WHO Technical Report Series, No. 863, 1996

Annex 5

Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms

General

The stability of finished pharmaceutical products depends, on the one hand, on environmental factors such as ambient temperature, humidity and light, and, on the other, on product-related factors, e.g. the chemical and physical properties of the active substance and of pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system and the properties of the packaging materials.

For established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance (1) are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms.

Since the actual stability, of a dosage form will depend to a large extent on the formulation and packaging-closure system selected by the manufacturer, 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. The possible interaction of the drug product with the packaging material in which it will be delivered, transported and stored throughout its shelf-life must also be investigated.

The shelf-life should be established with due regard to the climatic zone(s) (see section 2) in which the product is to be marketed. For certain preparations, the shelf-life can be guaranteed only if specific storage instructions are complied with.

The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety, and efficacy throughout the shelf-life of a product. The effect on products of the extremely adverse climatic conditions existing in certain countries to which they may be exported calls for special consideration (see section 6).

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.

Definitions

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

accelerated stability testing
Studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real-time stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

batch
A defined quantity of product processed in a single process or series of processes and therefore expected to be homogeneous. In continuous manufacture, the batch must correspond to a defined fraction of production, characterized by its intended homogeneity.

climatic zones
The four zones into which the world is divided based on the prevailing annual climatic conditions (see section 2).

expiry date
The date given on the individual container (usually on the label) of a drug product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

mean kinetic temperature
The single test temperature for a drug product corresponding to the effects on chemical reaction kinetics of a given temperature-time distribution. A mean kinetic temperature is calculated for each of the four world climatic zones according to the formula developed by Haynes (2). It is normally higher than the arithmetic mean temperature.

real-time (long-term) stability studies
Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf-life, to confirm the projected shelf-life, and to recommend storage conditions.

shelf-life
The period of time during which a drug product, if stored correctly, is expected to comply with the specification[1] as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

stability
The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life.

stability tests
A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions.

supporting stability data
Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers other than those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf-life and storage conditions.

utilization period
The period of time during which a reconstituted preparation or the finished dosage form in an opened multidose container can be used.

[1] "Shelf-life specification" means the requirements to be met throughout the shelf-life of the drug product (should not be confused with "release specification").

1. Stability testing

The main objectives and uses of stability testing are shown in Table 1.

1.1 In the development 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. Suitable measures should be taken to establish the utilization period for preparations in multidose containers, especially for topical use.

1.2 For the registration dossier

The drug regulatory authority will 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.

Table 1
Main objectives of stability testing

Objective	Type of study	Use
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control

Where the product is 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.

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.

1.3 In the post-registration period

The manufacturer must carry out on-going real-time stability studies to substantiate the expiry date and the storage conditions previously projected. 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. To ensure 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 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 studies must be communicated to the competent drug regulatory authorities.

2. Intended market

The design of the stability testing programme should take into account the intended market and the climatic conditions in the area in which the drug products will be used.

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.

(See Schumacher P. Aktuelle Fragen zur Haltbarkeit von Arzneimitteln. [Current questions on drug stability.] *Pharmazeutische Zeitung,* 1974, 119:321-324.)

The mean climatic conditions,, calculated data and derived storage conditions in these zones are summarized in Tables 2 and 3.

Since there are only a few countries in zone I, the manufacturer would be well advised to base stability testing on the conditions in climatic zone II when it is intended to market products in temperate climates. For countries where certain

regions are situated in zones III or IV, and also with a view to the global market, it is recommended that stability testing programmes should be based on the conditions corresponding to climatic zone IV.

In a stability study, the effect on the product in question of variations in temperature, time, humidity, light intensity and partial vapour pressure are investigated. The effective or mean kinetic temperature therefore reflects the actual situation better than the measured mean temperature; a product kept for 1 month at 20°C and 1 month at 40°C will differ from one kept for 2 months at 30°C. Moreover, the storage conditions are often such that the temperature is higher than the average meteorological data for a country would indicate.

