RECENT TRENDS OF STABILITY STUDY OF PHARMACEUTICAL DOSAGE FORMS AND ITS SELF LIFE – A REVIEW ARTICLE

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Abstract: The stability studies are one of the very important parameters of pharmaceutical products. Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. Stability assessment and shelf-life prediction is usually a major focus of a pharmaceutical scientist's attention in the development of all dosage forms. It is important in the development of small molecule drug products as well, particularly given the importance of the physical state of the drug in determining stability characteristics. The stability of the pharmaceutical formulation during its entire shelf life in its final packaging is an important matter. Stability study does not only cover the physiochemical aspects of the drug but also explains the safety and efficacy of the product during its entire shelf life. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies. Importance of various methods followed for stability testing of pharmaceutical products, guidelines issued for stability testing and other aspects related to stability of pharmaceutical products have been presented in a concise manner in the present review. . Stability is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labelling instructions. Current trends in stability testing also described.

Key words: **Stability, Stability studies, Shelf Life, Pharmaceutical drug products; Dosage forms and ICH guidelines.**

INTRODUCTION

Stability study of pharmaceutical items is a mind boggling course of action of frameworks including noteworthy cost, time use and consistent fitness to work in quality, ampleness and prosperity in a medicine plan. Coherent and business accomplishment of a pharmaceutical item should be ensured with the perception of the prescription headway process and the load errands

and perspectives that are essential to a broad change plan. The most fundamental steps in the midst of the developmental stages fuse pharmaceutical examination and quality considers that are required to choose and ensure the identity, power and righteousness of fixings, and furthermore those of the point by point products1. Strength testing of a pharmaceutical item may be described as the limit of a particular definition in a specific Container/end system to remain inside its physical, compound, microbiological, toxicological, guarded and illuminating specifications2. So to speak, it is how much an item holds, inside beyond what many would consider possible, every single through it time of limit and uses comparable properties and characteristics had at the period of its packaging. Strength testing consequently evaluates the effect of regular factors on the idea of the a solution substance or a nitty gritty item which is utilized for desire for its time allotment of reasonable ease of use, choose authentic limit conditions and propose naming bearings. Furthermore, the data made in the midst of the dependability testing is a basic essential for authoritative underwriting of any medicine or definition. Dependability testing is named as an unusual system by virtue of consideration of an arrangement of factors influencing the quality of a pharmaceutical item. These components consolidate strength of the dynamic ingredient (s); correspondence between unique fixings and excipients, manufacturing process took after, sort of estimations outline, compartment/end system used for packaging and light, warmth and clamminess conditions experienced in the midst of shipment, accumulating and managing. Moreover, corruption reactions like oxidation, diminishing, hydrolysis or racemization, which can accept vital part in Stability investigation of a pharmaceutical item, similarly depend upon such conditions like gathering of reactants, pH, radiation, driving forces et cetera. And also the rough materials used and the timeframe among manufacture and use of the item. A pharmaceutical item may encounter change in appearance, consistency, content consistency, clarity (course of action), suddenness substance, particle size and shape, pH, package respectability thusly impacting its soundness testing. Such physical changes may be an immediate aftereffect of impact, vibration, scratched territory and temperature fluctuations, for instance, setting, defrosting or shearing et cetera. The engineered reactions like solvolysis, oxidation, decreasing, and racemization et cetera. That occur in the Pharmaceutical items may provoke the advancement of defilement item, loss of quality of dynamic pharmaceutical settling (API), loss of excipient activity like antimicrobial added substance action and tumour counteractive action specialists . Quality of a pharmaceutical item can in like manner be affected in perspective of microbiological changes like improvement of microorganisms in non-sterile items and changes in added substance ampleness. Steadfastness testing of pharmaceutical items is a marvellous arrangement of techniques which incorporate amazing cost, time use and coherent dominance with a particular true objective to work in quality, sufficiency and prosperity in a medicine definition. Sensible and business accomplishment of a pharmaceutical item should be ensured with the cognizance of the drug progression process and he pile assignments and perspectives that are basic to a total change outline. Security testing is named as a complicated system in light of commitment of a collection

