Review Article

Regulation of stability studies to enhance the efficiency of drug registrations to regulatory authorities

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ABSTRACT

Stability testing is an important tool to assess the quality of drug substances and products which may vary with time under influence of variety of factors such as temperature, humidity, and light. Stability studies of drugs are designed according to the climatic zones to establish a retest period for active drug substance or a shelf life for the finished product as well as to recommend the storage conditions. The strict regulatory requirements on designing, performing evaluating stability study to claim the expiry date, and shelf life of drug products are based on a series of regulatory requirements and advisory guidelines that have been developed by regulatory authorities of US, Europe, and Japan which; were harmonized through the development of the International Conference on Harmonization (ICH) procedures. To assess the stability of drug substances and products, the design and conduct of stability studies, defining relevant thresholds for impurities testing is required with a current good manufacturing practice-based risk management approach to achieve a robust stability of pharmaceutical dosage forms. There are relevant requirements that cover new drug substances and products as well as new dosage forms containing existing active ingredients and vice versa.

INTRODUCTION

Within last few decades, the stability testing of drug substances or products has significantly advanced that shows significant variations in quality, both within and between various jurisdictions, to an operation based on sound scientific principles that indicate a high degree of similarity in almost all parts of the world.[1]

The stability of pharmaceutical drugs is a vast area that comprises many potential routes of degradation. Any change that occurs in a drug substance or product subsequent to its manufacturing, packaging, storage, distribution, or in-use, which drastically affects the quality of drug product in terms of its fitness for use by the patient, is a matter of concern for health regulatory authorities and pharmaceutical industries.[2]

Generically, degradation of pharmaceutical drugs is classified as chemical, physical, or biological degradation. However, many drugs or medical devices may degrade with more than one mode of degradation. The adverse effect of instability of drugs as modifying efficacy, safety, or ease of use or patient acceptability and in terms of efficacy, the most obvious effect is the loss of drug potency. Usually, we regard the range from 95 to 105% of the label claim as the lowest to highest accept value of potency. Thus, the stability of a pharmaceutical product is the capability of particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic, toxicological, protective, and informational specifications of respective climatic zone.[1,3]

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ROLE OF CLIMATIC ZONES IN DESIGNING STABILITY STUDY

The storage conditions and stability of medicines are designed and calculated on the basis of climatic zones which are classified as climatic zone I, II, III, and IV. The World Health Organization (WHO) recommended stability testing and storage condition of medicines for all four climatic zones. The general storage condition are subdivided into long-term (25 ± 2°C/60 ± 5% relative humidity (RH)) and accelerated (40 ± 2°C/75 ± 5% RH) which are followed by International Conference on Harmonization (ICH) guidelines to generate the stability data for registration applications of drug substances and products. An intermediate storage condition (30 ± 2°C/65 ± 5% RH) has been introduced in general long-term storage conditions of zone I and II to harmonize the long-term storage conditions of zone III and IV. This intermediate storage condition can be used as an alternative to long-term storage condition of zone I and II.[3,4] The difference in general storage conditions between zone I/II and zone III/IV is mentioned in Table 1.

The storage conditions for aqueous-based drug products packaged in semipermeable containers for climatic zones III/IV are mentioned below in Table 2.

In aqueous drug products, the ration of water loss rate can be calculated with respect to reference RH by multiplying the water loss rate measured at alternative RH at similar temperature using formula addressed in Equation 1 and the calculated ratio of water loss rate at similar temperatures is mentioned in Table 3.[3]

$$\text{Ratio of water loss rate} = \frac{(100 \text{ reference \% RH})}{(100 \text{ alternative \% RH})} \quad (1)$$

