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REVIEW ON ICH GUIDELINES

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ABSTRACT

The international conference on harmonization (ICH) guidelines provides a comprehensive framework for the development, registration, and post-marketing surveillance of pharmaceuticals. These guidelines aim to enhance efficiency in the drug development process while ensuring the safety, quality, and efficacy of medicines. It covers various aspects such as clinical trials, quality assurance, and pharmacovigilance, ICH facilitates the harmonization of regulatory requirements across member regions, including the European union, Japan, and the United States. By promoting international standards, ICH guidelines contribute to the globalization of pharmaceutical research and development, ultimately improving public health outcomes.

Key words

Harmonization, Pharmaceutical development, Clinical Trials, Quality assurance, Pharmacovigilance, Regulatory Requirements, Safety, Efficacy, Global standards, Public Health, Drug registration, post-marketing surveillance, Research and development, Member regions.

INTRODUCTION

A cooperative effort that was started in 1990 and involved representatives from the European Union, Japan, and the United States' research-based industry as well as regulatory bodies in scientific discussions of the testing methods needed to evaluate and guarantee the safety, effectiveness, and quality of medications. It also aimed to increase the efficiency of the process for creating

1. A more cost-effective use of human, animal, and material resources.

2. Get rid of needless delays in the development and accessibility of new medications worldwide.

3. Upholding legal requirements to preserve public health and safeguards on quality, safety, and efficacy.

4. Create a policy for the ICH medical lexicon for regulatory activities terminology (MedRA), which makes it easier to share regulatory data about human pharmaceuticals globally.

5. To promote the adoption and integration of common standards by means of cooperation and information exchange

PURPOSE OF ICH GUIDELINES

scientific and technical aspects of drug registration should be discussed by regulatory organizations. Due to the disparities in technical standards between nations, medication manufacturers had to invest a significant amount of time and resources in replicating test techniques in order to market their medicines internationally as the pharmaceutical business became increasingly globalized. It began to become crucial to provide patients worldwide with safe and effective medications without the delays brought on by regulations and restrictions that do not match across national regulatory bodies. Because of this, there was a need to rationalize and harmonize drug rules, which led to the creation of ICH in 1990.

PURPOSE OF ICH MAY BE SUMMERIZE AS FOLLOWING

1. Ensuringthe effectiveness, safety, and quality of medications.

2. Harmonizing the technical standards for drugs.

3. Steer clear of repeating human clinical trials.

4. Cut back on animal experimentation without sacrificing the validity and safety of medication evaluation

PARTICIPANTS OF ICH

The six parties to ICH represent the regulatory bodies and research -based industry in the three region -Europe Japan and USA where the vast majority of new medicines are currently developed

The six participants are as follows

1.The European Union Commission

2. Federation of Pharmaceutical Associations and Industries in Europe

3. The Japanese Ministry of Health, Labor, and Welfare

4. Japanese Pharmaceutical Manufacturers Association

5. The American Food and Drug Administration

6. American pharmaceutical research and manufactures

ORGANISATION OF ICH STEERING COMMITTEE

Figure :01

ICH steering committee - Is in charge of establishing the rules and regulations, after which the ICH chooses the subjects for harmonization and keeps track of the initiative's development. There are two seats on the ICH steering committee for each of the six parties.

ICH Secretariat -In this regard, it follows mainly the organization programs of the Steering Committee meetings and prepares the related documentation in addition to coordinating the preparations for meetings of working groups and discussion groups. There is also information on the ICH guidelines and the ICH process which is available from the ICH Secretariat.

ICH Coordinators - Each of the six parties has appointed ICH coordinators who serve as main points of contact with the ICH secretariat. Therefore, they are crucial to the efficient operation of the ICH.

ICH Working Group - The steering committee, depending on how intensive the harmonization activity is needed, will approve the formation of one among three kinds of working group expert working group (EWG) implementation working group (IWG) or informal working group)

Expert working group - The intended outcome from this task is the formulation of a harmonized guideline that satisfies the requirements as presented in the concept paper and the business plan.

Implementation working group: - Develops questions and answers to facilitate

Informal working group: - Constructing or completing a concept paper, likewise the crafting of a business plan is in the offing

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ICH works via the ICH steering committee supported by ICH secretariat and ICH coordinators.

The ICH Steering Committee usually meets two times in a year. In these conferences new topics for consideration and adoption are put forward, progress of ongoing topics is reported on, and care and execution of the guidelines are deliberated on.

PROCESS OF HARMONIZATION

Every activity pertaining to the harmonization is started by a concept paper, which refers to a brief synopsis of the idea put forth. Depending on the category of harmonization activity, a business plan may also be included in the proposal. The business plan outlines costs and benefits related to harmonization of the topic contained in the concept paper.

The procedure is followed for the harmonization of all ICH topics. It consists of 5 Steps.

Step 1 - Consensus building

The EWG helps prepare the latter by designing a consensus attitude draft of the technical document through e-mails, webcasts etc. Upon confirmation by the ICH management committee, EWG will arrange a meeting to discuss the prepared agenda draft. Once the EWG has come to an understanding, this is done and circulated to the steering committee.

