized Good Clinical Practice (GCP) guidance. A consolidated ICH GCP guidance was released for comment in late 1995 and was subsequently adopted in May 1996. This guidance has eliminated many of the considerable differences in clinical trial related regulatory requirement between the three ICH regions. It has also led to the elimination of much of the variability between the EU's Member States.

f) Stability testing

The members of the ICH have also materialized a set of harmonized procedures for determining the shelf life of new drugs. The procedures, known as "stability testing," could save money during the development stage of the new drug and during the re-examination stage of the new drug during its lifetime.

g) Reproductive Toxicology Studies

The testing procedures to determine whether a new drug causes birth defects and/ or affects fertility will also be harmonized. So far, the three ICH regions are in agreement that "all female reproduction toxicity studies and the standard battery of genotoxicity studies should be completed before any women who are of childbearing potential and who are not using effective birth control, of whose pregnancy status is unknown, are enrolled in clinical studies."

h) LD 50 and Other Animal Testing

Additionally, accomplishments have been made in the area of animal testing. A test known as Lethal Dose 50 has been abolished. This test, which was used to determine the lethal dose of new drugs, involved administering increasing dose of the drug to dogs and rodents until half of them died. They resolved to stop requiring twelve-month toxicity studies involving dogs and rodents. Instead the studies will last for 6 months. These arrangements are expected to save the lives of thousands of animals in addition to saving a great deal of money.

i) Guideline for Safety Pharmacology Studies

In November 2000, an ICH guideline pertaining to safety pharmacology studies reached step 4 of the ICH process. While this guideline has not yet been adopted in the United States and Japan, it has already been adopted in the EU. This guideline provides a general direction concerning which studies are necessary prior to the initiation of a Phase 1 study, which typically include safety pharmacology studies identified in the safety pharmacology core battery.

2. Evaluation of Pharmaceutical Harmonization

While some commentators have been less than optimistic regarding the movement toward global pharmaceutical harmonization, noting that several factors serve as obstacles to the goal, there have been some strong indications of progress resulting from the ICH initiative (see ICH Accomplishments discussed above). It has succeeded in arriving at agreements on topics "such as carcinogenicity testing, statistical principles in clinical trials, viral safety evaluation of biotechnology products, testing of impurities in new drug products, the duration of chronic-toxicity testing in animals, data elements needed for individual case reports of adverse events, and non-clinical safety studies necessary to support the conduct of human clinical trials." Each of these topics had previously been controversial and dealt with differently in each of the three ICH regions. The Development of the CTD in particular is a grand achievement. One of the primary objectives of the ICH "was to remove redundancy and duplication in the development and review process so that a single set of data could be generated to demonstrate the quality, safety, and efficacy of each new medicinal product." This objective is becoming a reality with the development and adoption of the CTD.

Moreover, the ICH has had a huge impact on Japan's drug approval process. Through its willingness to implement ICH developed standards and guidelines affecting both clinical and non-clinical data, Japan has evolved considerably "from an idiosyncratic system unique to Japan" to a process that is more consistent with the U.S. and E.U. market.

In fact, the impact that the ICH has had on pharmaceutical harmonization in the three regions has led one commentator to remark that "the days of confusion are over; the ever-changing local regulations are rapidly coming to an end."

However, as previously noted, there are considerable barriers to complete pharmaceutical harmonization. Health Policy is inextricably connected with cultural and societal values and as such has always been the focus of intense politicization by regional and national governments. With this in mind, it seems likely that the individual countries will maintain ultimate veto power with regard to approval of a single drug or drug product.

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

Table 1. Members and Observers

Members	Observers
Founding Regulatory Members	**Standing Observers**
EC, Europe FDA, US MHLW/PMDA, Japan	IFPMA WHO
Founding Industry Members	**Legislative or Administrative Authorities**
EFPIA JPMA PhRMA	CDSCO, India CECMED, Cuba COFEPRIS, Mexico INVIMA, Colombia MCC, South Africa National Center, Kazakhstan Roszdraynadzor, Russia TFDA, Chinese Taipei TGA, Australia
Standing Regulatory Members	**Regional Harmonisation Initiatives**
Health Canada, Canada Swiss medic, Switzerland	APEC ASEAN EAC GHC PANDRH SADC
Regulatory Members	**International Pharmaceutical Industry Organisation**
ANVISA, Brazil CFDA, China HAS, Singapore MFDS, Republic of Korea	APIC
Industry Members	**International Organisation regulated or affected by ICH**
BIO IGBA WSMI	Bill & Melinda Gates Foundation CIOMS EDQM IPEC PIC/S USP