STORAGE CONDITIONS AT RELATIVELY HIGH TEMPERATURE AND HUMIDITY

An additional study on single batch of drug product can be performed at 50°C/ambient humidity for up to 3 months to cover extremely hot and dry condition, whereas 25°C/80% RH to cover extremely humid condition during transportation. Stability testing of solid dosage forms in water vapor permeable packaging (tablets in polyvinyl chloride (PVC)/aluminium blisters), at high humidity conditions (25°C/80% RH) is important if the dosage form is intended to market in territories of zone IV conditions. However, if the primary packing of solid dosage form provide a barrier to water vapor (aluminium/aluminium blisters), and then the stability testing at extremely high humidity storage condition is not required.[3]

In circumstances, where the drug substance or product is unable to fulfill the acceptance criteria at 30 ± 2°C/65 ± 5% RH storage condition for the duration of proposed retest period or shelf life, either of the option; to reduce a shelf life or retest period or to enhance the protective efficiency of container closure system or to place a cautionary statement in the labeling.[3]

Table 1: Difference between the general storage conditions in zone I/II and zone III/IV[3]

Study design	Storage condition		Minimum time period covered by study for submission of data
	Zone I/II	Zone III/IV	
Long term	25°C±2°C/60% RH±5%	30°C±2°C/65% RH±5%	12 months
Accelerated	40°C±2°C/75% RH±5%	40°C±2°C/75% RH±5%	6 months
Intermediate*	30°C±2°C/65% RH±5%	-	6 months

*= Alternate stability study condition (i.e. Intemediate) in case the drug substance/product fails to meet the specifications at 'Accelerated stability condition, RH= Relative humidity

Table 2: Difference between the storage conditions of aqueous based drug products in zone I/II and zone III/IV[3]

Study design	Storage condition		Minimum time period covered by study for submission of data
	Zone I/II	Zone III/IV	
Long term	25°C±2°C/40% RH±5% or 30°C±2°C/35% RH±5%**	30°C±2°C/35% RH±5%	12 months
Accelerated	40°C±2°C/NMT* 25% RH	40°C±2°C/NMT* 25% RH	6 months
Intermediate	30°C±2°C/35% RH±5%	-	6 months

*Relative Humidity (RH) should not more than (NMT) 25% with Aqueous based drug products, **= Alternate Long Term' stability condition with 'Aqueous based drug products' can be utilized during stability study whatever is feasible, RH= Relative humidity

Table 3: Difference between the general storage conditions in zone I/II and zone III/IV[3]

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at similar temperatures
65% RH	35% RH	1.9
75% RH	25% RH	3.0

RH= Relative humidity

STABILITY OF DRUG SUBSTANCES AND PRODUCTS

Stability testing of drug substances and products is an integral part of the systemic approach to stability evaluation. Stress testing is recommended to identify the degradation products, to establish degradation pathways, to identify the stability of the drug substance, and to validate the analytical procedure to assess the stability of molecule. However, the conditions of stress testing are segregated for drug substances and products that are (a) if an active substance is described in an official pharmacopoeia and meet the pharmacopoeial parameters then no further data is required to address the degradation products if they are enlisted in section of impurities, (b) if an active substance is not mentioned in official pharmacopoeia, it is recommended to provide the relevant published data to support the proposed degradation pathways, and (c) if there is no scientific data available in literature then stress testing is required to generate the evidence of stability of an active drug substance and finished drug products where photostability should be an integral part of stress testing. Stress testing is recommended to be carried out on at least single batch of drug substance and product.[5,6]

STRESS TESTING

The stress testing includes the effect of temperature with 10°C increments (for example, 50 or 60°C) and humidity with 75% RH or greater in accelerated stability testing. In case of liquid (solution or suspension) dosage forms, the susceptibility of drug substance to hydrolysis should be evaluated across the wide range of pH values.[5]