of parts affecting the Stability investigation of a pharmaceutical item. These factors join strength testing of the dynamic settling (s); coordinated effort between unique fixings and excipients, delivering process took after, kind of measurement shape, holder/end structure used for packaging and light, warmth and moistness conditions experienced in the midst of shipment, amassing and managing. A pharmaceutical item may encounter change in appearance, consistency, content consistency, clearness (plan), sogginess substance, atom size and shape, pH, package uprightness thusly affecting its Stability think about. Such physical changes may be an immediate consequence of impact, vibration, scratched spot, and temperature instabilities, for instance, cementing, defrosting or shearing et cetera. The compound reactions like solvolysis, oxidation, abatement, racemization et cetera that occurs in the pharmaceutical items may provoke the improvement of corruption item, loss of quality of dynamic pharmaceutical settling (API), loss of excipient activity like antimicrobial added substance movement and tumor avoidance operators et cetera. Strength of a pharmaceutical product can likewise be influenced in view of microbiological changes like development of microorganisms in non-sterile products and changes in additive adequacy. [1, 2]

The USP portrays the quality of pharmaceutical item as "degree to which an item holds inside demonstrated points of confinement" and every through it time of limit and use (i.e. its opportunity range of ease of use) comparable properties and qualities that it had at the period of its manufacture. Reliability considers is a basic stake of the solution headway process. Constancy is the fundamental way that ensures whether the medicine is inside affirmation criteria or not. Quality comes into focus when the quality and efficiency of the drug are concerned. Demanding significance of Stability think about is the breaking point of a medicine item to remain inside judgments set up to ensure its identity, quality and perfection. Wobbliness of the drug can cause undesired change in execution that causes item disillusionments. In the present review essentialness of various techniques took after for reliability testing of pharmaceutical items, rules issued for soundness testing and diverse perspectives related to strength of pharmaceutical items have been presented compactly. [3, 4]

IMPORTANCE OF STABILITY STUDIES:

The basic clarification behind steadiness testing is the stress for the success of the patient encountering the infection for which the items are delineated. Beside corruption of the touchy item into unsafe disintegration items, loss of activity up to a level of 85% of that affirmed on the stamp may incite frustration of the treatment realizing passing e.g. nitro-glycerine tablets for angina and heart disappointment. In light of this stress, it has transformed into a legitimate essential to offer data to particular sorts of security tests for the managerial workplaces already underwriting of another item. Second fundamental concern is to anchor the reputation of the creator by ensuring that the item will hold wellbeing for use with respect to all basically appropriate qualities for whatever time span that they are accessible. Diverse points of interest of quality learns at the developmental stage or of the elevated items are to give a database that may be of a motivation in decision of adequate subtle elements, excipients and holder end structures

for headway of another item, to choose time range of ease of use and limit conditions for development of another item, preparation of selection dossier, to substantiate the ensured time period of practical ease of use for the enrolment dossier and to affirm that no movements have been displayed in the arrangement or collecting process that can negatively impact the strength of the item. [5, 6]

TYPES OF STABILITY TESTING:

Stability testing is a typical technique performed on calm substances and items and is used at various periods of the item change. In starting occasions, stimulated dependability testing (at reasonably high temperatures and also clamminess) is used as a piece of demand to choose the kind of debasement items which may be found after whole deal accumulating. Testing under less intensive conditions i.e. those endorsed for whole deal rack amassing, at possibly lifted temperatures is used to choose an item's time allotment of sensible ease of use and slip by dates. The huge purpose of pharmaceutical Stability think about testing is to give sensible insistence that the items will remain at an acceptable level of health/quality all through the period in the midst of which they are in business focus available for supply to the patients and will be fit for their use until the patient uses the last unit of the item Depending upon the point and steps took after, strength testing strategies have been arranged into the going with four forms. [7, 8]

1) Real Time Stability Testing:

Real time stability testing is routinely performed for longer term of the preliminary with a particular ultimate objective to allow important item degradation under proposed accumulating conditions. The season of the test depends on the quality of the item which should be adequately long to show clearly that no quantifiable degradation occurs and ought to enable one to perceive debasement from between measure assortment. In the midst of the testing, data is accumulated at an appropriate repeat with the true objective that an example examination can perceive precariousness think about from ordinary unclearness. The constancy of data interpretation can be extended by including a singular bunch of reference material for which security characteristics have quite recently been developed. Soundness testing of the reference material fuses the Stability investigation of reagents and furthermore consistency of the execution of the instrument to be used all through the season of steadfastness testing. In any case, structure execution and control for skim and brokenness coming to fruition in light of changes in the two reagents and instrumentation must be watched. [9, 10]

2) Accelerated Stability Testing:

In accelerated stability testing, an item is stressed at a couple of high (more sizzling than including) temperatures and the proportion of warmth input required to cause item dissatisfaction is settled. This is done to subject the item to a condition that revives corruption. This information is then foreseen to anticipate time span of practical ease of use or used to investigate the relative soundness testing of elective definitions. This for the most part gives an early indication of the item time range of ease of use and thusly shortening the refrigerated consequent to pushing, and

after that tried in the meantime. Since the length of the examination is short, the likelihood of instability in the estimation structure is lessened in relationship progression plan.

Despite temperature, push conditions associated in the midst of stimulated dependability testing are moistness, light, fomentation, gravity, pH and package. In stimulated strength testing the models are subjected to worry to the nonstop steadiness testing. Further, in revived solidness testing, examination of the unstressed item with concentrated on material is made inside a comparative test and the concentrated on test recovery is imparted as percent of unstressed model recovery. For genuine reasons, the treatment in stimulated constancy projections is endorsed to be coordinated at four assorted weight temperatures. Regardless, for thermolabile and proteinaceous sections, respectably exact robustness projections are gotten while denaturing weight temperatures are avoided. For truthful reasons, the treatment in enlivened security projections is endorsed to be coordinated at four different weight temperatures.

Quickened strength testing relies upon the Arrhenius condition (1) and balanced Arrhenius condition. [11, 12, 13]

$$K = Ae^{-E_a/(RT)}$$

$$\ln(K) = \frac{-Ea}{RT} + \ln(A)$$

Where,

K = degradation rate

A = Frequency factor/s

ΔE = Activation energy **(kJ/mol)**

R = Universal gas constant (**0.00831kJ/mol**)

T = Absolute temperature **(K)**

As modified. Equation:

$$K = A(T/T_0)^n . e^{-Ea/(RT)}$$

These conditions depict the connection between capacity temperatures and corruption rate. Utilizing Arrhenius condition, projection of solidness from the debasement rates saw at high temperatures for some corruption procedures can be resolved. At the point when the actuation vitality is known, the corruption rate at low temperatures might be anticipated from those seen at **"Stress"** temperatures. [14]

3) Retained Sample Stability Testing:

This is a common practice for each publicized item for which quality data are required. In this examination, Solidness tests, for held limit with regards to no short of what one bundle multiyear are picked. If the amount of clusters promoted outperforms 50, strength a test from two bundles are recommended to be taken. At the period of first introduction of the item in the market, the security trial of each gathering may be taken, which may be decreased to only 2% to 5% of advanced bunches at a later stage. In this examination, the quality tests are attempted at fated between times i.e. if an item has time allotment of reasonable ease of use of 5 years, it is normal to test tests at 3, 6, 9, 12, 18, 24 and 36 months. This customary methodology for gaining Stability consider data on held limit tests is known as steady break system. Solidness examine testing by evaluation of market tests is a balanced technique which incorporates accepting precedents starting at now in the business focus and surveying strength testing properties. This sort of testing is naturally more handy since it challenges the item not just in the respected held precedent storing conditions, yet furthermore in the veritable business focus. [15, 16, 17]

4. Cyclic Temperature Stress Testing

This is certainly not a standard testing procedure for promoted items. In this technique, cyclic temperature push tests are made on data out of the item to impersonate likely conditions in business focus amassing. The season of cycle generally considered is 24 hours since the diurnal beat on earth is 24 hour, which the exhibited pharmaceuticals are well while in transit to inclusion in the midst of limit. The base and most extraordinary temperatures for the cyclic weight testing is recommended to be picked on an item result preface and considering factors like proposed accumulating temperatures for the item and specific manufactured and physical defilement properties of the items. It is moreover recommended that the test should usually have 20 cycles. [18, 19, 20]

Table 01: ICH Stability Zones.