Step 2-confirmation of consensus on the technical document and adoption of draft guideline by regulatory members

The steering committee reviews the technical document and hereby endorses it in view of the findings of the EWG. The ICH regulatory members will take all necessary actions to prepare a draft guideline after proceeding from the technical document. Upon completion, the regulatory members will announce that the draft guideline has been adopted.

Step 3 – Regulatory consultation

Step 3 occurs in three distinct stages: -

Regional regulatory consultation: - The regulatory authorities and industry associations in other regions can may also comment on the draft guideline to the ICH secretariat.

Discussion of the expert draft guideline: - The EWG works to address the comments received and prepares the experts draft guideline.

Finalization of the Experts draft guideline: - Expert draft guideline is signed by the ICH regulatory members then forwarded to the steering Committee to request adoption of the ICH process.

Step 4 – Adoption of an ICH harmonized guideline

The steering committee agrees to the expert daft guideline if there is sufficient agreement on the guideline. And then declared as the ICH harmonized guideline.

Step 5 – Implementation of the ICH harmonized guideline

The harmonized guideline proceeds directly to the final objective of the process regulatory implementation. The step is performed as per the national or regional procedures within the ICH regions.

BRIEF OVERVIEW OF QSEM GUIDELINES

The ICH guidelines are divided into the following four categories: -

1.quality guidelines (Q series)

2.Safety guidelines (S series)

3.efficacy guidelines (E series)

4.Multidisciplinary guidelines (M series)

QUALITY GUIDELINES (Q SERIES)

Quality guidance refers to the aspect of chemical and pharmaceutical quality assurance. Some of the milestones achieved in the harmonization of the quality area include performing stabilitystudies, establishing thresholds for testing impurities, and a more risk-based and less rigid approach of pharmacological quality grounded on GMP principles.

SAFETY GUIDELINES (S SERIES)

Safety rules and regulations are those issues which encompass the broad range of safety rules in order to identify the possible risks within the in vitro and in vivo pre-clinical studies (such as carcinogenicity, genotoxicity etc. A new development was the evaluation of QT interval prolongation hazard assessment – one of the significant reasons for drug removals from the market.

EFFICACY GUIDELINES (E SERIES)

The Efficacy guidelines are the documents that are related to the clinical trials design, conduct, safety and reporting work which is performed by ICH as part of its harmonization efforts.

Additionally, it also comprises of medicines developed using biomolecular devices and the use of pharmacogenetics for optimizing medication.

MULTIDISCIPLINARY GUIDIELINES (M SERIES)

Multidisciplinary guidelines are issues which transcend disciplines and cannot be classified under quality, safety or efficacy. Medically, these include the ICH terminologies, CTD, and the frameworks developed in support of transfer of regulatory information using electronic means.

A DETAILED STUDY ON THE Q-SERIES GUIDELINES

Quality guidelines are mainly divided into 10 subdivisions: -

Q1 stability

Q2-Analytical Validation

Q3-Impurities

Q4-Pharmacopeias

Q5-Quality of biotechnological products

Q6-specifications

Q7-Good manufacturing practices

Q8-Pharmaceutical Development

Q9-Quality risk man

Q10-Pharmaceutical quality systems

Q11-Development and manufacture of drug substances

Q12-Technical and regulatory considerations for pharmaceutical product lifecycle management

Q13-continuous manufacturing of drug substances and drug products

Q14-Analytical procedure development

Q1A- Stability testing of new drugs substance and products

These instructions elaborate upon the fact that any new molecular entities and related drugs must accompany the registration application with appropriate evidence. The investigation of stability is intended to present justifications for the effects of ambient variables including temperature, light, and humidity on the quality of the active pharmaceutical ingredient and/or the drug product over a period of time and to provide a recommendation for a retest or shelf life, including optimally recommended storage conditions for the drug substance or drug product.

Guidelines

Drug substances

In order to inform on the stability issue associated with the active pharmaceutical ingredient, it is important to note, such considerations fit well within the holistic perspective on drug stability assessment.

Includes

Stress testing, Selection of batches, Container closure system Specification, Testing frequency Storage condition, Stability commitment, Evaluation, Statements/ labelling.

Drug products

The concept and the formal stability studies design for the drug product under development should be derived from the understanding of drug substance behaviour and properties, drug substance stability studies, as well as from the experience gathered during clinical formulation development. The anticipated changes during storage and the justification for the testing of certain attributes within the framework of the formal stability studies should be given.

Includes

Photo stability testing, Selection of batches, Container closure system Specification, Testing frequency Storage condition, Stability commitment, Evaluation, Statements /labelling.

The objective of this is to describe how Q1A(R) revision was affected by the incorporation of ICH Q1F stability data package in application for registration in climatic zones III and IV.