Table 2
Mean climatic conditions: measured data in the open air and in the storage room[1]

Climatic zone	Measured data in the open air		Measured data in storage room	
	°C	% RH	°C	% RH
I	10.9	75	18.7	45
II	17.0	70	21.1	52
III	24.4	39	26.0	54
IV	26.5	77	28.4	70

[1] RH = relative humidity.

Table 3
Mean climatic conditions: calculated data and derived storage conditions[1]

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	°C[2]	°C MKT[3]	% RH[4]	°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

[1] Based on: Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. Drug development and industrial pharmacy, 1993, 19:2795-2830.
[2] Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19°C were set equal to 19°C.
[3] MKT = mean kinetic temperature (see p. 67)
[4] RH = relative humidity.

Amendment from Draft of the **37th Report of The WHO Expert Committee on Specifications for Pharmaceutical Preparations**
Geneva, 22-26 October 2001

11.1 WHO guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms

The Committee discussed and adopted the recommended modification of storage conditions published in the *WHO guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms* to read 30°C (± 2°C) and 65% (± 5%) RH for real-time stability studies destined for climatic zone IV. It was also agreed that where special transportation and storage conditions were identified as being outside these criteria, additional study data supporting these conditions may need to be made available.

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 °C (freezer), freeze-thaw cycles or temperatures in the range 2-8 °C (refrigerator). For certain preparations it may be important to observe the effects caused by exposure to light.

3. Design of stability studies

Stability studies on a finished pharmaceutical product should be 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. Before stability studies of dosage forms are initiated, information on the stability of the drug substance should be sought, collected and analysed. Published information on stability is available on many well established drug substances.

3.1 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 manufacturing process, whether pilot plant or full production scale. Where possible, the batches to be tested should be manufactured from different batches of active ingredients.

In on-going studies, current production batches should be 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.

3.2 Test conditions

3.2.1 Accelerated studies

An example of conditions for the accelerated stability testing of products containing relatively stable active ingredients is shown in Table 4.

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.

Table 4
Example of conditions for accelerated stability testing of products containing relatively stable active ingredients

Storage temperature (°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

Alternative storage conditions may be observed, in particular, storage for 6 months at a temperature of at least 15 °C above the expected actual storage temperature (together with the appropriate relative humidity conditions). Storage at higher temperatures may also be recommended, e.g. 3 months at 45-50 °C and 75% relative humidity (RH) for zone IV.

Where significant changes (see below) 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 months' data from a 1-year study.

A significant change is considered to have occurred if:

- 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.

Storage under test conditions of high relative humidity is particularly 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.

3.2.2. Real-time studies

The experimental storage conditions should be as close to the projected actual storage conditions in the distribution system as practicable (see Table 3). 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. Real-time studies should be continued until the end of the shelf-life.

3.3 Frequency of testing and evaluation of test results

In the development phase and for studies in support of an application for registration, a reasonable frequency of testing of products containing relatively stable active ingredients is considered to be:

- for accelerated studies, at 0, 1, 2, 3 and, when appropriate, 6 months;
- for real-time studies, at 0, 6 and 12 months, and then once a year.

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.

4. Analytical methods

A systematic approach should be adopted to the presentation and evaluation of stability information, which should include, as necessary, physical, chemical, biological and microbiological test characteristics.

All product characteristics likely to 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; for solid or semi-solid oral dosage forms, dissolution tests should be carried out.

Test methods to demonstrate the efficacy of additives, such as antimicrobial agents, should be used to determine whether such additives 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 chosen should be those indicative of stability. 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 (Appendix 1) can be used to determine the other stability characteristics of the product.

5. Stability report

A stability report must be established for internal use, registration purposes, etc., giving 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. A standard form should be prepared in which the results for each pharmaceutical preparation can be summarized (see Appendix 2).

