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STRUCTURE OF ICH AND ITS SPECIFIC GUIDELINES FOR PRODUCING HIGH STANDARD OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

The aim of this review article is to highlight the various regulatory authorities which are concerned to form rules and regularize the product related issues during manufacturing of quality products. Harmonization process was initiated after tragedy of thalidomide in Europe in the 1960s. Harmonization of regulatory requirements was started by the European Community (EC), in the 1980s. As the EC (now the European Union) moved towards the development of a single market for pharmaceuticals, there was a bilateral discussion between Europe, Japan and U.S. on possibilities of harmonization of regulations for pharmaceuticals in 1984. ICH observed significant progress in various categories like quality guidelines, safety guidelines, efficacy guidelines, stability studies, clinical trials and dissolution studies.

***Key words**: European Union, Clinical trials, Harmonization, Quality management.*

Introduction

ICH is a unique project that brings together the regulatory authorities of Europe, Japan and United States and experts from the pharmaceutical industry in these regions to discuss scientific and technical aspects of product registration. It was developed to fulfill the objectives like harmonization of disparate objectives and needs of different regions, cultures and languages; negotiation and alignment of all the participating entities towards common goals; and obtaining the commitment to implement the agreed upon standards of drugs[1].

Initiation of ICH

Harmonization of regulatory requirements was first brought about by the European Community in 1980. In 1989, the meeting was held to think over the need of harmonization in Paris in ICDRA (International conference of drug regulatory Authorities). In 1990 the birth of ICH took place at a meeting hosted by the European federation of pharmaceutical industries and associations (EFPIA) in Brussels. In this meeting regulatory bodies of Europe, Japan and U.S. discussed a joint regulatory initiative on the international harmonization of drugs. In this meeting an ICH Steering Committee (SC) was established, which meets regularly at least twice a year at the locations rotating between Europe, Japan and U.S[1].

At the first SC meeting of ICH the three topics were selected for harmonization namely safety, quality and efficacy of drugs and pharmaceuticals. These three categories were selected as the basis for approving and authorizing new medicinal products. It was also agreed that the expert working groups should be set up to discuss scientific and technical aspects of each harmonization topic[1].

Structure of ICH

ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and asses the safety, quality and efficacy of medicines. The focus of ICH is on the technical requirements for medicinal products containing new drugs. The organization of ICH involves a steering committee that appoints MedDRA Management Board. The Global Cooperation Group (GCG) was originally formed as a subcommittee of the ICH Steering Committee in 1999. The details of ICH organization is as follows:

Steering committee

The ICH Steering Committee (SC) is the governing body that oversees the harmonization activities. Since its establishment in 1990, each of its six co-sponsors (EU, EFPIA, MHLW, JPMA, FDA, PhRMA) had two seats on the SC. Other parties have a significant interest in ICH and have been invited to nominate observers to the SC. The three observers are the World Health Organization (WHO), Health Canada and the European Free Trade Association (EFTA). The International Federation of Pharmaceutical Manufacturers association (IFPMA) participates as a non-voting member of the SC[2].

Global Cooperation Group

The Global Cooperation Group (GCG) was originally formed as a subcommittee of the ICH Steering Committee in 1999. A few years later, representatives from five Regional

Harmonization Initiatives (RHIs) were invited to participate in GCG discussions, namely, APEC, ASEAN, EAC, GCC, PANDRH and SADC. A further expansion of the GCG was agreed in 2007 and regulators were invited from countries with a history of ICH Guideline implementation (Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore)[3].

MedDRA Management Board

The MedDRA (Medical dictionary for regulatory activities) Management Board, appointed by the ICH Steering Committee, has overall responsibility for direction of MedDRA, an ICH standardized dictionary of medical terminology. The Board oversees the activities of the MedDRA "Maintenance and Support Services Organisation" (MSSO), which serves as the repository, maintainer, developer and distributor of MedDRA. The Management Board is composed of the six ICH Parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, the Health Canada and the WHO (as Observer). The IFPMA acts as a non-voting observer on the Management Board and chairs the Board[4].

Secretariat

The ICH Secretariat is located in Geneva, Switzerland. Its staff members are responsible for day-to-day management of ICH, namely preparations and documentation of meetings of the Steering Committee and its Working Groups. The ICH Secretariat also provides administrative support for the ICH Global Cooperation activities and the ICH MedDRA Management Board[5].