PHOTOSTABILITY TESTING

Considering photostability testing as an integral part of stress testing, covers the sensitivity of intrinsic characteristics of a new drug substance or product to light. A systemic approach to assess the photostability includes testing directly on active drug substance, on products outside immediate pack, inside immediate pack, and in marketing pack under influence of light similar to standard indoor and outdoor light, that is, standard ID65 and D65 emission, respectively. This testing includes forced degradation and confirmatory testing studies. The forced degradation testing are undertaken to degrade the sample deliberately to evaluate the overall photostability of material

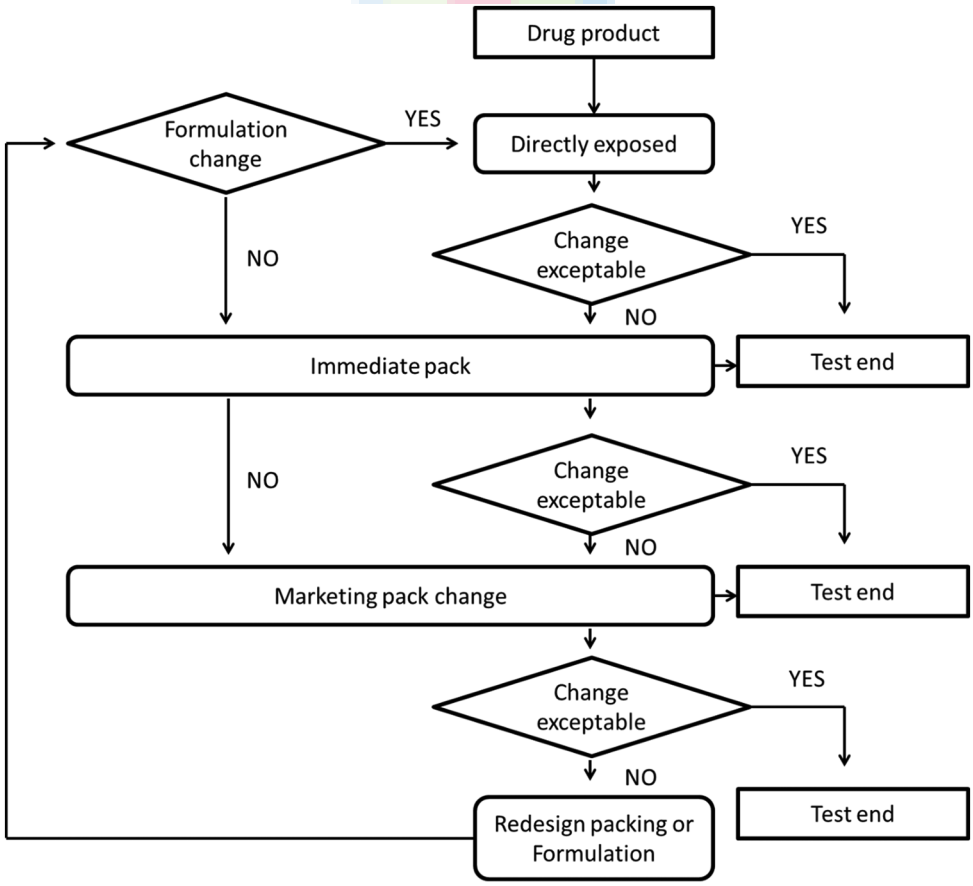

Figure 1: Decision tree to assess the action required with respect to the significance of change occurring during photostability study[7]

required for method and analytical development purpose. A variety of conditions may be used, depending on the photosensitivity of the substance involved and the intensity of light used. Under forced degradation, the decomposition products may be observed that are unlikely formed under the conditions used for confirmatory studies. Whereas, the confirmatory studies are undertaken to establish the photostability characteristics under standardized conditions to provide information necessary for handling, packaging, and labeling.[7]

After completion of study, the samples should be examined for changes in physical properties such as appearance, clarity of liquid dosage forms, dissolution, and disintegration of solid dosage forms, assay, and impurity profile. It is recommended that the forced degradation studies should be designed to generate suitable information required to develop and validate the test methods for confirmatory studies, where test should be capable of defining photolytic degradation that appear during confirmatory studies.[7] Photostability testing of drug product can be designed by assessing the changes through a decision tree mentioned below in Figure 1.