The stability of a given product, and therefore the proposed shelf-life and storage conditions, must be determined on the basis of these results.

6. 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 as outlined in section 3.2 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.

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. The proposed shelf-life should then 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;[1]
- store between 2 and 8 °C (under refrigeration, no freezing);
- store below 8 °C (under refrigeration);
- store between -5 and -20 °C (in a freezer);
- store below -18 °C (in a deep freezer).

Normal storage conditions have been defined by WHO (3) as: "storage in dry, well-ventilated premises at temperatures of 15-25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, contamination, and intense light have to be excluded."

These conditions may not always be met, bearing in mind the actual situation in certain countries. "Normal conditions" may then be defined at the national level. Recommended storage conditions must be deter-mined 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.

References

1. *Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions*. Geneva, World Health Organization, 1986 (unpublished document WHO/PHARM/86.529; available on request from Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland).
2. Haynes JD. *World wide virtual temperatures for product stability testing. Journal of pharmaceutical sciences,* 1971, 60:927-929.
3. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).

Official, international and national guidelines

Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e. V.

Arbeitsgemeinschaft for Pharmazeutische Verfahrenstechnik e.V Richtlinie and Kommentar [Guidelines and commentary]. Pharmazeutische Industrie, 1985, 47(6): 627-632.

[1] This statement may not always be required for products intended for areas with a temperate climate.

European Community

Stability test on active ingredients and finished products. Note for guidance concerning the application of Part 1, Section F. Annex to Directive 75/318. In: The rules governing medicinal products in the European Community. Vol, l, the rules governing medicinal products for human use in the European Community (111/3574/92). Brussels, EEC Office for Official Publications of the European Community, 1991:50.

European Organization for Quality Control

Cartwright AC. The design of stability trials (memorandum and conclusions). London, European Organization for Quality Control, Section for Pharmaceutical and Cosmetic Industries, 1986.

Food and Drug Administration, USA

Guidelines for stability studies for human drugs and biologics. Rockville, MD, Center for Drugs and Biologics, Office of Drug Standards, Food and Drug Administration, 1987.

Expiration dating and stability testing for human drug products. Inspection technical guide. Rockville, MD, Food and Drug Administration, 1985, No. 41.

Former German Democratic Republic

Testing of medicaments. International digest of health legislation, 1987, 38(2): 309-316. (For original reference, see: First regulations of 1 December 1986 for the implementation of the Medicaments Law. Testing, authorization, and labelling of medicaments intended for use in human medicine. Gesetzblatt der Deutschen Demokratischen Republik, Part I, 10 December 1986, 37:479-483.)

Pharmacopoeia of the German Democratic Republic, English version. Berlin, 1988:99 (AB DDR 85).

International Conference on Harmonisation

Stability testing of new drug substances and products. Harmonised tripartite guideline. 1993 (available from ICH Secretariat, c/o IFPMA, 30 rue de St-Jean, 1211 Geneva, Switzerland).

Japan

Draft policy to deal with stability data required in applying for approval to manufacture (import) drugs and draft guidelines for stability studies. Tokyo, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, 1990.

Pharmaceutical Inspection Convention

Stability of pharmaceutical products: collected papers given at a seminar, Salzburg, 9-11 June 1976 (available from the Secretariat to the Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products, c/o EFTA Secretariat, 9-11 rue de Varembe, 1202 Geneva, Switzerland).

Appendix 1

Survey on the stability of pharmaceutical preparations included in the WHO Model List of Essential Drugs: answer sheet

A checklist similar to that shown here can be used to determine the stability characteristics of a product.