Q1B Stability testing

Photo stability testing of new drug substances and products

The ICH harmonized tripartite guideline on new drug substance and stability testing for products emphasizes the importance of light testing in stress testing. This document, an appendix to the parent guideline, discusses photostability evaluation guidelines and a longer cycle photostability test on a single batch of materials, in compliance with the parent guidelines.

Q1C Stability testing for new dosage form

The ICH Tripartite Guidelines on stability testing of new active substances and products, effective October 27, 1993, provide recommendations for owners of original applications regarding the stability of new dosage forms introduced after the original submission for new drugs and their formulations. These guidelines maintain a vertical level approach, including new dosage formulation stability protocols, but can accept a reduced stability database at submission time in specific situations.

Q 1D Bracketing and matrixing designs for stability testing of new drug substances and products

The guideline outlines the use of bracketing and matrixing in stability studies, following the ICH Q1A harmonized tripartite guideline on new drug substances and products. It provides recommendations for full study designs and reduced designs, with a reduced design being suitable for multiple design factors and retest period estimation. Geographical sites are also considered, and variations in the design should be examined and defended before consideration.

Bracketing

1.Tests multiple strengths or packages of a product, using a smaller number of samples.
2.Assumes that if the extremes (e.g., highest and lowest strength, largest and smallest package) are stable, intermediate strength/packages will also be stable.

3.Reduce testing requirements while maintaining confidence in product stability.

Matrixing

1.Tests a subset of samples, using a statistical design to minimize the number of samples.

2.Evaluates multiple factors (e.g., temperature, humidity, packaging) simultaneously.

3.Uses statistical analysis to predict stability of untested samples.

Q1E Evaluation of stability data

This guideline explains under which circumstances extrapolation may be applied to justify the recommended duration of re-assessment for drug substances or drug products that exceeds 'long-term storage condition information available from stability studies. External studies may determine the design and conduct of any official stabilization research performed outside the parent guideline values. The objective of the stability research is to create an appropriate retest or shelf-life period and storage standards for all subsequent production runs of the same batch produced and packed in identical conditions starting from the minimal three batches of drug substance or products provided. The variability between individual batches also influences the confidence that a future production batch will be within the acceptance criteria limits during its retest or shelf life.

Q2[R1] Validation of analytical procedures

Text and methodology

It contains the characteristics that should be addressed in regard to the validation of the analytical methods which are incorporated within the registration applications made within the EC, Japan, and USA. This document does not explicitly intend to include the criteria for the evaluation that may be necessary for registration in or importation to, any other regions of the world. Additionally, this presentation in text form is a glossary of concepts and concepts only,

without the intention of showing what techniques are used to perform validation. These terms and definitions are designed to overcome the gaps that usually exist between the various compendium and regulatory s of the EC, Japan and USA. The aim of the validation of any analytical procedure is to establish that it is fit for its intended use. A tabular summation of the characteristic applicable to identification, control of impurities and assay procedure is included. Other analytical procedure may be considered in future additions to this document.

Types of analytical procedures to be validated

The focus of analytical method validation is primarily on four types of analytical procedures

involved in identification tests; These include the following:

• Specific impurity quantitative analytical tests.

• Tests meant to ensure that impurities do not exceed a given limit.

• And specific component quantitative analysis of drug substance or drug product in a dosage form.

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristic which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
- Intermediate precision
- Specificity
- Detection limit
- Quantization limit
- Linearity
- Range

Q3A (R2) Impurities in new drug substances

This guidance is applicable to the registration application on the content and qualification of impurities related to any new drug substances synthesized chemically and not registered in the region or member state before all the chemical structures or drug formulations prepared by the chemical researchers in the very early stage of drug development. This particular guideline does not include the following types of drug substances. Biological/biotechnological, peptide oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived there from, plant-based synthetic products, animal and animal products.

Impurities in new drug substance are addressed from two perspective:

Chemistry aspects include classification and identification of impurities, report generation, listing of impurities in specification and a brief discussion of analytical procedure and safety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

lassification of impurities:

Impurities can be classified into the following:

- Organic impurities (process-and drug-related)

- Organic impurities
- Residual solvents

Reporting impurity content of batches

Analytical results must be included in the application for all clinical, safety and stability testing batches of new drug substance, plus those representing the proposed commercial process. Results could be quantitative and expressed in numbers or in broad terms like, "comply", "meet limits" etc. any impurities above (>) the reporting threshold (see attachment) and total impurities in the new drug substance for these batches should be mentioned with the analytical procedures that accompanied. Below 1.0% the results must be published in two decimal places (for instance, 0.06%, 0.13%); whereas at 1.0% or above, the results need to be reported in one decimal places (for instance, 1.3%). The results should be rounded in accordance with general rules (see attachment). Data in table form (e.g. spreadsheet) would be encouraged. Specific coded or other appropriate designs imperatively justified should be used to distinguish the impurity. All levels of impurities above (>) the reporting threshold would be summed and total impurities will be presented.

examine the use of the new active substance in any clinical study.