ZONE	TYPES OF CLIMATE
Zone **1**	Mediterranean / Subtropical zone
Zone **2**	Hot dry zone
Zone **3**	Hot humid/Tropical zone
Zone **4 a**	ASEAN testing conditions
Zone **4 b**	Hot / Higher humidity

Table 02: Long Term Testing Conditions.

Climate Zone	Temperature	Humidity	Minimum Duration
Zone **1**	21°c ± 2°c	45 % ± 5 % RH	12 Months
Zone **2**	25°c ± 2°c	60 % ± 5 % RH	12 Months
Zone **3**	30°c ± 2°c	35 % ± 5 % RH	12 Months
Zone **4 a**	30°c ± 2°c	65 % ± 5 % RH	12 Months
Zone **4 b**	30°c ± 2°c	75 % ± 5 % RH	12 Months
Refrigerated	5°c ± 3°c	No Humidity	12 Months
Frozen	-15°c ± 5°c	No Humidity	12 Months

Table 03: Accelerated and Intermediate Testing Conditions:

Test Type	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40 °c ± 2°c	75 % ± 5 % RH	6 Months
Accelerated Refrigerated	25 °c ± 2°c	60 % ± 5 % RH	6 Months
Accelerated Frozen	5 °c ± 3°c	No Humidity	6 Months
Intermediate	30 °c ± 2°c	65 % ± 5 % RH	6 Months

STAGES OF STABILITY STUDY:

Stability studies are conducted at every stages of the drug life cycle from 1st stages of product development to late stage follow up studies. There are 6 different stages: [21, 22]

Stage 1: Early stage i.e., stress and accelerated testing with drug substances.

Stage 2: Stability on pre-formulation lots/ batches.

Stage 3: Stress test done on scale up batches.

Stage 4: Accelerated and long term testing for registration purposes.

Stage 5: Enduring stability testing.

Stage 6: Follow up studies.

IMPORTANCE OF STABILITY STUDY STAGES:

The stability testing that we did assume a noteworthy part in the lifecycle of an effective pharmaceutical plan and product. Stability study consider does not just cover the physiochemical parts of the medication yet in addition clarifies the wellbeing and adequacy of the product amid its whole time span of usability. [23, 24]

FACTORS INFLUENCING DRUG STABILITY STUDY: [25, 26, 27]

a) **Moisture:** Water soluble solid dosage form will dissolve when comes in contact with any moisture layer and leads to create many physical and chemical changes in the dosage leading it to lose its properties.

b) **Excipients:** Some excipients like starch and povidone have high water contents and affect the stability by increasing the water content of the formulation. Sometimes chemical interactions between the excipients and the drug can occur and lead to decrease in stability.

c) **Temperature:** Changes in temperature have sometimes drastic effect on the stability of drug. Increase in temperature usually causes increase in hydrolysis rate of drugs. The effect of temperature on stability described by Arrhenius equation.

d) **P^H:** pH has great effect on the rate of decomposition of drugs that are hydrolysed in solution. To minimize this effect drug are formulated at the pH of maximum stability using buffers.

e) **Oxygen:** The presence of oxygen promotes oxidation in some drugs. Drugs which have higher rate of decomposition when exposed to oxygen are stabilized by replacing the oxygen in the storage container with nitrogen or carbon dioxide.

f) **Light:** Certain drugs are photosensitive and their rate of decomposition enhances when exposed to light. Their susceptibility can be tested by comparing it stability when exposed to light to that when stored in dark. Photosensitive drugs should be stored in amber glass containers and should be kept in dark.