Coordinators

ICH Coordinators act as the main contact point with the ICH Secretariat. Coordinators ensure proper distribution of ICH documents to the appropriate persons from their party (SC members, Topic Leaders, Experts) and are responsible for proper follow up on actions by their respective party within assigned deadlines[6].

Working Groups

SC appointed a Working Group to review the differences in requirements between the three regions and develop scientific consensus required to reconcile those differences. Working groups do not have a fixed "membership but each of the six parties have nominated a Topic Leader (and, frequently, a Deputy Topic Leader) as the contact for the topic. There are several different types of ICH working groups' like[7]:

- 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 to develop Q&A's 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.

Sponsors of ICH[1,2]

There are six founder members of ICH which represent the regulatory bodies and research based industry in the Europe, Japan and USA.

European Union (EU)

It is also called European commission having 25 members. This commission is working through ICH to achieve a single market in pharmaceuticals which would allow free movement of products throughout Europe.

European Medicines Agency (EMEA)

It is a body of EU having its head quarters at London. It has a secretariat of 360 members. Its main responsibility is the protection and promotion of human and animal health through the evaluation and supervision of medicines for human and veterinary use throughout Europe.

European Federation of Pharmaceutical Industries and Association (EFPIA)

It represents the research based pharmaceutical industry operating in Europe. It was established in 1978 in Brussels. Its member comprises of 29 national pharmaceutical company associations and 43 leading pharmaceutical companies involved in research, development and manufacture of medicinal products in Europe. The mission is to promote pharmaceutical research and development and provide best conditions for companies to bring high quality medicines in the market. Its other goal is to maintain high standards of intellectual property protection in Europe.

Japan Pharmaceutical Manufacturers Association (JPMA)

JPMA is a voluntary organization of research based pharmaceutical manufacturers of Japan that contribute to society by developing new and improved pharmaceuticals. It has 90 members. Its major aim is to develop a competitive pharmaceutical industry with great awareness and understanding of international issues. It promotes and encourages the adoption of international standards by its member countries.

United States Food and Drug Administration (USFDA)

USFDA is the world's largest drug regulatory agencies that are responsible for the approval of all drug products used in USA. It has wide range of responsibilities for drugs, biologicals, medical devices, cosmetics and radiological products. FDA consists of administrative, scientific and regulatory staff organized under the office of the commission of FDA. FDA grew from the department of agriculture in 1862 in USA then an act was passed in 1906 naming federal food and drugs act in July 1930, this act was renamed and termed as U.S. food and drug administration. At present USFDA has become the largest scientific, regulatory and public health agency.

Ministry of Health Labour Welfare (MHLW)

MHLW is a regulatory agency for approval of drugs, cosmetics and medical devices in Japan. The technical and scientific support for activities of MHLW is provided by National Institute of Health Services (NIHS). NIHS was established in Tokyo in 1874 having initially the name as Tokyo Drug Control Laboratory (TDCL). This name was changed in 1880 to NIHS. NIHS is the oldest health research institute in Japan. It has 18 divisions and 5 experimental stations for medicinal plants. The experimental stations are located at Hokkaido, Tsukuba, Izu, Wakayama

and Tanegashima. These 5 stations provide a wide range of climatic conditions from freezing zone to subtropical zone for research related to growth of medicinal plants.

Pharmaceutical Research and Manufactures of America (PhRMA)

PhRMA represents the research based industry in USA. It represents the leading pharmaceutical research and biotechnology companies of USA that are devoted to invent the medicines allowing the patients to live longer, healthier and more productive lives. PhRMA has 67 companies as its members, which are involved in the discovery, development, and manufacture of drugs. Till date it has invested more than 60 billions dollars for discovering new drugs. PhRMA has 24 allied research affiliated centers which conduct biological research related to the development of drugs.

Observers of ICH[1,2,3]

There are four observers of ICH:

World Health Organization (WHO)

WHO is the United Nations specialized agency for health. It was established on 7th April 1948. Its objective is the attainment of the highest possible level of health by all persons. According to WHO constitutions, health is defined as a state of complete physical, mental and social well being and not merely absence of disease. WHO is governed by 192 members sates through the world health assembly. The world heath assembly is composed of representatives from WHO member's states. The major task of world health assembly is to approve the WHO programme and budget for each year as well as to decide the main policies of the year.

