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ICH GUIDELINES AND MAIN FOCUS ON STABILITY GUIDELINES FOR NEW FORMULATION AND DOSAGE FORMS

Yogita Somvanshi[1*] and Prakash Satbhai[2]

[1*]Department of Pharmaceutics, Sandip Institute of Pharmaceutical Sciences, Mahiravani, Nashik, India.

[2]Technology Transfere Dept. Ajanta Pharma, Charkop, Kandiwali.

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***Correspondence for Author**
Yogita Somvanshi
Department of Pharmaceutics, Sandip Institute of Pharmaceutical Sciences, Mahiravani, Nashik, India.

ABSTRACT

This guidance is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration apllication within the three regions of the European Union(EU), Japan, and the United States. It does not seek to address the testing for registration in orexport to other areas of the world. The guidance exemplifies the core stability data package fornew drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations andcharacteristics of the materials being evaluated. Alternative approaches can be used when thereare scientifically justifiable reasons.The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

KEYWORDS: Accelerated stability, Photostability, long term stability , Bracketing , Matrixing.

INTRODUCTION:

ICH, launched in 1990, is an unique organisation that brings the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States together.[1] Regulatory harmonisation 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 minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development.[1]

Substantial benefits to DRAs resulted when ICH shifted emphasis from the input of information by industry to the output of information by regulators. This transition was made possible by the development of a common submission format—the CTD—which greatly influenced regulatory review process ultimately leading to a harmonized electronic submission and e-review initiatives, which, in turn, have enabled implementation of good review practices. These activities are having a global effect on information review and sharing among drug regulator. Since ICH's inception in 1990, the ICH process has gradually evolved. ICH's first decade saw significant progress in the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document).[9,10]

ICH GUIDELINES[1,7,9]

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines is more logical, consistent and clear. Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1). The ICH guidelines are divided into four categories and codes are assigned according to these categories.

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

"S" Guidelines : These are Safety guidelines which includes a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.

"E" Guidelines : Efficacy guidelines concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.

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

"Q" Guidelines	
Q1 A – Q1 F	Stability Guidelines
Q2	Analytical validation
Q3 A – Q3 D	Impurities
Q4 – Q4 B	Pharmacopoeias
Q5 A – Q5 E	Quality of Biotechnological products
Q6 A – Q6 B	Specifications
Q7	Good Manufacturing Practices
Q8	Pharmaceutical Developement
Q9	Quality Risk Management
Q10	Pharmaceutical quality system
Q11	Development and manufacture of Drug Substances
Q12	Lifestyle Management
"S" Guidelines	
S1 A – S1 C	Carcinogenicity studies
S2	Genotoxicity studies
S3 A – S3 B	Toxicokinatics and Pharmacokinatics
S4	Toxicity testing
S5	Reproductive Toxicology
S6	Biotechnologycal Products
S7 A – S7 B	Pharmacology studies
S8	Immunotoxicology studies
S9	Nonclinical Evaluation for anticancer

	Pharmaceuticals
S10	Photosafety Evaluation
S11	Nonclinical safety Testing
"E "Guidlines	
E1	Clinical safty for drugs used in long term treatment.
E2 A- E2 F	Pharmacovigilance
E3	Clinical study reports
E4	Dose responce studies
E5	Ethinic factors
E6	Good clinical practice
E7	Clinical trials in Geriatric Population
E8	General considerations for clinical trials
E9	Statistical Principals of clinical trials
E10	Choice of control group for clinical trials
E11	Clinical trials in Pediatric Population
E12	Clinical Evaluation by Therapeutic Category
E14	Clinical Evaluation
E15	Definitions in Phramacogenetics and Pharmacogenomics
E16	Qualifications for gwnomic Biomarkers
E17	Multi-regional Clinical Trials
E18	Genomic sampling methodologies
"M" Guidelines	
M1	MedDRA terminologies
M2	Electronics standards
M3	Nonclinical Safety Studies
M4	Common Technical document
M5	Data Elements and standards for drug dictionaries
M6	Gene therapy
M7	Genotoxic impurities
M8	Electronic common technical document (eCTD)

ICH CLIMATIC ZONES[9]

Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows.