Also, for each batch of the new drug substance, the report should also include:

• Identity of the batch and its size

• Date of manufacturing

• Place of manufacturing

• Process of Manufacturing

• Content of Impurities, individual and total

• Application of batches

• Citing of the analytical method executed

Q3B (R2) Impurities in new drug products

In addition, it complements the guidelines on impurities in new pharmaceutical ingredients and gives recommendations regarding impurities in formulations containing newly developed synthetic drug substances. This guideline is explicitly concerned with those impurities that result either as degradation products of the new chemical entity or from cross-interaction between the new chemical entity and excipients or components of primary packaging. In the guideline such impurities it gives a logic behind the need for and approach to, reporting, identification and qualification of such impurities, which is based on assessment of likely and observed impurities and their associated safety concerns as described in the parent guideline. Some proposed threshold limits for the reporting and control of impurities have been established based on the highest administered dose of the drug substance in the product.

Q3C (R5) Residual solvents

The guideline focuses on ensuring patient safety by controlling the level of residual solvents in pharmaceutical products. Residual solvents are organic volatile substances left over from the manufacturing process of active pharmaceutical ingredients or finished dosage forms. The guideline recommends minimizing the use of solvents, as they confer no clinical advantage and can pose health risks.

Classification of residual solvents by risk assessment

The phrase "tolerable daily intake" (TDI) is used within exposure limits of toxic chemicals by International Program on Chemical Safety (IPCS) while "acceptable daily intake" (ADI) is used by World Health Organization (WHO) and other national and international health authorities and institutes. This term ADI has been ameliorated in this guideline where "permitted daily exposure" (PDE) means a pharmaceutically acceptable level of carryover solvents for the sake of avoiding the angst of the different values for the same substance solids ADI's.

Residual solvents they are three classes as follows:

Class 1 solvents: Solvents to be avoided

Recognized human carcinogens, presumed human carcinogens and environmental risks.

Class 2 solvents: Solvents to be limited

Animal carcinogen which does not interact with the genome or perhaps agents responsible for

other modes of irreparable toxicity, for instance, neurocidal or developmental malformations. Solvents considered toxic for additional reasons but reversible in nature.

Class 3 solvents: Solvents with low toxic potential

Solvents characterized by a very low degree of toxicity to humans, which do not require any health-based exposure limit. The PDEs associated with Class 3 solvents tend to be 50 mg or more per day.

Q3D Guidelines for elemental impurities

In addition to the ICH Q3A guidance, which defines organic, inorganic and residual solvents while offering guidelines for the control of impurities anticipated in any drug substance, quality and safety dose issues for organic impurities have largely been dealt with in Q3A and Q3B guidelines respectively. Clarifications on the control of residual solvents were provided in a new guideline Q3C.

The following are the factors taken into account during safety evaluation in deciding PDE, roughly in order of importance:

- The oxidative potential of the element incorporated in the drug product.
- Data on human exposure and safety, if rated as applicable.
- The most pertinent animal toxicology of study.
- The route of administration.
- The relevant endpoint(s).

Q4B Evaluation and recommendation of pharmacopeia texts for use in "ICH" regions

The following document outlines a process concerning the evaluation and proposal of specific pharmacopoeia texts by the Q4B Expert Working Group (EWG) in order to help achieve their acceptance by regulatory agencies overseeing the ICH regions, for purposes of use.

Q5A (R1) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin

This document outlines the testing and evaluation requirements for the viral safety of products derived from characterized cell lines (human or animal origin, including in marketing applications for products like monoclonal antibodies, interferons, and recombinant DNA-derived products (e.g., subunit vaccines).

- **In scope:** products from in vitro cell cultures (e.g., interferons, monoclonal antibodies, recombinant vaccines) and hybridoma cells grown in vivo as ascites (with special considerations).
- **Excluded:** inactivated vaccines, live vaccines with self-replicating agents, and genetically engineered live vectors.
- The document excludes viruses related to bovine spongiform encephalopathy (BSE) and scrapie, and applicants should consult regulatory authorities for issues related to these nonconventional transmissible agents.

Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:

- Selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans;
- Assessing the capacity of the production processes to clear infectious viruses;
- Testing the product at appropriate steps of production for absence of contaminating infectious viruses.

All testing suffers from the inherent limitation of quantitative virus assays, i.e., that the ability to detect low viral concentrations depends for statistical reasons on the size of the sample. Therefore, no single approach will necessarily establish the safety of a product. Confidence that infectious virus is absent from the final product will in many instances not be derived solely from direct testing for their presence, but also from a demonstration that the purification regimen is capable of removing and/or inactivating the viruses.

The type and extent of viral tests and viral clearance studies required at different steps of production will depend on various factors and should be considered on a case-by-case and step-by-step basis. The factors that should be taken into account include the extent of cell bank characterization and qualification, the nature of any viruses detected, culture medium constituents, culture methods, facility and equipment design, the results of viral tests after cell culture, the ability of the process to clear viruses, and the type of product and its intended clinical use.