The European Free Trade Area (EFTA)

EFTA is the supervisory authority of Switzerland for therapeutic products. It is a public service organization of the federal government with headquarters at Bern. EFTA has a council called FDHA (Federal Department of Home Affairs). This council approves the annual budget, annual accounts and annual report of EFTA. The principles of EFTA include protection of human and animal health. It strives to ensure that medicines and medical devices in Switzerland are effective and safe. Thus it makes an important contribution to the quality of health care system. It thoroughly checks the therapeutic products, promptly identifies new risks and rapidly takes safety measures. It also informs appropriate professionals as well as general public about specific issues and new discoveries in the therapeutic product sector.

Health Canada

Health Canada is a federal department responsible for helping the people of Canada to maintain and improve their health. In partnership with provincial and territorial governments, Health Canada provides national leadership to develop health policy, enforce health regulations, promote disease prevention and enhance healthy living for all Canadians. According to Health Canada individual health is affected by various factors like family history, social and financial status, physical environment and personal life style. Hence general public should be made aware of these factors to promote health standards.

International Federation of Pharmaceutical Manufacturers association (IFPMA)

IFPMA is a federation of members associated with pharmaceutical industry. It includes 56 member countries throughout the world. IFPMA is non government, on profit organization

representing the national industry associations and companies from both developed and developing countries. The member companies associated with IFPMA are research based pharmaceutical, biotech as well as vaccine companies. At present IFPMA is working on 700 new medicines and vaccines for disease including HIV-AIDS, cancer, heart diseases, stroke, osteoporosis etc. The main objective of IFPMA is to encourage a global policy environment that is helpful in encouraging innovation in medicines for the benefit of patient around the world.

Process of ICH Harmonization

The 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. The EWG works to develop a draft Guideline for implementation in the ICH regions[8].

The harmonization is conducted in five steps[1,8,9]:

Step 1: Consensus building

The EWG works to prepare a consensus draft of the technical document, based on the objectives set out in the Concept Paper. Work is conducted via e-mail, teleconferences and web conferences. If endorsed by the SC, the EWG will also meet face-to-face at the biannual SC meetings. Interim reports on the progress of the draft are made to the SC on a regular basis. When consensus on the draft is reached among all six party EWG members, the EWG will sign the *Step 1* Experts sign-off sheet. The *Step 1* Experts Technical Document with EWG signatures is then submitted to the Steering Committee to request adoption under *Step 2* of the ICH process.

Step 2:

a) Confirmation of six-party consensus on the Technical Document

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

b) Adoption of draft guideline by Regulatory Parties

On the basis of the Technical Document, the three ICH regulatory parties will take the actions necessary to develop 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 three regions. In the EU it is published as a draft CHMP Guideline, in Japan it is translated and issued by MHLW for internal and external consultation and in the USA it is published as draft guidance in the Federal Register. Regulatory authorities and industry associations in non-ICH regions may also comment on the draft consultation documents by providing their comments to the ICH Secretariat.

Stage II: Discussion of regional consultation comments

After obtaining all comments from the consultation process, the EWG works to address the comments received and reach consensus to obtain 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 three ICH regulatory parties. The *Step 3* Expert Draft Guideline with regulatory EWG signatures is submitted to the Steering Committee to request adoption as *Step 4* of the ICH process.

Step 4: Adoption of an ICH Harmonized Tripartite Guideline

Step 4 is reached when the Steering Committee agrees that there is sufficient consensus on the draft Guideline. The Step 4 Final Document is signed-off by the SC signatories for the regulatory parties of ICH as an ICH Harmonized Tripartite Guideline at Step 4 of the ICH process.

Step 5: Implementation

The harmonized tripartite guideline moves immediately to the final step of the process for the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the European Union, Japan and the USA.

ICH guidelines

The objective of ICH guidelines is to provide principles regarding manufacturer of active ingredients under as appropriate system for managing the quality. ICH guidelines are related to all APIs that are being manufactured by chemical synthesis, extraction, cell culture, fermentation or by recovery from natural sources. ICH guidelines have following major points[10, 11, 12, 13, 14]:

Quality management

Quality is the responsibility of all persons involved in manufacturing. There should be quality unit in each industry that is independent of the production unit and performs all the quality control functions like Approving or rejecting the APIs, Approving or rejecting raw materials and intermediates, Approving or rejecting the packaging and labeling materials, Establishing laboratory control records, Making sure that critical deviations from the permitted limit are investigated and resolved, Ensuring that effective systems are used for maintaining and calibrating critical equipments, Reviewing and approving validation protocols and reports.

Effective production management

The production unit has to perform several major functions like producing APIs according to the preapproved procedures, reviewing all production batch records, ensuring the production equipments and premises are effectively managed, and performing the necessary calibration of equipments.