SELECTION OF BATCHES FOR STABILITY STUDY

For registration of drug substance, a stability study data from at least three batches manufactured following the same route and method is required to submit to regulatory authorities. The batches should be at least from pilot scale if full production scale batches are not available. The overall quality of samples of batches placed in stability is the representative quality of other batches manufactured following the same procedure. However, the data required for submitting an application of drug product should be from same dosage form and formulation in the same container closure intended to be marketed.[8,9] The types of stability data vary with type of dosage form, the details are addressed in Table 4.

GENERAL STORAGE CONDITIONS

A long-term, accelerated, and intermediate conditions are assessed during stability studies in required storage conditions, the minimum time period stability data of other storage conditions such as drug substance or product intended to be stored in refrigerator or to be stored in freezer required at the time of submitting drug application is mentioned below in Tables 5-8.[5,6,9]

STABILITY OF AQUEOUS-BASED DRUG PRODUCTS

For aqueous based drug product packaged in impermeable containers, the test for moisture sensitivity and solvent loss is not required as these containers provide a permanent barrier for the passage of moisture or solvent. Whereas, the assessment of physical, chemical, biological, and microbiological stability is required for products packaged in semipermeable containers.[3] The stability of aqueous-based drug products can be assessed following the storage condition addressed in Table 2.

During accelerated stability testing, 5% or more loss in water content after 3 months in semipermeable container is considered significant; but this water loss after the similar duration can be considered for small containers (1 mL or less) or unit-dose products if justified.[3]

If a significant change occurs during an accelerated storage condition, the proposed retest period should be based on the real time data of long-term storage condition and a discussion should be mentioned on the label to address the effect of short-term excursions during shipping and handling.[10]

The proposed retest period should be based on the real-time data of long-term storage condition as there is no accelerated storage condition for drugs intended to store in freezer. In this case, a single batch should be tested at elevated temperature (for example at 5 ± 3°C or 25 ± 2°C) for an appropriate time to address the short-term excursions outside the label which may occur during shipping and handling.[10]

Table 4: General stability conditions and the data required for drug substance or product at the time of submission[8,9]

Category of dosage form	Type of dosage form	Data from minimum number of batches required/type of batches (pilot/production scale)
Conventional (when active substances are known stable)	Immediate release dosage forms/solutions	At least two pilot/full scale batches are acceptable
Critical (when active substances are known unstable)	Any dosage form	Three batches where at least two pilot/full scale batches and third may be smaller

Table 5: General stability conditions and the data required for drug substance or product at the time of submission[5,6,9]

Study design	Storage condition	Minimum time period covered by study for submission of data
Long term*	25°C±2°C/60% RH±5% or 30°C±2°C/65% RH±5%	12 months (choice-1) or 6 months (choice-2)
Accelerated	40°C±2°C/75% RH±5%	6 months
Intermediate**	30°C±2°C/65% RH±5%	6 months

*= Alternate long term' stability condition based on feasibility, **= Alternate stability study condition (i.e. Intemediate) in case the drug substance/ product fails to meet the specifications at 'Accelerated stability condition, RH= Relative humidity

Table 6: General stability conditions and the data required for aqueous based drug product at the time of submission[3]

Study design	Storage condition	Minimum time period covered by study for submission of data
Long term	25°C±2°C/40% RH±5% or 30°C±2°C/35% RH±5%	12 months (choice-1) or 6 months (choice-2)
Accelerated	40°C±2°C/NMT 25% RH	6 months
Intermediate**	30°C±2°C/65% RH±5%	6 months

**= Alternate stability study condition (i.e. Intemediate) in case the aqueous based drug products fails to meet the specifications at 'Accelerated stability condition, NMT= Not more than, RH= Relative humidity