Q5B Quality of biotechnological products

This document presents guidance regarding the characterization of the expression construct for the production of recombination DNA protein products in eukaryotic and prokaryotic cells. This document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA derived proteins. This document is not intended to cover the whole quality aspect of rDNA derived medicinal products. The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. Segments of the expression construct should be analysed using nucleic acid techniques in conjunction with other tests performed on the purified recombinant protein for assuring the quality and consistency of the final product. Analysis of the expression construct at the nucleic acid level should be considered as part of the overall evaluation of quality, taking into account that this testing only evaluates neither the coding sequence of a recombinant gene and not the translational fidelity nor other characteristics of the recombinant protein, such secondary structure, tertiary structure, and post-translational modifications.

5C Quality of biotechnological products

Stability testing of biotechnological/biological products

guidance refers to well-defined polypeptides and proteins, their products and derivatives that are isolated from body fluids, tissues, cell cultures, or developed using r-DNA technology. The document thus includes the development and submission of stability information

for production such as cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietin's, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin's, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides.

Q5D Derivation and characterization of cell substrates

This document provides broad guidance on appropriate standards for the derivation of human and animal cell lines and microbes used to prepare biotechnological/biological products and for the preparation and characterization of cell banks to be used for production.

Q5E Comparability of biotechnological/biological products subject to changes in the manufacturing process

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical or clinical strategy. The main emphasis of the document is on quality aspects.

Q6A Specifications: test procedures and acceptance criteria, for new drug substances and new drug products

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan. The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not it only.

This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient to adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products. The ICH Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products address guideline specifications, tests and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products and crude products of animal or plant origin are similarly not covered.

6B Specifications: Test procedures .and acceptance criteria for biotechnological/biological products

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components. A separate ICH Guideline, "Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substances" addresses specifications, and other criteria for chemical substances. This document does not recommend specific test procedures or specific acceptance criteria nor does it apply to the regulation of preclinical and/or clinical research material.

Q7 Good manufacturing practice guide for active pharmaceutical ingredients

This document (guide)provides guidance on GMP for APIs manufacturing under a suitable quality management frame work. It guarantees that APIs meet the requirements of consistency and purity criteria that they possess. This guide describes "manufacturing" as relating to all operations involving product receipt, manufacture, labelling, re-labelling, packaging, repackaging, quality control, shipment, storage, and distribution of APIs and related control. As a whole, this document does not address the safety aspects of production workers or environmental protection issues. Such checks are the manufacturer's intrinsic obligations and are regulated by national laws. This guide does not define pharmacopeia requirements for registration, filling, or adjustment. This guide refers to the production of APIs for human drug products. It also includes APIs generated through chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes.

Q8 (R2) Pharmaceutical development

This guideline is intended to provide guidance on the contents of section 3.2.P.2 (pharmaceutical development) for drug products as defined in the scope of module 3 of the common technical document (ich guideline m4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities.

Q9 Quality risk management

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including

the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products).

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk

Q10 Pharmaceutical quality system

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle. The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of each stage.

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

Pharmaceutical development

- Drug substance development
- Formulation development
- Manufacture of investigational products
- Delivery system development
- Manufacturing process development and scale-up
- Analytical method development.

Technology transfer

New product transfers during Development through Manufacturing.

Transfers within or between manufacturing and testing sites for marketed products. **Commercial manufacturing** Acquisition and control of materials

- Provision of facilities, utilities, and equipment
- Production (including packaging and labelling)
- Quality control and assurance
- Release
- Storage
- Distribution (excluding wholesaler activities).

Q11 Development and manufacturing of drug substances (chemical entities and biotechnological/biological entities)

It addresses aspects of development and manufacture the pertain to drug substance, including the presence of steps designed to reduce impurities in addition, ICH Q11 provides further clarification on the principle and concepts described in ICH guidelines on pharmaceutical development (Q8), quality risk management (Q9) and pharmaceutical quality system (Q10) as they pertain to the development and manufacture of drug substance.

A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and development appropriate controls strategies applicable over the lifecycle of the drug substance which may include the establishment of design space. As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provides in the application for marketing authorisation.

Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation.

Q13 Continuous manufacturing of drug substances and drug products

The new ICH guideline will establish harmonized scientific and technical requirements needed to fulfil regulatory expectations for the implementation and assessment of CM to improve access to medicines. An ICH guideline would facilitate international harmonization and could reduce barriers to the adoption of CM technology.

Q14 Analytical procedure development

The new guideline is proposed to harmonize the scientific approaches of Analytical Procedure Development, and to provide the principles relating to the description of Analytical Procedure Development process. This new guideline is intended to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures.

ICH STABILITY TESTING GUIDELINES

Importance of stability testing

1.Determining conditions of shelf life and processing for the development of new goods

2.Toxic products may be formed during the decomposition of active drugs

3.Ensuring that the brand is fit for uses as long as they are in the market with all functionally acceptable attributes to protect the manufactures reputation

4.To ensure that no modification in the production or formulation method have been

implemented that can negatively impact product stability

5.It offers a database that can be of value for current product growth when choosing excipients,

formulations, and closure schemes for container

6.developing an understanding of APIS degradation that can affect the quality of the pharmaceutical product

7.It is the only way to assures whether the drug is within the acceptance criteria or not.