Personnel management

Personnel should be adequate in numbers and well qualified; they should be properly trained by experts and should practice good sanitation and health habits. Smoking, eating, drinking, chewing and storage of food should be restricted in the manufacturing areas. Personnel suffering

from an infectious disease or having wound on body surface should be excluded from production department.

Building and facilities

▪ Building should have adequate space for orderly placement of equipments and materials, so as to prevent mix-ups and contamination. There should be separate, well defined areas for the activities like receipt, identification and sampling of raw materials, store of APIs and store for rejected materials, production operation unit, packaging and labeling area.
▪ Adequate cleaning or wash rooms should be provided for personnels that should be equipped with hot and cold water, soap and detergent, air driers and single service towels.
▪ Adequate ventilation, air filtration and exhaust system should be provided. Appropriate drainage facilities should be available in the manufacturing area.
▪ Proper lighting should be available to facilitate proper manufacturing operations.

Process equipments

Equipment used in manufacture of APIs should be of appropriate design and adequate size. Equipment should be constructed so that surface in contact to API should not alter the quality of API beyond the official specifications. Any substance associated with the operations of equipment such as lubricants, heating fluids or coolants should not react with APIs; instrument should be carefully calibrated. Equipments and utensils should be cleaned, stored, sanitized and sterilized to prevent contamination of APIs.

Documentation and records

All documents related to manufacture of APIs should be prepared, reviewed, approved and distributed according to written procedures. Following records must be maintained and reviewed from time to time:
Raw material records:

It includes list of raw materials brought, name of manufacturers, quantity of each batch of raw materials purchased along with batch no. and date of receipt.
Master production records:

It includes name of APIs being manufactured, the raw materials used for their preparation, sequence of steps involved in process of preparation, percentage yield and special precautions to be followed during manufacture of APIs.
Laboratory control records:

It includes the list of samples received for testing with its batch no., name and reference of test method, quantity of sample used for test and a complete record of all data generated during the test. It should also state how does test sample complies with established acceptance criteria; date and signature of the persons involved in test should be recorded.

Packaging and labeling

Container used for packaging should provide adequate protection against degradation or contamination of APIs. Containers should be cleaned and sanitized before use. The container should not be reactive or absorptive so as to alter the quality of APIs beyond the specified limits.

Labeling of containers should be as per official specifications, access to the label storage areas should be limited to the authorized personnels only, all excess labels bearing batch numbers should be destroyed to prevent confusion, labels should clearly indicate the product name, chemical specifications, use batch no, manufacturing and expiry date, special precautions if exists and storage conditions.

Rejection and reprocessing of materials

- APIs failing to meet the established official specifications should be identified and checked whether they can be reprocessed or not; if they can't be reprocessed they should be destroyed.
- On the other hand if APIs failing the official test can be reprocessed, they are separately reprocessed by crystallization, distillation, filtration, chromatography or milling. Any of the above methods can be used to bring the rejected API back into process.
- Solvents should be recovered even after using them by means of distillation steps until they become similar in quality to fresh solvents.
- Use of recovered solvents and other recovered materials should be adequately documented.

Guidelines for clinical trials

The major ICH guidelines for clinical trials are[11,12, 15]:

- Clinical trials should be conducted in accordance with the ethical principles. Before initiating clinical trial, its risks and inconveniences should be weighed against the anticipated benefits. A trial should be conducted only if benefits justify the risks.
- The rights, safety and well being of trail subjects are the most important considerations and should prevail over interests of science and society. The available clinical as well as non clinical information about the investigational product should be adequate to support the proposed clinical trial.
- The trial should be described in a clear detail protocol that is approved by IRB (Institutional Review Board) and IEC (Independent Ethics Committee). Each individual involved in conducting a trial should be provided proper training to perform his respective tasks.
- Freely given informed consent should be obtained from every subject. All clinical trial information should be properly recorded, reported, interpreted and verified. As per the privacy and confidentiality rules the identity of trial subjects should be kept secret.