Figure 1. ICH Organisation

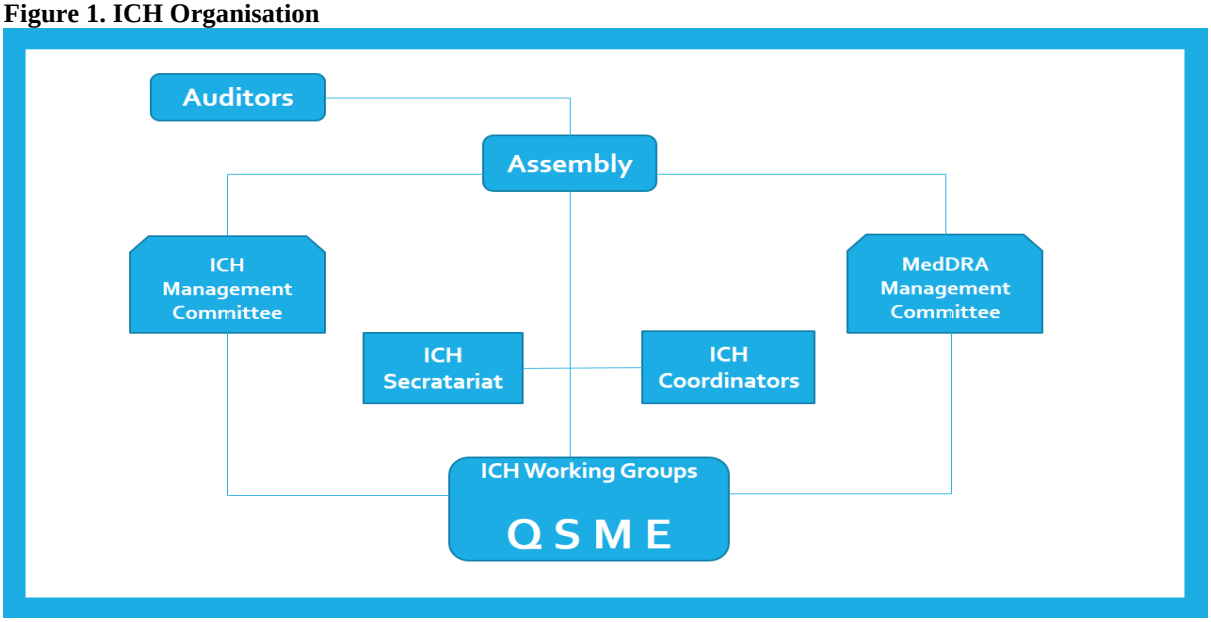
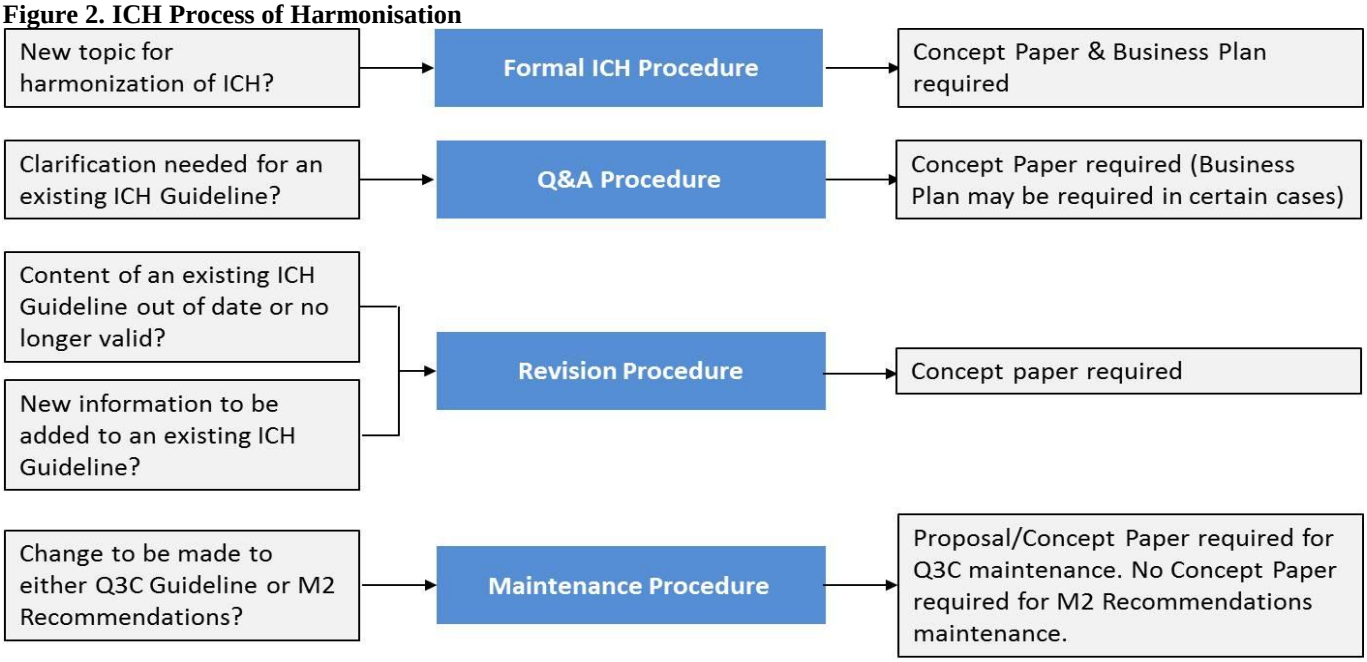


Figure 2. ICH Process of Harmonisation



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.

CONCLUSION

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. Harmonization of the technical regulations for drug approval in the United States, Europe, and Japan is a worthy goal. The United States, the EU, and Japan each regulate pharmaceuticals for the welfare of their citizens. However, each country advocates its own system of laws controlling production and testing of pharmaceuticals. Differences in the national regulations generate costs for drug manufacturers and ultimately for consumers. Moreover, they lead to delays in the worldwide introduction of new drugs. The International Conference on Harmonization has been a significant effort in eliminating the problems of unnecessary costs and delays in drug approval.

With the successful completion of the first phase of activity behind them, the ICH will move into the second phase with the continuing commitment to increased international harmonization. Due to the success of the initiative thus far, more interest has been generated in the initiative from regulatory and industry bodies outside of the U.S., the EU, and Japan. It will therefore be increasingly important to make certain that the goals and outcomes of the ICH are comprehensible and more widely disseminated.

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