Factors affecting drug stability

Temperature

The stability of a drug substance affected by changes in temperature when the temperature is increased, it causes an increase in the hydrolysis rate of drugs.

Moisture

Some physical and chemical dosage changes when the water -soluble solid doses is absorbed into any moisture surface and therefore loses its properties.

PH

The deterioration rate of hydrolysis solution drugs is influenced by PH and reduced the effective drugs that are formulated using buffers at the PH of optimum stability.

Excipients

Starch and povidone excipients have greater water content and effect and affect stability by enhancing the formulation of water content. Furthermore, there are chemical interaction between excipients and drugs that to a reduction of instability.

Oxygen

Oxygen presence facilitates oxidation in some products. Products with a higher decomposition rate is stabilized when exposed to oxygen by substituting carbon dioxide and nitrogen for oxygen in the storage container.

Light

When exposed to light, the rate of decomposition increases. Certain drugs are photosensitive and their stability can be measured when exposed to light or stored in the dark by comparing their stability. Photosensitive medicines must be packed in a glass amber bottle and held in a dark place.

Types of stability of drug substances

Physical stability

1.Physical stability is important for safety and efficacy as it affects drug uniformity and release rate.

2.Physical characteristics include size, palatability, homogeneity, dissolution, and suspension

Chemical stability

Chemical stability of drugs is less active as deterioration takes place. The chemical quality and the labelled strength of each active ingredient remain within the specific limits.

Microbiological stability

Antimicrobial agents retain their effect within specified limits, also sterilization or resistance to microbial growth as per the requirements stated.

Therapeutic stability

The therapeutic effect will remain unchanged.

Toxicological stability

Enhanced toxicity significantly does not occur.

Stability testing method

Stability tests or a routine operation used in the various phases of product development for drug substance and products. Early stages use accelerated stability tests to measure the type of degraded products found following long term storage. The main objectives of the pharmaceutical stability test are to ensure the products remain on the market for the duration of their acceptable fitness or quality and are fit for consumption until the last pharmaceutical unit is used stability testing procedures are divided into four groups.

1.real time stability testing

2.accelerated stability testing

3.retained sample stability testing

4.cyclic temperature stress testing

Real time stability testing

This involves testing drug product for a longer duration to find out what is the maximum product degradation when stored as recommended.

Accelerated stability testing

Here, product is subjected to stress in the form of higher temperatures, moisture, agitation,

light, pH, and packaging conditions to study its degradation profile.

"Accelerated stability testing theory is based on Arrhenius equation 1 and modified Arrhenius equation 2:"

$$\ln K = \ln A + RT/\Delta$$

Were, K = Degradation rate/s

A = Frequency factor/s

ΔE = Activation energy (KJ/mol)

R = Universal gas constant (0.00831 KJ/mol)

T = Absolute temperature (K)

$$\text{Log}\ (k2/k1) = -Ea/2.303R\ (1/T2 - 1/T1)$$

Were,

k1 and k2 = Rate constants

T1 and T2 = Temperature expressed in degree kelvins

Ea. = Activation energy

R = Gas constant.

Retained sample stability testing

This is testing of samples retained from each batch that has been sent into the market.

Cyclic temperature stress testing

Not routinely used. It involves subjecting the products to temperature stresses in a way to mimic likely market storage conditions.

Stability testing equipment

The stability chamber is the equipment used for stability testing and is environmental specialist chambers which can stimulate storage condition and real-time stability, accelerated stability, and protocol for the long term and enables evaluation of product stability. Both reach-in styles and walk-in are accessible to the rooms. Small chambers are preferred for rapid testing because product retention time in these cabinets is much less, while long-term tests prefer walk-in chambers. Due to the need for years of continuous use, it is expected

that these chambers will be reliable, robust, and equipped with appropriate recording, safety, and alarm devices. Furthermore, there are also picture stabilization chambers that can be used with and without control of temperature and moisture. In the photostability chamber, 2 types of light sources are used.

1. Cool white and near UV fluorescent tubes are combined

2. Daylight artificial lamps (e.g., metal halide or xenon).

A maximum of 1.2 million lux hours of exposure is needed. The visible light intensity and how many hours of exposure required are measured using a lux mete.

Guidelines for stability testing

In 1980, these guidelines were issued, and later the ICH harmonized (made uniform) to solve

the bottleneck for marketing and registration in other nations. In the drug regulation, the regulatory authority in several nations has created regulations for the producers to submit stability information to ensure that molecules and products are generated with optimum stability, circulated, and provided to the patient. These guidelines aimed to introduce consistency in testing from supplier to supplier and also involve fundamental problems linked to stability, stability information for application dossier requirements, and implementation steps.

