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World Health Organization's Guidelines for Stability Testing of Pharmaceutical Products

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ABSTRACT

This study is about the guidelines of World Health Organization for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. For these pharmaceutical products the stability studies may be restricted to dosage forms because for established drug substances, literature data is available on the decomposition process and degradability of the active substances along with adequate analytical methods. Thus the actual stability of these dosage forms depends on the formulation and packaging-closure system selected by the manufacturer so the stability considerations, e.g. selection of excipients, determination of their level and process development, should be given high priority in the developmental stage of the product. With the approval of the drug regulatory authority, a tentative (provisional) shelf-life is often established, provided that the manufacturer has undertaken, by virtue of a signed statement, to continue and complete the required studies and to submit the results to the registration authority.

Key words: Stability, Accelerated studies, Real-time studies, Shelf-life, Climatic zones.

INTRODUCTION

The drug regulatory authorities require the manufacturer to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and real-time studies. Published and/or recently obtained experimental supporting stability data may also be submitted, e.g. on the stability of active ingredients and related formulations. The shelf-life should be established with due regard to the climatic zones in which the product is to be marketed. For certain preparations, the shelf-life can be guaranteed only if specific storage instructions are compiled with. The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety, and efficiency throughout the shelf-life of a

product. To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and, when necessary, the storage conditions are indicated on the label [1,2].

EXPERIMENTAL SECTION

The secondary data used in the study was obtained from various official reports published by World Health Organization and internet. The study is of descriptive type and method used is the description.

Objectives of Stability Testing

Main objectives of stability testing in different phases of life cycle of a pharmaceutical product are:

In the Development Phase

In this phase accelerated stability tests provide a means of comparing alternative formulations, packaging materials, and/or manufacturing processes in short-term experiments. As soon as the final formulation and manufacturing process have been established, the manufacturer carries out a series of accelerated stability tests which will enable the stability of the drug product to be predicted and its shelf-life and storage conditions determined. Real-time studies must be started at the same time for confirmation purposes.

For the Registration Dossier

For the registration of dosage form the manufacturer is required to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and real-time studies. Published and/or recently obtained experimental supporting stability data on the stability of active ingredients and related formulations may also be submitted.

In the Post-registration Period

To substantiate the expiry date and the storage conditions previously projected the manufacturer must carry out on-going real-time stability studies. The data needed to confirm a tentative shelf-life must be submitted to the registration body. Other results of on-going stability studies are verified in the course of GMP inspections. The quality and safety of products with particular reference to degradation, national health authorities should monitor the stability and quality of preparations on the market is ensured by means of a follow-up inspection and testing programme. Once the product has been registered, additional stability studies are required whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation. The results of these must be communicated to the competent drug regulatory authorities [2].

The intended market and the climatic conditions in the area in which the drug product will be used should be taken into account for the design of the stability testing programme. Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:

- Zone I : temperate
- Zone II : subtropical, with possible high humidity
- Zone III : hot/dry
- Zone IV : hot/humid

The mean climatic conditions, calculated data and derived storage conditions in these zones are summarized in table 1 and 2.

Table 1 Mean climatic conditions: measured data in the open air and in the storage room

Climatic zone	Measured data in the open air		Measured data in the storage room	
	^{0}C	%RH	^{0}C	%RH
I	10.9	75	18.7	45
II	17.0	70	21.1	52
III	24.4	39	28.0	54
IV	26.5	77	28.4	70

RH = relative humidity

Table 2 Mean climatic conditions: calculated data and derived storage conditions

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	^{0}C	^{0}C MKT	%RH	^{0}C	%RH
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	70

MKT = mean kinetic temperature.
RH = relative humidity

Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19 ^{0}C were set equal to 19 ^{0}C.

