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STABILITY TESTING IN DEVELOPMENT OF DRUG PRODUCT

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Abstract

Every Pharmaceutical Product is having a specific shelf-life. It means up to that time the product will remain robust i.e. it will remain unaffected by variety of environmental factors such as humidity, light and temperature.

Pharmaceutical Companies perform stability studies on every Drug Substance and Drug Product manufactured by them to full fill the Regulatory requirements for grant of Approval as well as stability is conducted on annual batch to keep an eagle eye on the quality of drug product throughout the shelf life.

There are different types of stability studies viz-a-viz Physical, chemical and microbial study. The objective of all type of stability studies is same i.e. maintenance of Product quality. Regulatory Guidelines suggest that there is no need of complete testing every time. Pharma company on the basis of requirements can select a particular pattern of testing without compromising the quality of Product. The present article will discuss all possible ways to reduce testing burden along with general requirements.[1]

Key Words: stability studies, Accelerated Stability data, Long Term, Skip testing, Bracketing and Matrixing.

Introduction

Stability of a pharmaceutical product indicates that how long Drug Substance and Drug Product can maintain its integrity without any chemical and visible changes under the influence of various environmental factors like temperature, humidity and light. Stability studies are conducted for following purposes:

- To establish Re-Test period of Drug Substance.
- To establish Expiry date of Drug Product.
- To determine the storage condition of Drug substance and Drug Product.
- To determine the type of Impurity generated in stability sample or limits exceeded beyond safety levels so that proper method development to control the impurity.
- To develop production strategies. On the basis of stability studies product manufacturing method is evaluated and in-case of any breach new production method is developed.
- To assure the physical, chemical and biological robustness of the product by conducting stress studies.
- To determine the product safety in Packaging material. In case any variability in data e.g. moisture content and Microbial contamination new packaging material will be proposed.
- To get the approval for commercialization. When the product passes stability testing as per quality standards defined by ICH and WHO only then get approval for commercialization.

The drug product which are not stable, can result in physical changes (like rate of dissolution hardness, phase separation etc.) as well as chemical characteristics (breakdown of existing substance and formation of new potent substances). Therefore, physical and chemical stability of drug are of great importance. Also, the drug degradation yields intolerable and potent by-products which are hazardous to the end users. Apart from above mentioned instabilities, microbiological instability also maybe hazardous specially in case of sterile drug products. Stability evaluation is key factor to determine the quality of drug substance and drug product. Stability evaluation of proposed and existing drug products and drug substances are primary functions of Regulatory Agencies. Regulatory Agencies keep an eagle eye on stability-testing failures which plays a major role in audit findings, shelf life reduction and product withdrawals. Stability testing problems generally leads to issuance of warning letters and costly product recall.[1,2,5,6,7&8]

Discussion

While designing the stability study grid for a product it is necessary to know the physical, chemical properties and general behavior of the drug substance and drug product. The previous experience gained from stability data of drug substance and formulation studies can contribute in selecting the type of study.

There are different types of stability studies which are being performed during development of drug product. General testing frequency, the description of studies, selection criterion and reason for performance are listed below:

Testing frequency[1,2&3]

Type of Study	Testing Station
Accelerated Studies	0, 3, 6 Months
Long Term Studies	0, 3, 6, 9, 12, 18, 24 Months
Intermediate Studies	0, 6, 9, 12 Months

Stress testing

When the testing at a temperature above accelerated condition i.e. temperature 50˚C, 60˚C and 70˚C,humidity conditions 75% RH and 90% RH, the atmospheric conditions oxidative and wide range of pH are being used to performed and check the robustness of the formulation and to elucidate the intrinsic stability of the product are known as stress testing.[1,2&3]

Photostability Testing

The substances which are affected by light or having sensitivity towards light are need to be tested for photostability. The photostability is generally conducted on at least one stability batch if the appropriate results obtained through studies.

For photostability testing following light sources can be used:

Option 1: The light sources indicating similar output to D65/ID65 emission standard such as combined visible and ultraviolet (UV) fluorescent lamp, xenon, or metal halide lamp.