Table 7: Stability conditions for drugs intended to store in refrigerator and the data required at the time of submission[3,9]

Study design	Storage condition	Minimum time period covered by study for submission of data
Long term	5°C±3°C	12 months (choice-1) or 6 months (choice-2)
Accelerated	25°C±2°C/60% RH±5%	6 months

RH= Relative humidity

Table 8: Stability conditions for drugs intended to store in freezer and the data required at the time of submission[9]

Study design	Storage condition	Minimum time period covered by study for submission of data
Long term	−20°C±5°C	12 months (choice-1) or 6 months (choice-2)

During storage, thermal stability of drug product should be evaluated and if applicable its sensitivity to moisture and solvent loss. If the product needs reconstitution or dilution, the information should be addressed on label for preparation, storage, and in-use stability. The length of study should be designed to cover storage, shipment, and usage of drug product where the testing of reconstituted or diluted product through the in-use period should be evaluated on three batches.[10]

IN-USE STABILITY OF DRUG PRODUCTS

The in-use stability testing is to establish a period of time for a multidose product to use within an accepted specification once the container is opened; as repeated opening and closing may pose a risk to its content with respect to microbiological contamination, proliferation, and/or chemical degradation. Therefore, designing a framework for selection of batches, test design, test parameters, test procedures, storage conditions, etc., is crucial to understand the integrity of products in multidose containers. If the product is to be marketed in more than one strength or container size, the in-use stability test should be applied to the product which presents the highest susceptibility to change. To enhance the confidence, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life, testing should be performed on the final amount of product remained in the container. The in-use shelf life and storage condition recommendation should be stated on the label.[3,8,10]

REQUIREMENTS OF STABILITY SPECIFICATION

Stability studies include testing of those attributes of the drug substance and product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover physical, chemical, biological, and microbiological attributes; whereas, an additional testing of preservative content and functionality test for a dose delivery system needs to be assessed in case of drug product. The shelf life of drugs is calculated based on the stability data and the differences between release and shelf life acceptance criteria should be justified and supported by a validation data. The acceptance criteria should include individual and total upper limits for impurities and degradation products.[11]

TESTING FREEQUENCY DURING STABILITY STUDY

To generate a detailed stability profile, the frequency of testing for drug substance or product should be sufficient to track the changes during study period. For long-term study with a proposed retest period of 12 months, the frequency of testing should be every

3 months in 1st year, every 6 months in 2nd year, and annually thereafter through the proposed retest period and the maximum retest period is not more than (NMT) 12 months.[3,5,6,10]

For accelerated storage condition, the frequency of testing includes three time points that are initial, 3rd month, and final (6th month) as 6-month study is recommended. The frequency of testing can be increased depending upon the appearance of changes in samples stored at accelerated condition.[3,6]

The intermediate storage criteria is applied when a significant change results from accelerated study and intermediate condition is recommended for 12 months with testing frequency at 0, 6, 9, and 12 months.[3,10]

During stability study, a change should be considered significant if i) there is 5% or more change in assay from its initial value, ii) the level of impurities or degradation products exceeds the acceptance criteria of appearance, physicochemical properties, pH, or dissolution.[12]

The reduced testing can be applied through matrixing and bracketing where a reduction in testing frequency or testing certain strengths/combinations of similar dosage form is reduced or considered untested, if justified. During a reduced designed study, a change to full design study or increasing the listed test parameters can be considered if a proper justification is provided.[13]

Reduced testing design: Both reduced designs (bracketing and matrixing) are based on different principles; the use of both designs simultaneously needs a scientific justification.