In a stability study, the effect of variations in temperature, time, humidity, light intensity and partial vapour pressure on the pharmaceutical product are investigated. The storage conditions are often such that the temperature is higher than the average meteorological data for a country. For some dosage forms, especially liquid and semi-solid ones, the study design may also need to include subzero temperatures, e.g. -10 to -20 ^{0}C (freezer), freeze-thaw cycles or temperatures in the range 2 - 8 ^{0}C (refrigerator). For certain preparations it may be important to observe the effects caused by exposure to light [5].

Design of Stability Studies

Stability studies on a finished pharmaceutical product are designed in the light of the properties and stability characteristics of the drug substance as well as the climatic conditions of the intended market zone. Information on the stability of the drug substance should be sought, collected and analyzed before the stability studies of dosage forms are initiated.

Test Samples

For registration purposes, test samples of products containing fairly stable active ingredients are taken from two different production batches; in contrast, samples should be taken from three batches of products containing easily degradable active ingredients or substances on which limited stability data are available. The batches to be sampled should be representative of the, pilot plant or full production scale manufacturing process. In on-going studies, current production batches are sampled in accordance with a predetermined schedule. The following sampling schedule is suggested:

- One batch every other year for formulations considered to be stable, otherwise one batch per year;

- One batch every 3-5 years for formulations for which the stability profile has been established, unless a major change has been made, e.g. in the formulation or the method of manufacture.
-

Detailed information on the batches should be included in the test records, namely the packaging of the drug product, the batch number, the date of manufacture, the batch size etc [2].

Test Conditions

The test conditions for different types of stability studies are as follows:

For Accelerated Studies

Conditions for the accelerated stability testing of products containing relatively stable active ingredients are shown in Table 3.

Table 3 Conditions for the accelerated stability testing

Climatic zone	Storage temperature (^{0}C)	Relative humidity (%)	Duration of studies (months)
Zone-IV for Hot climatic zones or Global market:	40±2	75±5	6
Zone-II for Temperate and subtropical Climatic zones:	40±2	75±5	3

For products containing less stable drug substances, and those for which limited stability data are available, it is recommended that the duration of the accelerated studies for zone-II should be increased to 6 months. Alternative storage condition that may be followed is the storage for 6 months at a temperature of at least 15°C above the expected actual storage temperature (together with the appropriate relative humidity condition). For zone - IV storage at higher temperatures may also be recommended, e.g. 3 months at 45-50 °C and 75% relative humidity (RH). Where significant changes like,

- the assay value shows a 5% decrease as compared with the initial assay value of a batch;
- any specified degradation product is present in amounts greater than its specification limit;
- the pH limits for the product are no longer met;
- the specification limits for the dissolution of 12 capsules or tablets are no longer met;
- the specifications for appearance and physical properties, e.g. colour, phase separation, caking, hardness, are no longer met.

occur in the course of accelerated studies additional tests at intermediate conditions should be conducted, e.g. 30 ± 2 °C and 60 ± 5% RH. The initial registration application should then include a minimum of 6 month's data from a 1-year study. Storage under test conditions of high relative humidity is important for solid dosage forms in semi-permeable packaging. For products in primary containers designed to provide a barrier to water vapour, storage conditions of high relative humidity are not necessary. As a rule, accelerated studies are less suitable for semi-solid and heterogeneous formulations, e.g. emulsions.

For Real-time Studies

The experimental storage conditions for real – time studies should be as close to the projected actual storage conditions in the distribution system as practicable. Real-time studies are continued until the end of the shelf-life. For registration purposes, the results of studies of at least 6 months' duration should be available at the time of registration. However, it should be

possible to submit the registration dossier before the end of this 6 month period [2].

Frequency of Testing and Evaluation of Results

For studies in support of an application for registration and in the development phase, reasonable frequency of testing of products containing relatively stable active ingredients is at 0, 1, 2, 3 and when appropriate, 6 months for accelerated studies and at 0, 6 and 12 months, and then once a year for real-time studies. For on- going studies, samples may be tested at 6 - month intervals for the confirmation of the provisional shelf-life, or every 12 months for well established products. Highly stable formulations may be tested after the first 12 months and then at the end of the shelf-life. Products containing less stable drug substances and those for which stability data are available should be tested every 3 months in the first year, every 6 months in the second year, and then annually. Test results are considered to be positive when neither significant degradation nor changes in the physical, chemical and, if relevant, biological and microbiological properties of the product have been observed, and the product remains within its specification [6].