Guidelines for stability testing

To assure that optimally stable molecules and products are manufactured, distributed and given to the patients, the regulatory authorities in several countries have made provisions in drug regulations for the submission of stability data by the manufacturers. Its basic purpose was to bring uniformity in testing from manufacturer to manufacturer. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for their execution. The codes and titles covered under ICH guidance can be depicted as[16]:

Q1A: Stability testing of new drug substances and products (Second Revision)
Q1B: Photo stability testing of new drug substances and products
Q1C: Stability testing of new dosage forms
Q1D: Bracketing and matrix designs for stability testing of drug substances and products
Q1E: Evaluation of stability data
Q1F: Stability data package for registration applications in climatic zones III and IV
Q5C: Stability testing of biotechnological/biological products

For conducting stability testing successfully, the whole world has been classified into four zones (I - IV) based upon the environmental conditions during the storage of pharmaceutical products. These conditions have been derived on the basis of the mean annual temperature and relative humidity data in these regions. Based upon this data, long-term or real-time stability testing conditions and accelerated stability testing conditions have been derived. The standard climatic zones for use in stability studies of pharmaceutical product have been categorized in **Table 1**.

ICH guideline defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within three regions of EC, Japan and United states. The purpose of stability testing is to provide evidence on how the quality of a drug varies with time under the influence of a variety of environmental factors like temperature, humidity and light. The choice of test conditions defined in ICH guidelines is based on the analysis of the effect of climatic conditions in Europe, Japan and United States. Following are its main steps[16,17]:

- Stability studies should be conducted on the drug packaged in a container that is same as the packaging proposed for distribution and storage of the product.
- Stability studies should include the physical, chemical and biological attributes of drug. Data from stability studies should be provided on at least three batches of the drug product.
- The batches should be of same formulation and packaged in the same container.
- Stability studies should be performed on every strength of the drug.

Stability studies can be of two types:
Long term studies: The frequency of testing for long term storage conditions is every 3 months over the first year, every 6 months over second year and annually thereafter through the proposed life cycle.

Accelerated studies: Under accelerated storage conditions, a 6 months total study is recommended and frequency should be at 0, 3 and 6 months.

The storage temperature and relative humidity (RH) for stability studies is as follows:
▪ General case: Long term temperature $25^0C\pm2^0C$ and RH 60%±5% and for accelerated case temperature $40^0C\pm2^0C$ and RH 75%±5%.
▪ Drug substances intended to be stored in refrigerator: Long term temperature $5^0C\pm3^0C$ for accelerated $25^0\pm2^0C$ and RH 60%±5%.
▪ Drug substance intended to be stored in freezer: Long term temperature ($-20^0C\pm5^0C$).
▪ Product is supposed to be passed if it shows not more than 5% change in its assay than the initial value and it doesn't show not more than 5% change in its physical parameters and biological activity.
The test schedule for stability testing of a new product has been presented in **Table 2.** The stability test protocol should define the test parameters that would be used for evaluation of the stability samples. The test that monitors the quality, purity, potency, and
identity is chosen as stability test. Therefore appearance, assay, degradation products, microbiological testing, dissolution, and moisture are standard tests performed on stability test samples. Microbiological tests include sterility, preservative efficacy and microbial count as

applicable e.g. for liquid injectable preparations. The batches used for stability study must meet all the testing requirements including heavy metals, residue on ignition, residual solvents etc[17,18]. Stability is measured in equipment called stability chamber. These are specialized environmental chambers that can simulate the storage condition and enable evaluation of product stability based on real-time, accelerated and long-term protocols. They are available in both walk-in and reach-in styles. Smaller chambers are used for accelerated testing, as the retention time of products is much less in these cabinets, while long-term testing is performed in walk-in chambers. In addition, Photostability chambers are also available and utilized both with and without temperature and humidity control. Two types of light sources are usually employed in Photostability chambers, one is the combination of cool white and near UV fluorescent tubes, while second are the artificial daylight lamps, e.g., xenon or metal halide[17,18].

ICH guidelines for dissolution studies

The dissolution test is required for various dosage forms for product release testing. It is also used as a predictor of the *in- vivo* performance of a drug product. The USP and FDA also provide guidelines on development and validation of dissolution procedures (USP 32-NF 27, 2009; ICH guideline, 2005; Guidance for Industry 1997, 2000). In vitro dissolution data, together with bioavailability and chemistry, manufacturing and control data, is a critical component of any new drug application (NDA) submitted to the FDA. A dissolution test is really a simple concept; a tablet or capsule is placed into a known volume of media and as it dissolves the resulting solution is sampled over time, and assayed (often by HPLC or by spectrophotometry) for the level of active pharmaceutical ingredient (API) present. However, the design, development, and the validation of the procedure are critical[19].