In 1991, ICH was established which was a consortium created by the European Commission, Japan, and the USA with inputs from both regulatory and business. These guidelines are referred to as guidelines for quality, safety, efficacy, and multidisciplinary (also referred to as QSEM). In 1996, these guidelines were modified by the WHO because ICH guidelines did not address the extreme climatic conditions in many nations, but only new drug substances and products were covered and not the product already in use which was circulated in the entire nations by the WHO.

In June 1997, the United States Food and Drug Administration (USFDA) also issued guidance documents entitled "Expiration dating of solid oral dosage form containing Iron." In 2004, WHO also issued guidelines for worldwide environment stability research. These ICH guidelines for veterinary products were subsequently expanded. The Indian Drug Manufacturers Association also published a technical monograph on drug and product stability testing in India.

Q1A (R2): Stability testing of new drug substances and products

These guidelines address that new molecular entities and associated drug product information must be submitted in the registration application. Stability testing aims to provide evidence on how the quality of the drug substances or drug product changes over time under the influence of multiple environmental factors such as temperature, light, humidity, and also to establish a retest or shelf life for drug substance or drug product and recommend the storage conditions.

Q1B: Photostability testing of new drug substances and products

The ICH Harmonized tripartite guideline on new drug substances and stability testing for products (referred to as parent guidelines) states that light testing should be an essential component of stress testing. This document is an appendix to the parent guideline and discusses the guidelines for photostability evaluation. Photostability testing is performed on one batch of selected materials in compliance with the parent guidelines.

Q1C: Stability testing for new dosage forms

These guidelines address a recommendation made by the original applicant on the stability of new dosage forms following the original application for new drug substances and products. The new dosage form is defined as a pharmaceutical product containing the same active substance as the existing drug product approved by the regulatory authority differing in the route of administration (e.g., oral to parental), new delivery system (e.g., tablet to modified tablet immediate release), and different dosage forms of the same dosage route (e.g., capsule to tablet, a solution to suspension). The parent stability guideline should be the concept of stability for a new dosage.

Q1D: Bracketing and matrixing design

This guideline proposes the use of bracketing and matrixing instability research. This guideline proposes the use of bracketing and matrixing instability research. Bracketing is described as designing a timetable for stability where only specimens are always tested to the extreme layout variables such as strength, container size, or complete design filling. The structure also presumes that any intermediate level of stability is the stability of the test ends. Matrixing is defined as the development of a stability schedule in which selected subsets of the total number of samples should be tested for all combinations of factors at a specified time point and specific sample subsets should be checked later. The design assumes that each sample's stability at a given time is the strength of all samples.

Q1E: Evaluation of stability data

This guideline defines when and how to consider extrapolation when recommending a re-assessment duration for the drug substance or drug product shelf life that goes beyond the period covered by "long-term storage conditions information accessible from the stability research." The design and performance of the official stabilization research should follow the parent guideline values. The stability research aims to develop standards for the retest or shelf life and storage of all future batches produced and packaged. under comparable conditions based on the minimum testing of three batches of drug substances or products. The degree of variability on individual batches also impacts the assurance that a future production batch will remain within acceptance requirements during its retest or shelf life.

Q1F: Stability data package for registration applications in climatic Zone

In February 2003, these documents were accepted by the ICH Steering Committee and then enforced in the ICH regions. This guideline sets the storage requirements for stability testing in climatic zone (hot and dry) and (hot and humid). To promote access to medicinal products by reducing the number of storage conditions, it specifies harmonized international stability testing requirements. In general cases, accelerated and long-term storage conditions recommended for climatic zone (described in the parent guideline).

Q5C: Stability testing of biotechnological/biological products

This guidance refers to well-defined polypeptides and proteins, their products, and derivatives that are isolated from body fluids, tissues, cell cultures, or developed using r-DNA technology. The document thus includes the development and submission of stability information for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietin's, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin's, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides.

Q7: Good manufacturing practice (GMP) guide for APIs

This document (Guide) provides guidance on GMP for APIs manufacturing under a suitable quality management framework. It guarantees that APIs meet the requirements of consistency and purity criteria that they possess. This guide describes "manufacturing" as relating to all operations involving product receipt, manufacture, labelling, re-labelling, packaging, repackaging, quality control, shipment, storage, and distribution of APIs and related control. As a whole, this document does not address the safety aspects of production workers or environmental protection issues. Such checks are the manufacturer's intrinsic obligations and are regulated by national laws. This guide does not define pharmacopeia requirements for registration, filling, or adjustment. This guide refers to the production of APIs for human drug products. It also includes APIs generated through chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes.

The committee for proprietary medicinal products (CPMP)

In the framework of the European Agency for the Evaluation of Medicinal Products (EMEA), CPMP has issued a set of stability testing recommendations to assist those seeking authorization to sell medicinal products in the European Union. The CPMP stability guidelines.