GUIDELINES FOR STABILITY TESTING:

To ensure that in a perfect world stable particles and items are created, appropriated and given to the patients, the regulatory specialists in a couple of countries have made courses of action in the drug controls for the convenience of security data by the creators. Its fundamental outline was to gain consistency in testing from creator to maker. These principles join basic issues related to quality, the robustness data necessities for application dossier and the methods for their execution. Such guidelines were at first issued in 1980s. These were later arranged (made uniform) in the International Conference on Harmonization **(ICH)** remembering the true objective to vanquish the bottleneck to advertise and select the items in various countries. The ICH was a consortium formed with commitments from both regulatory and industry from European commission, Japan and USA. The World Health Organization **(WHO),** in 1996, changed the standards in light of the fact that the ICH rules did not address the uncommon climatic conditions found in various countries and it just anchored new drug substances and items and not the authoritatively settled items that were accessible for use in the WHO umbrella countries. In **June 1997, US FDA** furthermore issued a bearing record entitled 'Slip by dating of solid oral measurements shape containing Iron. WHO, in 2004, also released rules for security ponders in overall condition, ICH rules were in like manner expanded later for veterinary items. A particular monograph on steadiness testing of pharmaceutical substances and items existing in India has also been released by India Drug Manufacturers Association. Further, one of a kind test condition and essentials have been given toward the path reports for dynamic pharmaceutical

fixings, calm items or definitions and excipients. The codes and titles anchored under ICH course have been spread out in the Series of tenets related to strength testing have in like manner been issued by the Committee for Proprietary Medicinal Products **(CPMP)** under the European Agency for the Evaluation of Medicinal Products **(EMEA)** to help those searching for exhibiting endorsement for therapeutic items in European Union. [28, 29, 30]

❖ GUIDELINE FOR ACTIVE PHARMACEUICAL INGREDIENT GENRAL CASE:

Data on the stability testing of the API is a fundamental piece of the efficient way to deal with dependability assessment. Potential ascribes to be tried on an API amid stability testing are recorded in the cases of testing parameters will be portrayed in the lower some portion of this rule. Regardless of whether long haul solidness examines are performed at 25 ℃ ± 2 ℃/60% RH ± 5% RH or 30℃ ±2 ℃/65% RH ± 5% RH or 30℃ ± 2 ℃/75% RH ± 5% RH is controlled by the climatic condition under which the API is planned to be put away. Testing at a more serious long haul condition can be a contrasting option to testing condition, i.e. 25 ℃/60% RH or 30 ℃/65% RH. On the off chance that 30℃ ± 2℃/65% RH ± 5% RH or 30℃ ± 2℃/75% RH ± 5% RH is the long haul condition there is no moderate condition. [31, 32, 33]

Table 04: Long term, Intermediate and Accelerated testing condition for General case.

Study	Storage Condition	Minimum Duration
Long Term	25°c ± 2°c , 60 % ± 5 % RH 30°c ± 2°c , 65 % ± 5 % RH 30°c ± 2°c , 75 % ± 5 % RH	12 Months or 6 Months
Intermediate	30°c ± 2°c , 65 % ± 5 % RH	6 Months
Accelerated	40°c ± 2°c , 75 % ± 5 % RH	6 Months

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❖ Active Pharmaceutical Ingredients Intended For Storage in a Refrigerator:

Whether accelerated stability studies are performed at 25 ± 2 ℃/60% RH ± 5% RH or 30 ℃ ± 2 ℃/65% RH ± 5% RH or 30 ℃ ± 2 ℃/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe long term condition can be an alternative to storage testing at 25 ℃/60%RH or 30 ℃/65%RH. [34, 35, 36]

Table 05: Active pharmaceutical ingredients intended for storage in a refrigerator.

Study	Storage Condition	Minimum Duration
Long Term	5 ℃ ± 3 ℃	12 Months
Accelerated	25°c ± 2°c , 60 % ± 5 % RH 30°c ± 2°c , 65 % ± 5 % RH 30°c ± 2°c , 75 % ± 5 % RH	6 Months

❖ **GUIDELINE FOR FINISHED PHARMACEUTICAL PRODUCTS GENERAL CASE:**

Whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30°C/65% RH. [37, 38, 39]

- If 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition. [40]
- If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months' data from a 12-month study at the intermediate storage condition.

Table 06: Long term, Intermediate and Accelerated testing condition for General case.