The dissolution procedure has several distinct components**.** These components include a dissolution medium, an apparatus, the study design (including acceptance criteria) and the mode of assay. All of these components must be properly chosen and developed to provide a method that is reproducible for within laboratory day-to-day operation and robust enough to enable transfer to another laboratory[19].

The USP dissolution apparatus are of seven types ranging from Type I to Type VII **(Table 3).** Physical and chemical data for the drug substance and drug product should be considered while selecting the dissolution medium, e.g. the solubility and solution state, and stability of the drug as a function of pH value. Other critical drug product properties include the release mechanism (immediate, delayed or modified) and disintegration rate as affected by formulation hardness, friability, and presence of solubility enhancers[19,20].

When selecting the composition of the medium; the influence of buffers, molarity, pH, and surfactants on the solubility and stability of the drug also need to be evaluated. The most common dissolution medium is dilute hydrochloric acid, however other media commonly used includes buffers in the physiologic pH of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water and surfactants such as polysorbate 80, sodium lauryl sulfate and bile salts. The volume of dissolution medium in the dissolution studies should be ranging from 500-1000 ml. It had been historically 900 ml, but with nowadays apparatus, it can be now 1000 ml. The pH of dissolution medium can be in the range 1-8. Use of pH value other than this range must be properly justified. Two types of standard apparatus namely rotating basket and paddle

type can be used for dissolution studies. The temperature of dissolution medium should be 37 ± 0.5^0C for oral dosage form, 32 ± 0.5^0C for transdermal drug delivery system and 38 ± 0.5^0C for rectal system. The choice of dissolution apparatus for a particular dosage form is based on the dosage form performance in the *in- vitro* test system[19,20] **(Table 4).**

Dissolution is evaluated by measuring rate release profile or the amount dissolved over time. Single or multiple points in time can be measured, depending upon the dosage type or data desired. There are two common ways of analyzing dissolution test samples, spectrophotometric (UV) determinations and HPLC. Typically the drug substance UV spectrum is observed to choose the optimum wavelength for analysis. Cells with path lengths ranging from 0.02 to 1 cm are used. HPLC methods, however, have distinct advantages, particularly when there is significant interference from excipients or between multiple active ingredients in the formulation. It also requires less sample volume[20,21].

Conclusion

ICH guidelines help to achieve greater harmonization in the interpretation and application of technical guidelines for the registration of new active substances or products obtained by biotechnology; to improve the efficiency of global drug development; to reduce redundant studies; and to improve pharmaco-vigilance activities and quality assurance. Moreover it is looking to make available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States. Regulatory harmonization offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimizing the use of animal testing without compromising safety and effectiveness. 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.

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Table 1: ICH Climatic zones and long term stability conditions

Climatic Zone	Climate/ Definition	Major Countries /Region	Long-term testing conditions
I	Temperate	United Kingdom Northern Europe Russia United states	21°C/45%RH
II	Subtropical and Mediterranean	Japan Southern Europe	25°C/60%RH
III	Hot and Dry	Iraq India	30°C/35%RH
IVa	Hot and humid	Iran Egypt	30°C/65%RH
IVb	Hot and very humid	Brazil Singapore	30°C/75%RH

Table 2: Test Schedule for stability testing of new products

Environment	Sampling time points (months)	Method and climatic zone
25°C/60% RH	3, 6, 9, 12, 18, 24,36	Long term for zones I and IV
30°C/35% RH	3, 6, 9, 12, 18, 24,36	Long term for zones III
30°C/65% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IVa, or intermediate condition for zones I and II
30°C/75% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IVa, or intermediate condition for zones I and II
40°C/75% RH	3, 6	Accelerated condition for all zones

Table 3: USP Dissolution Apparatus

Type of Apparatus	**Name of apparatus**
Type I	Basket apparatus
Type II	Paddle apparatus
Type III	Reciprocating cylinder
Type IV	Flow through cell apparatus
Type V	Paddle over disk
Type VI	Cylinder
Type VII	Reciprocating holder

Table 4: Selection of dissolution apparatus

S. No.	**Dosage form**	**Apparatus**
1	Solid dosage form, chewable tablets	Type I apparatus Type II apparatus
2	Bead type modified release dosage form	Type III apparatus
3	Modified release dosage form that contain active ingredients with limited solubility	Type IV apparatus
4	Soft gelatin capsules, suppositories, poorly soluble drugs, implants	Type III & IV apparatus
5	Transdermal dosage form	Type V & Type VI apparatus
6	Non-disintegrating oral modified dosage form	Type VII apparatus