Zone I: temperate.

Zone II: subtropical, with possible high humidity.

Zone III: hot/dry.

Zone IV: hot/humid.

Conditions	Zone of ICH
40ºC/75 %RH	Accelerated trial conditions for climatic zones I – IV
30ºC/75 %RH	Long term trial conditions for zone IVb only
30ºC/65% RH	Intermediate and long term trial conditions for zones I, II, III and IVa
25ºC/60 %RH	Long term trial conditions for climatic zones I and II

GUIDELINES FOR STABILITY STUDIES[1,2]

Stability testing is now the key procedural component in the pharmaceutical development program for a new drug as well as new formulation. Stability tests are carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life.

Regulatory requirements have been made increasingly stringent to achieve the above goal in all possible conditions to which the product might be subjected during its shelf life. Thus the stability tests should be carried out following proper scientific principles and after understanding of the current regulatory requirements and as per the climatic zone.

Q1A(R2) GUIDELINES :STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS[1,2]

The guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

Drug Substance

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Stress Testing: Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions .Results from these studies will form an integral part of the information provided to regulatory authorities.

Testing Frequency: For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period .At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended .

Storage Conditions: The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use .The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period .

General case.

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	25°C± 2°C /60% RH ± 5% RH OR 30°C± 2°C /65% RH ± 5% RH	12 months
Intermediate	30°C± 2°C /65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C /75% RH ± 5% RH	6 months

Drug substances intended for storage in a refrigerator.

Study	**Storage condition**	**Minimum time period covered by data at submission .**
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C /60% RH ± 5% RH	6 months

Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission .
Long term	- 20°C ± 5°C	12 months

Stability Commitment

When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

Evaluation

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

Labeling

The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided. A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

Drug Product

The stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

Selection of Batches

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing.

Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label).

Specification

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Shelf life acceptance criteria should be derived from consideration of all available stability information.

Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Long term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below.

General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C± 2°C /60% RH ± 5% RH OR 30°C± 2°C /65% RH ± 5% RH	12 months
Intermediate	30°C± 2°C /65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C /75% RH ± 5% RH	6 months

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Drug products packaged in impermeable containers.

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

Drug products packaged in semi-permeable containers.

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below.

Study	Storage condition	Minimum time period covered by data at submission .
Long term	25°C ± 2°C /40% RH ± 5% RH OR 30°C ± 2°C /35% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C /65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C /not more than (NMT) 25% RH	6 months

For long-term studies conducted at 25°C ± 2°C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs

during the 6 months' testing at the accelerated storage condition.

Drug products intended for storage in a refrigerator.

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition. If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

Drug products intended for storage in a freezer.

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for

example, dissolution rate for solid oral dosage forms).

Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

Q1 B : STABILITY TESTING: PHOTOSTABILITY TESTING OF NEW DRUG

SUBSTANCES AND PRODUCTS[4]

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described under Selection of Batches in the Parent Guideline. Under some circumstances these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). The guideline primarily addresses the generation of photostability information for submission in Registration Applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e. under conditions of use) and those applications not covered by the Parent Guideline.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as.

i) Tests on the drug substance;

ii) Tests on the exposed drug product outside of the immediate pack;

and if necessary;

iii) Tests on the drug product in the immediate pack;

and if necessary;

Tests on the drug product in the marketing pack.

The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements.

Light Sources

For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1 : ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation .

Option 2 : For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.

A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993) ; and A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

Procedure

For confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product.

Drug substance

For drug substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing. The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used.

Under forcing conditions, decomposition products may be observed that are unlikely to be

formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be further examined.

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the Parent Guideline if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be exposed in chemically inert and transparent containers .At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

Drug product

It may be appropriate to test certain products such as infusion liquids, dermal creams, etc., to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be

chosen to provide a minimal interference with the irradiation of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity or color of solution, dissolution/disintegration for dosage forms such as capsules, etc.) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Depending on the extent of change special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf life.