Study	Storage Condition	Minimum Duration
Long Term	25°c ± 2°c , 60 % ± 5 % RH 30°c ± 2°c , 65 % ± 5 % RH 30°c ± 2°c , 75 % ± 5 % RH	12 Months or 6 Months
Intermediate	30°c ± 2°c , 65 % ± 5 % RH	6 Months
Accelerated	40°c ± 2°c , 75 % ± 5 % RH	6 Months

❖ **FPPS PACKED IN SEMI- PERMEABLE CONTAINER:**

Aqueous based products bundled in semi-porous holders ought to be assessed for potential water misfortune notwithstanding physical, substance, organic and microbiological security. This assessment can be done under states of low relative dampness, as examined underneath.

Regardless of whether long haul Stability study thinks about are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH is controlled by the climatic condition under which the FPP is proposed to be advertised. Testing at 30°C/35% RH can be a contrasting option to the capacity condition at 25 °C/40% RH. [[41, 42, 43]

Table 07: Stability studies for FPPS Packaged Semi-permeable Containers.

Study	Storage Condition	Minimum Duration
Long Term	25°c ± 2°c , 40 % ± 5 % RH 30°c ± 2°c , 35 % ± 5 % RH	12 Months
Intermediate	30°c ± 2°c , 65 % ± 5 % RH	6 Months
Accelerated	40°c ± 2°c , **NMT** 25 % RH	6 Months

❖ **FPPS INTENDED FOR STORAGE IN A REFRIGERATOR:**

Whether accelerated stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25°C/60% RH or 30 °C/65% RH. [44, 45]

Table 08: Stability studies for FPPS Packaged Semi-permeable Containers intended for storage in a refrigerator.

Study	Storage Condition	Minimum Duration
Long Term	5 °C ± 3 °C	12 Months
Accelerated	25°c ± 2°c , 60 % ± 5 % RH 30°c ± 2°c , 65 % ± 5 % RH 30°c ± 2°c , 75 % ± 5 % RH	6 Months

EXAMPLES OF TESTING PARAMETERS:

SECTION I: FOR ACTIVE PHARMACEUTICAL INGREDIENTS

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable. [46, 47, 48]

SECTION II: FOR FINISHED PHARMACEUTICAL PRODUCTS

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage

1. Tablets:

Dissolution (or disintegration, if justified), water content and hardness/ friability.

2. Capsules:

- **Hard Gelatine Capsules**

Brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.

- **Soft Gelatine Capsules**

Dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage and pellicle formation.

3. Oral Solutions, Suspensions and Emulsions:

Formation of precipitate, clarity (for solutions), pH, viscosity, extractabilities, level of microbial contamination. Additionally for suspensions, dispensability, rheological properties, mean size and distribution of particles should be considered.

4. Powder and Granules for Oral Solution or Suspensions

Water content and reconstitution time, Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions", after preparation according to the recommended labelling, through the maximum intended use period.

5. Metered-Dose Inhalers and Nasal Aerosols

Estimations content consistency, checked number of solution incitation's per holder meeting measurements content consistency, streamlined atom gauge dissemination, infinitesimal appraisal, water content, discharge rate, level of microbial contamination, valve movement (shot weight), extractable/leachable from plastic and elastomeric fragments, weight decrease, direct transport, outside particulate issue and extractable/leachable from plastic and elastomeric portions of the compartment, end and pump. Tests should be secured in upright and reworked/as untimely idea presentations. [49]

For suspension-type pressurized canned products, minuscule examination of appearance of the valve segments and holder's substance for substantial particles, changes in morphology of the API particles, degree of agglomerates, precious stone development, remote particulate issue, consumption of within the compartment or disintegration of the gaskets.

6. Nasal Sprays: Solutions and Suspensions:

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/ or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractable/ leachable from plastic and elastomeric components of the container, closure and pump. [50]

7. Topical, Ophthalmic and OTIC Preparations:

Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops and cutaneous sprays.

• Topical preparations should be evaluated for clarity, homogeneity, pH, suspend ability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

• Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.

• Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions). [51]

8. Suppositories

Softening range, disintegration and dissolution (at 37°C).

9. Small Volume Parenteral (SVPS)

Color, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

• The stability studies for Suspension for injection should include, in addition, particle size distribution, dispensability and rheological properties. The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

10. Large Volume Parenteral (LVPS)

Color, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

11. Transdermal Patches

In vitro release rates, leakage, level of microbial contamination/sterility, and adhesive forces.