CONCEPT OF BRACKETING DURING STABILITY STUDY

It is the design of stability schedule in which only samples of extremes (minimum and maximum) of certain design factors (strength, container size, and/or fill) are tested at all the time points of the stability protocol and the other intermediates can be assumed to represent the stability similar to extremes. The design factors are variables (for example, strength, container size, or fill) that needs to be evaluated in a study design to assess their effect on product stability.[13]

DESIGN OF REDUCED TESTING THROUGH BRACKETING

Before applying a bracketing design, its effect needs to be carefully evaluated to assess the product stability and to estimate the retest period or shelf life. During study, if the variations are observed among the stability of extremes, the intermediates will not be considered more stable than the least stable extreme and the shelf life should be estimated accordingly.[14]

CONCEPT OF MATRIXING DURING STABILITY STUDY

It is the design of stability schedule in which a selected subset of sample from the total number of samples would be tested at a specified time point. At different time point, another subset of samples would be tested. The matrixing design can be applied to the samples of the same drug product covering different strengths and container sizes of same container closure system. However, matrixing design can be applied to formulations of different strengths where the relative amounts of drug substance and excipients changed or different excipients used or in different container closure system, if justified.[13]

DESIGN OF REDUCED TESTING THROUGH MATRIXING

It depends on number of samples and time points to get a perfect fit matrix, however, the complete balancing of study design to matrix all time points with samples is difficult in matrixing design. In matrixing, all selected factor combinations should be tested at the initial and final time points; whereas, certain fractions of each combinations should be tested at each time point. If full, long-term data is not available to propose a shelf life before approval, the all selected combinations of batch including strength, container size, or fill should also be tested at 12 months prior to submission.[14]

CONDITIONS OF REDUCED TESSTING

In case after applying bracketing and matrixing design, if one strength or container size or fill is no longer intended for marketing, the stability testing of that strength or container size or fill should be continued to support the other strengths or container sizes or fills in the design. Generally, bracketing or matrixing design is applicable if the supporting data is able to predict

the products stability. Only minor variability with supporting data is acceptable to apply the reduced testing; but if the supporting data shows moderate variability, the reduced design should be statistically justified and the reduced design cannot be applied if the supportive data show significant variability.[13,14]

STRENGTH OF FORMULATION DURING REDUCED STABILITY TESTING

Bracketing and matrixing can be applied to formulations of different strengths (for capsules, the strength vary with different fill plug sized from the same powder blend; for tablets, the strength vary with the compressed amount of same granules; and for oral solutions, the different strength of formulation with minor variation in color and flavor).[13]

CONTAINER CLOSURE SIZES OR FILL DURING REDUCED STABILITY TESTING

Bracketing and matrixing can be applied to container closure system that is either fill or size of container varies, while the other parameters remains constant; whereas, bracketing will not be applicable in case of simultaneous variation of both, fill and size of container when smallest and largest containers represent the extremes of all packaging configurations. While selecting extremes, various characteristics such as wall thickness, surface area to volume ratio, headspace to volume ratio, water vapor permeation rate, container closure geometry, and oxygen permeation rate per dosage unit or unit fill volume.[13]

EVALUATION AND COMMITMENT OF STABILITY DATA

If the analysis of stability data shows minor batch-to-batch variability, the data can be clubbed to conclude the stability performance of drug substance or product and the shelf life should be calculated on the basis of minimum time a batch can be expected to remain within the acceptance criteria. In case, if the stability data is not available or fewer than three production batches, a commitment should be made to place the three production batches or to place an additional batch, respectively, on long-term and accelerated stability condition and to continue the studies through the proposed shelf life. Importantly, the stability protocol for commitment batches should be same as applied for initial batches, unless justified.[1,15]

To analyze the stability data of parameters susceptible to change with time is to determine the time at which the 95% confidence limit reaches the acceptance criteria. It is recommended to combine the data to calculate an overall estimate of total data if batch to batch variability is low. This can be calculated by applying statistics to the slopes of regression lines and zero intercepts to the data of individual batches. In case if combining data of several batches is not practical, the overall retest period should be based on minimum time a batch can be expected to remain within acceptance criteria. The evaluation of stability study should cover all aspects of degradation products and only the assay. Apparently, the degradation relationship with stability of drug substance and product can be represented by linear, quadratic, cubic function, arithmetic, or logarithmic scale.[10,16]

