Guidelines for Stability testing of Active Pharmaceutical Ingredients (Bulk Drugs) and finished pharmaceutical products

Introduction

The present stability testing guidelines have been prepared for the purpose of conduct of stability studies for additional product licence to be issued by the State Licensing Authority as per the decision taken in the 53rd DCC meeting dated 9th April, 2018 which deliberated the matter and agreed that the manufacturers are required to ensure stability of all drugs manufactured by them throughout their shelf life so that patients get quality, effective and safe medicines and these guidelines. Final rules under G.S.R 360(E) has been published on 10.04.2018 replacing the words 'patent or proprietary medicines' with the word ' drugs' making it mandatory that for all drugs, the applicant shall have to submit stability data etc. as per the provision before grant of product licence by the respective State Licensing Authority

The guideline has been prepared in accordance with the stability study guideline in the draft Govt. Of India Gazette notification vide GSR No. 104E dated 1st Feb, 2018 published in the website and in consonance with the WHO Technical Report Series identifying India as country located in Zone IVb (hot /higher humidity)

Scope of these guidelines

These guidelines apply to all new and existing APIs and finished formulation granted as additional products by the State Licensing Authorities

Guidelines

Stability testing is to be performed to provide evidence on how the quality of a drug substance or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish shelf life for the formulation and recommended storage conditions.

The stability testing includes the study of product related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials. In fixed-dose combination FPPs (FDCs) the interaction between two or more APIs also has to be considered

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.

In case of formulations 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).
Validated stability-indicating analytical procedures should be applied. For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance.

In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

Stress testing of the drug substance should be conducted to identify the likely degradation products, which in turn establish the degradation pathways, evaluate the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of formulation involved.

Stress testing may generally be carried out on a single batch of the drug substance. It should include the effect of temperatures), humidity where appropriate, oxidation, and photolysis on the drug substance.

Data should be provided for (a) Photostability on at least one primary batch of the drug substance as well as the formulation, as the case may be and (b) the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.
Long-term testing should cover a minimum of 12 months' duration on at least three primary batches of the drug substance or the formulation at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Accelerated testing should cover a minimum of 6months duration at the time of submission.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

The stability studies for drug substances should be conducted either in the same container - closure system as proposed for storage and distribution or in a container - closure system that simulates the proposed final packaging. In case of formulations, stability studies should be conducted in the final container - closure system proposed for marketing.

Stability testing of drug substances and formulations:

Study conditions for drug substances and formulations intended to be stored under general conditions

Study	***Study conditions***	***Duration of study***
Long-term	30°C± 2° C/75% RH ± 5% RH	12 months
Accelerated	40°C± 2° C/75% RH ± 5% RH	6 months

If at any time during 6 months testing under the accelerated storage condition, such changes occur that cause the product to fail in complying with the prescribed standards, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

Study conditions for drug substances and formulations intended to be stored in a refrigerator.

Study	***Study conditions***	***Duration of study***
Long-term	5°C± 3° C	12 months
Accelerated	25°C± 2° C/60% RH ± 5% RH	6 months

Study conditions for drug substances and formulations intended to be stored in a freezer

Study	***Study conditions***	***Duration of study***
Long-term	-20° C ± 5° C	12 months

Drug substances intended for storage below -20° C shall be treated on a case-by- case basis. Stability testing of the formulations after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in- use period.

A guidance checklist for evaluation of submitted stability data is enclosed as **Annexure A**

Annexure-A

Stability testing of APIs(bulk drugs)		
1.	Stability Protocol	
1.1	Shelf life and storage condition assigned	
1.2	Quality Control methods and specifications and rationale for the choice of tests for determining stability specifically for drugs not in Pharmacopoeia	
2.	Stability Summary in tabular form mentioning Batch Number, Batch Size (scale of production), Date of manufacturing and date of onset of stability study along-with package/container-closure	
3.	Stability study conclusion	
4.	Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as "pass" or "fail".	
Stability testing of finished formulation (Drug Products)		
1.	Stability Protocol	
1.1	Shelf life and storage condition assigned	
1.2	Quality Control methods and specifications and rationale for the choice of tests for determining stability specifically for drugs not in Pharmacopoeia	
2.	Stability Summary in tabular form mentioning Batch Number, Batch Size (scale of production), Date of manufacturing and date of onset of stability study along-with package/container-closure	
3.	Stability study conclusion	
4.	Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as "pass" or "fail".	
5.	Stability test results for diluent and reconstituted products incase of lyophilised powder product	

References:

1. 53rd DCC meeting, 9th April, 2018
2. G.S.R. 104(E), published on 01st February 2018.