Name of reporting person Address Country
Climatic zone

NAME OF ESSENTIAL DRUG:

Description of product

Dosage form

1. tablet	coated ☐	uncoated ☐
2. capsule	hard ☐	soft ☐
3. injection	liquid ☐	powder ☐
4. oral liquid	solution ☐	suspension ☐
5. topical semi-solid	cream ☐	ointment ☐
6. eye preparations	liquid ☐	semi-solid ☐
7. other (please state)		

Packaging (material and type)

1. glass	bottle ☐	vial ☐	ampoule ☐
2. plastic	bottle ☐	vial ☐	ampoule ☐
3. paper	box ☐	bag ☐	
4. metal	☐		
5. blister pack	☐		
6. other (please state)			

State of packaging intact ☐ damaged ☐

Storage conditions
according to the manufacturer's indications? yes☐ no ☐

Shelf-life (if available)
claimed by the manufacturer ……years ……months
percentage elapsed when tested …… %

Source of product tested

1. manufactured in country of use	☐
2. imported from neighbouring country/countries	☐
3. imported from distant country/countries	☐

Problems encountered

Occurrence

1. very frequent	☐
2. occasional, but important	☐
3. rare	☐

Pharmacopoeial non-compliance

1. Identification	☐
2. assay	☐
3. purity tests	☐
4. other pharmacopoeial test(s)	

Organoleptic

1. change of colour	☐
2. visible changes, i.e. capping, cracking, foam	☐

Microbial

1. microorganisms visible	☐
2. tests for bacteria positive	☐

Organoleptic (continued)

3. inhomogeneous appearance ☐
4. crystallization ☐
5. particles, turbidity, precipitation ☐
6. sedimentation, caking, agglomeration ☐
7. smell, i.e. gas formation ☐
8. rancidity ☐
9. phase separation of emulsion ☐
10. interaction with packaging material ☐
11. other (please state)

Microbial (continued)

3. tests for fungi positive ☐
4. tests for pyrogens positive ☐
5. other (please state)

Additional information

. . . . . .

. . . . . .

. . . . . .

Date:

Instructions

1. The answer sheet is to be completed for drug products mentioned in the following list of essential drugs for which you have experienced stability problems:

acetylsalicylic acid
aminophylline
ampicillin
benzylpenicillin
chloramphenicol
chloroquine
chlorpromazine
epinephrine
ergometrine
ethinylestradiol
glyceryl trinitrate
ibuprofen
indometacin
Isosorbide dinitrate
methyldopa
nifedipine
paracetamol
phenoxymethylpenicillin
propranolol
spironolactone
sulfamethoxazole + trimethoprim
suxamethonium bromide
tetracycline
thiamine
warfarin

2. A separate answer sheet should be completed for each of the above preparations in a specific finished dosage form, e.g. one for tetracycline capsules and another for tetracycline ointment.
   Also applicable for other categories such as packaging material, source of drug product, etc.

3. Climatic zones (Schumacher P. Aktuelle Fragen zur Haltbarkeit von Arzneimitteln. [Current questions on drug stability.] Pharmazeutische Zeitung, 1974, 119:321-324):

   zone I - temperate
   zone II - subtropical with possible high humidity
   zone III - hot and dry
   zone IV - hot and moist.

Appendix 2

Stability testing: summary sheet

An example of a form in which the results of stability testing can be presented is shown below. A separate form should be completed for each pharmaceutical preparation tested.

Accelerated/real-time studies

Name of drug product ……
Manufacturer ……
Address ……..

Active ingredient (INN) …….
Dosage form ……...
Packaging ……

Batch number	Date of manufacture	Expiry date
1 .....…	../../19..	../../19..
2	../../19..	../../19..
3	../../19..	../../19..

Shelf-life …year(s) ... month(s)

Batch size	Type of batch (experimental, pilot plant, production)
1	…….
2	…….
3	…….

Samples tested (per batch) ……..

Storage/test conditions:
Temperature ... °C Humidity … %
Light … cd

Results

1. Chemical findings …….
   ……..
2. Microbiological and biological findings ……...
   ……
3. Physical findings ……
   ……
4. Conclusions ……
   …….

Responsible officer ..... Date ../../19..