LABELING

A statement should be addressed on label addressing the storage conditions according to the national health regulatory requirements and should in line with the stability data. Specific instruction should be mentioned on the label such as protect from direct sunlight, store in a cool/cold condition, and avoid freezing for the product susceptible to degrade under such conditions.[3,5]

ESTIMATION OF SHELF LIFE OR RETEST PERIOD

The normal manufacturing and analytical variations are expected, but it is important to maintain the 100% of drug substance in formulation as per label claim at the time of batch release. If the assay is higher than 100% of label claim at the time of batch release, the proposed shelf life can be overestimated. In case if assay value is lower than 100% of label claim at the time of batch release, the proposed shelf life might fall below the acceptance criteria of shelf life. The proposed shelf life or retest period should not exceed the predicted testing schedule where each attribute should be assessed separately, and an overall assessment to propose shelf life or stability should be made based on findings.[17,18]

EXTRAPOLATION OF RETEST PERIOD OR SHELF LIFE

Extrapolation of stability data to extend the retest period or shelf life beyond the period covered by long-term study can be proposed if there is no significant change in accelerated condition. After

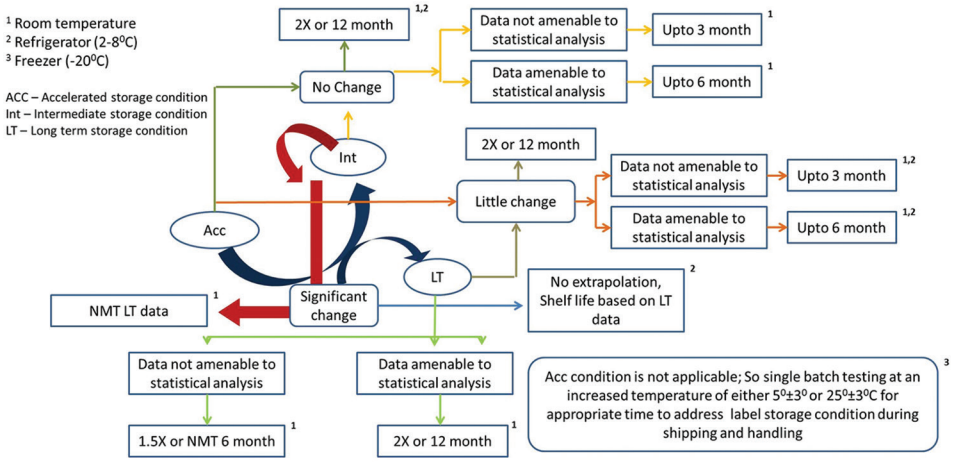

Figure 2: Evaluation and estimation of retest period or shelf life for active substances or drug products stored at room temperature, refrigerator (2–8°C), or freezer (−20°C).[9] Acc = Accelerated storage condition, Int = Intermediate, LT = Long-term storage condition, NMT = Not more than, 1 = Room temperature, 2 = Refrigerator (2–8°C), 3 = freezer (−20°C)

extrapolation, a similar stability pattern is assumed beyond the period covered by long-term study. Thus, the shelf life or retest period granted on the basis of extrapolation should always be verified at next test interval in long-term condition.[18]

When no significant change occurs at accelerated condition, the shelf life and retest period would depend on the nature of the long-term and accelerated data. If there is little or no change in long-term or accelerated condition, a justification about the change pattern is required and extrapolation of retest or shelf beyond the period covered by long-term data can be up to twice, but NMT 12 months. In case of changes observed in long-term or accelerated data, a statistical analysis can be used to establish the retest period or shelf life. The extrapolation of retest period or shelf life beyond the period covered by long-term depends on statistical analysis. If the available data is not amenable to statistics, the retest period or shelf life can be up to one and a half times, but should NMT 6 months beyond the period covered by long-term data. But if data is amenable, the statistical analysis can be performed and the proposed retest or shelf life can be up to twice, but NMT 12 months beyond the period covered by long-term data.[19]