Analytical Methods

A systematic approach is followed for the presentation and evaluation of stability information, which should include, as necessary, physical, chemical, biological and microbiological test characteristics. All product characteristics which can be affected by storage, e.g. assay value or potency, content of products of decomposition, physicochemical properties (hardness, disintegration, particulate matter, etc.), should be determined; dissolution tests should be carried out for solid or semi- solid oral dosage forms. Test methods should be used to determine whether additives used such as antimicrobial agents, remain effective and unchanged throughout the projected shelf- life. Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. The assay methods which are indicative of stability should be chosen. The tests for related compounds or products of decomposition should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity. A checklist similar to that used in the WHO survey on the stability of pharmaceutical preparations included in the WHO Model List of Essential Drugs can be used to determine the other stability characteristics of the product [3].

Stability Report

For internal use and for registration purposes a stability report must be established, that gives details of the design of the study, as well as the results and conclusions. The results should be presented as both a table and a graph. For each batch, the results of testing both at the time of manufacture and at different times during storage should be given. To summarize the results for each pharmaceutical preparation a standard form of stability report should be prepared. On the basis of these results the stability, proposed shelf-life and storage conditions, of a given product must be determined [1].

Shelf-life and Recommended Storage Conditions

Shelf-life is always determined in relation to storage conditions. If batches of a product have different stability profiles, the shelf-life proposed should be based on the stability of the least stable, unless there are justifiable reasons for doing otherwise. The results of stability studies, covering the physical, chemical, biological, microbiological and biopharmaceutical quality characteristics of the dosage form, as necessary, are evaluated with the objective of establishing a tentative shelf-life. Statistical methods are often used for the interpretation of these results. Some extrapolation of real-time data beyond the observed range, when accelerated studies support this, is acceptable. A tentative shelf-life of 24 months may be established provided the following conditions are satisfied:

- the active ingredient is known to be stable (not easily degradable);
- stability studies have been performed and no significant changes have been observed;
- supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more;
- the manufacturer will continue to conduct real-time studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the registration authority.
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Products containing less stable active ingredients and formulations not suitable for experimental studies on storage at elevated temperature (e.g. suppositories) will need more extensive real-time stability studies. In that case the proposed shelf- life should not exceed twice the period covered by the real-time studies. After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:

- store under normal storage conditions;
- store between 2 and 8 ^{0}C (under refrigeration, no freezing);
- store below 8 °C (under refrigeration);
- store between -5 and -20 ^{0}C (in a freezer);
- store below -18 ^{0}C (in a deep freezer).
-

Normal storage conditions have been defined by WHO as "storage in dry, well-ventilated premises at temperatures of 15 - 25 ^{0}C or, depending on climatic conditions, up to 30 ^{0}C. Extraneous odors, contamination, and intense light have to be excluded." These conditions may not always be met so in certain countries "Normal conditions" may be defined at the national level based on different actual climatic conditions. Recommended storage conditions must be determined in the light of the conditions prevailing within the country of designated use. General precautionary statements, such as "protect from light" and/or "store in a dry place", may be included, but should not be used to conceal stability problems. If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution [3,4].

RESULTS AND DISCUSSION

The present study provides and understanding of World Health Organization for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. The conditions outlined in these guidelines must be adopted by manufacturers for the registration of pharmaceutical product at WHO. Where the product is required to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension), “in use” stability data must be submitted to support the recommended storage time and conditions for those dosage forms. The shelf-life should be established with due regard to the climatic zones in which the product is to be marketed. For certain preparations, the shelf-life can be guaranteed only if specific storage instructions are compiled with. It is recommended that all manufacturers provide WHO with the necessary information to support the claimed shelf-life and storage conditions.

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