Protocol for stability testing

Stability testing protocol is a pre-condition for initiation of stability tests and is essentially a written document describing the main components of a well-controlled and regulated stability test. The protocol relies upon the drug substance type or the product because it depends on the compound's intrinsic stability, dosage form, and process of closing the container implied. It is also possible to determine whether the drug is new or already on the market. Stability tests are designed to determine a pharmaceutical product expiry date and shelf life. The protocol should also include the areas where the product is expected to be put on the market, for example, where it is planned for use in climatic Zones I-III, IVa, and IVb.

The following information should be included in the stability protocol:

- Number of batches
- Containers and closures
- The orientation of storage of containers
- Sampling time points
- Sampling plan
- Test storage conditions
- Test parameters
- Test methodology
- Acceptance criteria.

Number of batches

Stability studies are usually conducted in one single batch at the development stage, while new product or product created registration studies are conducted in the first three batches; well-established and stable batches are allowed in two different batches. In the absence of complete manufacturing information, long-term studies should include the first three batches of the drug product produced after approval using the procedure used in the authorized application for the drug product. Laboratory data collected during pharmaceutical advances are not known as primary stability data, but as data support. The random sample selection of the pilot population or production batches should generally be a random sample.

Containers and closures

Tests are carried out on the material in immediate containers or marketing closures. Packaging materials include aluminium strips, AluAlu packs, blister packs, HDPE bottles, and so on secondary packs are also required but not shippers. Products are to be tested individually in all separate container types or closures, before delivery and marketing. However, testing in prototype containers is permitted for bulk containers if the actual packaging is stimulated.

The orientation of storage of containers

For studies of stability, to allow full product contact with the container closing, samples of a solution, dispersed process, and semi-solid drug material must be held upright and placed either inverted or sideways. The guiding principle helps to determine if the interaction

between the pharmaceutical material or solvent and the closure results in the removal of chemical substances from the closed components or the adsorption of the product's components in the container.

Sampling time points

The stability profile of new drug products should be at the test rate. During the 1st year of products with a planned shelf life of at least 12 months, the long-term storage monitoring frequency should be every 3 months, every 6 months in the 2nd year, and annually after that for the expected shelf life. It is recommended that the initial and end stages are at least 3 times, with accelerated storage conditions as 0 or 6 months. Due to major improvements in accelerated storage conditions, a maximum of four test points, including the initial and final time points such as 0, 6, 9, and 12 months will be needed to test intermediate storage conditions.

Sampling plan

Stability testing for the sampling method includes the preparation in a stabilization chamber of several samples and the evaluation of the charged batch for the entire study. For a thorough assessment of all the test parameters first, the time-points for sampling and the number of samples must be calculated at every drawn stage. About 100 tablets, 10 for each test, hardness and moisture detecting, 6 for every disintegration and dissolution, and 50 for each friability, would be sufficient for long-term or accelerated stabilization studies. This is the total number of tablets needed for the study multiplied by the number of results. The sampling plan is then established that involves the uneven choice of the containers that represent the whole batches.

Test storage conditions

The conditions of storage to be chosen shall depend on the climatic zone where the product is expected to be sold on the market or for which regulatory approval is sought. The ICH, CPMP, and WHO has given a general recommendation on the storage conditions. The stability test storage conditions for drug products.

Test parameters

The study on stability sample analysis shall include a protocol with parameters for conducting the stability test. A stability test is chosen that assesses the performance, purity, capacity, and identity of the item after storage. Such tests include those performed on test samples for presentation, processing, material degradation, dissolving, moisture, and microbiology. The batches applied for the stability study must comply with all test restrictions: those on heavy metals, residual solvents, and products of combustion. Some are required for the or else the product cannot be released into the market, while others, such as stability testing, are not needed repeatedly. Additional checks under Q6A, including enantiomeric purity, polymorphic quality, sizes of particles, etc., are elaborated in ICH guidelines.

Test methodology

The official compendia protocol is crucial for drug tests, while alternative techniques should be thoroughly checked. Stability indication techniques should be used for stability studies, ensuring linearity, reliability, accuracy, and precision. The system should include a limit for product degradation analysis, and each test should follow a standard protocol recommendation.

Acceptance criteria

The ICH guideline Q3B (R2) addresses the degradation of new pharmaceutical substances in their formulations, with upper limits for individual and total degradants. The level of impurities in drugs is determined by the extent of dose administered, with a maximum daily dose of 0.1%) not exceeding 1 g and a minimum of 0.05% above 1.

Estimation of shelf life

The period over which a drug can be stored in its original packaging without any drop in its

quality is known as its shelf life which is determined by long-term storage data. The linearized data is analysed to assess the degree of match of the slopes and the intercepts. Almost all the commodities have a single shelf life whereas there are some few particular commodities like that freeze-dried protein, are having two different shelf lives of 2 years freezing and d2 drying.

Recent trends in stability testing

The global development of the market makes it necessary to focus on enhancing the stability testing of drug products. This translates into longer testing periods, more extreme conditions, such as exposure to light and moisture, to minimize unnecessary tests and maximize resources without compromising the quality of the product. These initiatives serve to safeguard patients and are in line with the international standards for good manufacturing practices.

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