If a significant change occurs at accelerated condition, the retest period or shelf life will depend on data of intermediate storage condition. Some changes like softening of suppository at accelerated condition is acceptable as it is designed to melt at 37°C and will fail in dissolution test. However, other significant changes apart from the prementioned parameter is not acceptable.[1,19]

At intermediate condition, and in case of no significant change, the extrapolation again depends on statistical analysis of data. If data is not amenable to statistical analysis, the proposed retest or shelf life will be NMT 3 months beyond the period covered by long-term data, but if it is amenable to statistics, the proposed retest or shelf life will be NMT 6 months beyond the period covered by long-term data. In case of significant changes at intermediate condition, the proposed retest or shelf life should not exceed the period covered by long-term data. Similarly, the extrapolation of retest period or shelf life of drug substances or products intended to store below room temperature. The summary to estimate a retest period or shelf life of drug substances or products stored at room temperature, refrigerator, and freezer is addressed in [Figures 1 and 2].[9]

SUMMARY AND CONCLUSION

Number of studies done by various research organizations and regulatory authorities to assess the effect of temperature on appearance and physicochemical properties of drug substances and products for different climatic zones (zone I–IV), and based on the guidelines are finalized by three major regulatory authorities of United States of America, Europe, and Japan to regulate the stability of drugs during manufacturing, packaging, shipping, marketing, and in-use condition. An assessment of drug stability is an important section which needs to be critically observed before submitting an application to market the drug substance or product in regulated, semiregulated, and emerging market. During stability testing, stress testing, is a useful tool to assess the

intrinsic stability of drug substances, formation of degradation products as well as to establish the degradation pathways and validating the analytical procedures where the container closer system plays a crucial role in regulating the stability of drug product.[4]

Based on stability data of long-term and accelerated storage condition, the integrity and efficiency of container to provide a robust barrier against the moisture content, the retest period, and shelf life can be proposed. Any significant change during the study results a change in proposed shelf life and retest period as well as in label information about the in-use stability of drug product.[18]

In case, if a drug application is lagging any stability information or a study performed on fewer than three production batches, a stability commitment should be made to continue the study post approval in order to firmly establish the shelf life. Short-term excursions due to the door opening of stability chamber is justified and acceptable, but the long-term excursion due to equipment failure or an excursion that exceeds more than 24 h need to be evaluated for its impact on drug product stability and should be addressed.[17,20,21]

There are number of other factors which affect the stability of a pharmaceutical product, including the stability of drug substance are the potential interaction between active and inactive ingredients, the manufacturing process, and container closure system. In order to maintain the climatic zone specific stability; the storage, handling, the length of time between manufacture, and usage are important parameters which need to be monitored critically. In regulatory perspective, the expiry date and shelf life are one of the prime focuses in evaluating the quality and robustness of dosage form and an active ingredient. Based on the recommended storage condition, the drug substance or product should adhere to the storage requirements specified in the product labeling, which will help ensuring the product stability to manufacturers' labeled expiry date. For shelf life, if the storage conditions followed appropriately, the drug substance or product will retain fitness for use, that is, between 95 and 105% of the label claimed potency. Although, in some cases the shelf life may be estimated by accelerated stability testing protocols and the real-time product stability is necessary to validate the stability claims.[2,17,19]

Today, the increasing attention of health regulatory authorities are towards the review of stability study design, submitted stability data, and its interpretation with the possible effects of storage and transport on the stability of drug substance and products. The critical evaluation of stability data of drug substance and product is well deserved as it is the vast area which needs a high level of confidence to assure the quality of drug products that are supplied to patients.

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