Option 2: The same sample can be exposed to both the cool white fluorescent and near ultraviolet lamp. A 1: cool white fluorescent lamp produces an output similar to specified in ISO 10977(1993); and A 2: near UV fluorescent lamp having a spectral range from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm can be used.

The confirmatory studies are performed by providing an overall illumination of not less than 1.2 million lux hours.[5]

Accelerated Stability Testing

In these types of studies, a product is stored at stress conditions (such as temperature, humidity, and pH) called elevated stress conditions. Degradation at the controlled and recommended storage conditions take place which can be predicted by known relationships between the degradation rate and the acceleration factor.

The studies conducted to know the physical change of a drug substance or to raise the rate of chemical degradation or change in drug product by exaggerated storage conditions are general part of the accelerated stability studies. The data from elevated studies generally called accelerated stability studies in addition to long term studies, are used to assess long term chemical effects at normal conditions. These studies also useful in evaluation of the effect of short-term excursions which stand outside the label storage conditions which might occur during shipping.[1& 2]

General testing frequency at Accelerated Storage Conditions are listed below:

Type of Study	Storage condition	Minimum time period covered by data at submission
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6months

Long Term Stability Testing

These type of Stability studies are performed under the recommended storage condition for the verification of re-test period or for approval of shelf life proposed for Labeling. The conditions for performing Long Term Stability Testing are selected as per climatic conditions of country of export.[1& 2]

Type of Study	Storage condition	Minimum time period covered by data at submission
Long Term	25 °C ± 2 °C/60% RH ± 5% RH	12 months
	30 °C ± 2 °C/65% RH ± 5% RH	
	30 °C ± 2 °C/75% RH ± 5% RH	

Intermediate Stability Testing

While performing stability testing at the accelerated storage condition, minimum three-time points reporting is recommended which includes initial and final time points (e.g., 0, 3, and 6 months).When on the review of development studies, a significant change in the stability result is expected, increased testing should be conducted either by adding samples at the final time point or including an extra time point in the study design called intermediate stability testing. When there is need of conducting intermediate stability testing as a result of significant change in accelerated stability data minimum four time including initial and final time points (e.g., 0, 6, 9, 12 months) are recommended. [1& 2]

Type of Study	Storage Condition	Minimum time Period Required
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	12 Months

Stability studies at Refrigerated Conditions

Stability studies at refrigerated conditions performed for those drugs which may be stored in a refrigerator like vaccines and injections.

During the evaluation of the batch on stability studies if significant change is observed between three and six months of accelerated testing the shelf life or the retest period will be based on the data available at long term storage conditions.

Type of 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 or	06 months
	30 °C ± 2 °C/65% RH ± 5% RH	06 months
	30 °C ± 2 °C/75% RH ± 5% RH	06 months

If there is significant change observed within the first three months testing at the accelerated storage condition a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.[1, 2 ,5&6]

Stability Studies at Freezing Stability Conditions

The stability studies performed for freezing conditions are generally conducted only for long term storage conditions. No accelerated conditions for such cases. Minimum 12 months data included in the study.[1, 2&3]

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

Skip Testing

The concept of skip testing was introduced to reduce the analytical testing burden during production of a drug product so that frequency of batch production can be increased. In the scope of skip testing there is no need of testing all the batches for selected criterion to pass the

batch. Preselected batches are only assessed and other batches can be skipped from testing. The skipped testing can be implemented with a justification that there is no risk of failing of batches. The skip testing is generally proposed after evaluation of following factors:

- **Risk assessment:** Risk assessment to be done to evaluate the impact of not testing a batch and dealing of consequences like patient outcome, quality, yield, batch recall strategy etc. in case the batch fails to meet specification limits.
- **Related tests:** Provision of any alternative test that will be performed to predict the quality if skip test strategy is applied.
- **Robust control strategy**: A fool proof strategy to control the attribute and to commit that no out-of-control process is expected
- **Historical knowledge**: prior experience with production of same drug substance and drug product so that complete knowledge about the attributes which routinely passes specification.[9]

In-Use Stability Testing

The robustness of the formulation needs to be evaluated during its use viz-a-viz a multidose product can be opened and sealed many times for use therefore the stability of remaining drug in container should retain the claimed quality and must meet the approved specification.