EXPIRATION DATE / SHELF LIFE:

A expiration date is characterized as the time up to which the item will stay stable when put away under suggested stockpiling conditions. In this way, a termination date is the date past which it is anticipated that the item may never again hold qualification for utilize. On the off chance that the item isn't put away as per the maker's guidelines, at that point the item might be relied upon to debase all the more quickly. Time span of usability is the time amid which the item, whenever put away suitably according to the producer's directions, will hold readiness for utilize (>90% of mark guarantee of intensity). The termination date is additionally characterized as the date put on the compartment/marks of a medication item assigning the time amid which a group of the item is relied upon to stay inside the affirmed time span of usability particulars, whenever put away under characterized conditions and after which it ought not be utilized. [52, 53]

ESTIMATION OF SHELF LIFE:

The shelf life is determined from the data obtained from the long term storage studies. The data is first linearized and test for goodness of fit is applied. The linearized data is then analysed to see that the slope and the intercepts are matching. Table below gives the different possibilities in the pattern of the concentration-time data of the three batches. The data is pooled accordingly and used for estimation of the common slope. [54, 55]

ICH GUIDELINES FOR STABILITY STUDY:

This Guideline has been revised a second time and has reached Step 4 of the ICH process in February 2003. This Guideline provides recommendations on stability testing protocols including temperature, humidity and trial duration for climatic Zone I and II. Furthermore, the revised document takes into account the requirements for stability testing in Climatic Zones III and IV in order to minimise the different storage conditions for submission of a global dossier. [56, 57, 58]

ICH Code	Guideline title
Q1A	Stability testing of New Drug Substances and Products (Second Revision)
Q1B	Stability testing : Photostability testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
Q5C	Stability testing of Biotechnological/Biological Products

Fig.No.01: - Codes and Titles Used in ICH Guidelines

CPMP code	Guideline title
CPMP/QWP/ 576/96 Rev. 1	Guideline on Stability Testing for Applications for Variations to a Marketing Authorization
CPMP/QWP/ 6142/03	Guideline on Stability Testing for Active Substances and Medicinal Products Manufactured in Climatic Zones III and IV to be marketed in the EU
CPMP/QWP/ 609/96 Rev. 1	Note for guidance on Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances
CPMP/QWP/ 122/02 Rev. 1	Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
CPMP/QWP/ 072/96	Note for Guidance on Start of Shelf Life of the Finished Dosage Form
CPMP/QWP/ 2934/99	Note for Guidance for In-Use Stability Testing of Human Medicinal Products
CPMP/QWP/ 576/96	Note for Guidance on Stability Testing for a Type 2 variation to a Marketing Authorization
CPMP/QWP/ 159/96	Note for Guidance on Maximum Shelf-Life for Sterile Products after First Opening or Following Reconstitution

Fig. No.02: CPMP Guidelines for Stability

CURRENT TRENDS IN STABILITY TESTING:

Current pattern, particularly among the multinational pharmaceutical organizations, is to characterize conditions for dependability testing for worldwide promoting. For this the organizations are arranging their conventions to single arrangement of conditions that spreads extraordinary ecological conditions. The particular changes for worldwide testing incorporate increment in term of quickened testing period from 6 to a year, and lead of extra tests at 50°C/75% RH for 3 months .The idea driving this change is to evade reiteration of solidness testing for different areas and effective and ideal utilization of assets as all tests are done in one research facility. Besides testing under mix of three ecological elements, viz., temperature, moistness and light, has been accounted for to result in more grounded harmful impact on sedate substances and items, than under temperature and mugginess conditions as it were. [59, 60, 61]

CONCLUSION:

Stability testing is currently the key procedural part in the pharmaceutical improvement program for another medication and additionally new detailing. Solidness tests are completed with the goal that prescribed stockpiling conditions and timeframe of realistic usability can be incorporated on the mark to guarantee that the prescription is protected and successful all through its time span of usability. Over some stretch of time and with expanding knowledge and consideration, the administrative prerequisites have been made progressively stringent to accomplish the above objective in every single conceivable condition to which the item may be subjected amid its timeframe of realistic usability. Along these lines, the soundness tests ought to be done after legitimate logical standards and subsequent to comprehension of the current administrative necessities and according to the climatic**.**

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