Q1C: STABILITY TESTING FOR NEW DOSAGE FORMS,ANNEX TO THE ICH HARMONISED TRIPARTITE GUIDELINES ON STABILITY TESTING FOR NEW DRUGS AND PRUDUCTS[4]

The ICH harmonised Tripartite Guideline on Stability Testing of New Drug Substances and Products was issued on October 27, 1993. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.

New Dosage Forms

A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority. Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems and different dosage forms of the same administration route .

Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.

Q1D: BRACKETING AND MATRIXING DESIGNS FOR STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS[5]

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R) Harmonised Tripartite guideline on Stability Testing of New Drug Substances and Products.

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved .During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change.

Bracketing

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

Design factors are variables (e.g., strength, container size and/or fill) to be evaluated in a study design for their effect on product stability.

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation.With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

Matrixing

Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point .The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system.When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems. Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems.

Due to the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design.

A study design that matrixes on time points only would often have similar ability to that of a full design to detect differences in rates of change among factors and to establish a reliable shelf life. This feature exists because linearity is assumed and because full testing of all factor combinations would still be performed at both the initial time point and the last time point prior to submission.

Q1E: EVALUATION FOR STABILITY DATA[6]

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below “room temperature”. It covers stability studies using single- or multi-factor designs and full or reduced designs.

A systematic approach should be adopted in the presentation and evaluation of the stability

information. The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

Data presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application .If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified.

Extrapolation

Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition.

Stability data for each attribute should be assessed sequentially. For drug substances or products intended for storage at room temperature, the assessment should begin with any significant change at the accelerated condition and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long-term data.

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances.

Before pooling the data from several batches to estimate a retest period or shelf life, a preliminary statistical test should be performed to determine whether the regression lines from different batches have a common slope and a common time-zero intercept. Analysis of covariance (ANCOVA) can be employed, where time is considered the covariate, to test the differences in slopes and intercepts of the regression lines among batches.

The statistical analysis should clearly identify the procedure and assumptions used. For instance, the assumptions underlying the model in which interaction terms are negligible should be stated. The use of a matrixing design can result in an estimated shelf life shorter

than that resulting from a full design.

COCLUSION

The brief understandingof stability guidelines for post graguate students can be easily recognized by this article. Stability testing provide a evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.Because physical, chemical or microbiological changes have impact on the quality and therapeutic efficiency of the drug products, it is very much important to go for accelerated stability testing. The USFDA and ICH stability guidelines has been given appropriate and considerable data as per references mentioned so, the data available with regarding stability studies of New drug Substances and Drug Products were easy to understand and refer.

REFERENCES

1. ICH.org
2. ICH Harmonised Tripartite Guidelines – Stability Testing of New drug Substances and Products Q1A (R2).
3. ICH Harmonised Tripartite Guidelines- Stability Testing: Photo stability testing Of New Drug Substances and Products Q1B.
4. ICH Harmonised Tripartite Guidelines- Stability Testing for New Dosage Forms Q1C.
5. ICH Harmonised Tripartite Guidelines- Bracketing And Matrixing Designs For Stability Testing of New Drug Substances And Product.
6. ICH Harmonised Tripartite Guidelines- Evaluation For Stability Data Q1E.
7. Anilkumar S. Chinchole,B.N.Poul,C.V. Panchal,D.V. Chavan.A Review on Stability Guidelines by ICH and USFDA Guidelines for New Formulation and Dosage form.Pharmatutor., 2014; 2(8): 32-53
8. Sanjay Bajaj, Dinesh Singla and Neha Sakhuja.Stability Testing of Pharmaceutical Products.Journal of Applied Pharmaceutical Science., 2012; 02(03): 129-138.
9. q1scientific.com
10. Guidance for Industry. Q1A(R2) Stability Testing of New Drug Substances and Products.U.S. Department of Health and Human Services Food and Drug Administration. November 2003. ICH.Revision 2.