The stability can be breached very easily by repeatedly opening and closing of container and may pose a risk for microbiological contamination, proliferation and physicochemical degradation. It is necessary that the product maintains the integrity continuously while packed in multidose containers. The maintenance of stability after the first opening is an important quality issue which has been acknowledged in the Ph. Eur. and EU Guidelines.[10]

Matrixing

The design of a stability schedule can be designed in such a way that a selected unit or subset of possible samples are tested at a specified time point for a particular set of parameters. At a consequential time, another subset of samples is tested for other parameters. Each subset of samples reflects the robustness of all samples at a given time point. For preparing subsets of same drug product to perform different testing, demarcation of the samples should be done viz-a-viz different strengths, different pack sizes, different types of packs of same product can be assigned different color codes.[11]

Bracketing

The design of a stability schedule can be designed such that the samples only for the extreme factors will be charged e.g. particular pack size, strength and pack type. Testing will be done at all time points as in a full design. It is assumed that the stability of any intermediate levels

is reflected by the results obtained at the extreme levels. When a product is having multiple strengths and the strengths are identical or compositions are very closely related, bracketing can beapplied.[12]

Reconstitution and Dilution Studies

The drug products need to be tested for stability after constitution or dilution. The dilution and reconstitution testing results support in shelf life after dilution of drug substance before use. Generally, these types of studies need not to be repeated on every batch. The studies can be performed on submission batch and on every 10th batch after that.[12]

List of Tests to be included in Stability Schedule[13&14]

Sr. No.	Name of Test	Parameters
1.	Physical	Color, Clarity, Closure Integrity, Particulate Matter and Particle Size
2.	Chemical	Active Substance Assay(s), Antimicrobial Preservative and Antioxidant Content(s), Degradation Product Level(s) and pH
3.	Microbial	Total Viable Count and Sterility

Conclusion

Robustness is an important criterion for a drug substance and drug product during product development phase, In-process testing, Finished Product testing as well for Release Testing. Stability results are markers of capacity to withstand the adverse conditions during storage and transportation and assist a drug substance and drug product to stay within the approved specification limits throughout the shelf-life. international Regulatory Agencies viz-a-viz WHO, ASEAN, USFDA and Health Canada to regulate the stability guidelines worldwide. ICH acts as mother guideline for all. By knowing different types of stability testing it is easy to propose right stability testing grid and evaluations assist in proposing the correct storage conditions.

References

1.Stability Testing of New Drug Substances and Products Q1A(R2), 4th version dated 6 February 2003, available at https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf

2.Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99) available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-r2-stability-testing-new-drug-substances-products-step-5_en.pdf

3. Mani, Shankar. (2013). STABILITY STUDIES: A REVIEW. Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry. 1. 184. Available at https://www.researchgate.net/publication/318877092_STABILITY_STUDIES_A_REVIEW

4. Stability Testing: Photostability Testing of New Drug Substances and New Drug Products Q1B available at https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1B/Step4/Q1B_Guideline.pdf

5.Rina H. Gokani and Kinjal N. Desai, International Journal of Advances in Pharmaceutical Analysis, IJAPA Vol. 2 Issue 4 (2012) 73-78

6.A. Arunachalam, M. Shankar, Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry,1(4), 2013, 184 - 195.ISSN: 2321-0923

7.EMA Guidelines for stability testing for new drugs available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-6-test-procedures-acceptance-criteria-new-drug-substances-new-drug-products-chemical_en.pdf

8.EMA Guidelines for stability testing for human use available at https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-use-stability-testing-human-medicinal-products_en.pdf

9.ICH Guidelines for stability testing for new drugs available at https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1D/Step4/Q1D_Guideline.pdf

10.https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

11. Jessica C, Timothy G, Philip L, Joseph S. stability studies. Separation Science and Technology. 2011; 10:459-505

12.European Pharmaceutical Review , discussion on application on skip testing, https://www.europeanpharmaceuticalreview.com/article/39262/the-application-of-skip-testing-to-drug-substance-manufacture/

13. International Conference on Harmonization; “Specifications: Test procedures and acceptance criteria for new drug substances and new products: Chemical substances. Q6A”, 1999

14. ICH Q6B: “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products”