



**WHO GUIDELINES ON STABILITY TESTING OF
PHARMACEUTICAL PRODUCTS CONTAINING WELL-ESTABLISHED DRUG
SUBSTANCES IN CONVENTIONAL DOSAGE FORMS**

These draft guidelines have been widely circulated and comments received from WHO experts, national drug regulatory agencies and academia, have been supportive. A number of clarifications and other improvements have been offered and wherever possible, these have been incorporated into the present text. This document assumes that products containing well-known and relatively stable active substances may need a less rigorous stability testing programme than that needed for new substances and products.

In the combined comments offered by the pharmaceutical industry, it was suggested that the WHO guidelines should be as stringent as those of the ICH (see references, p. 10) regarding batch selection, storage test conditions and frequency of testing. In response to these comments, it is important to note that the two guidelines, do not cover the same field (NCE in climatic zones I and II for ICH, and generic products on a global market, mostly in zones III and IV for WHO). While some of the pharmaceutical industry's proposals have been accommodated, the principal difference in philosophy has not been resolved. The revised version of the document is therefore recirculated for comments to ascertain the views of members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

Kindly address any comments to Dr A. Mechkovski, Chief, Quality Assurance, Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland, within two months of the mailing date of the document.

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The present guidelines have been developed in response to a request by the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* to produce general principles of ensuring drug stability. Their purpose is to offer assistance particularly to small drug regulatory authorities with regard to requirements on stability testing of generic products in the final dosage form.

GENERAL

Quality must be assured for all drug products independent of their source. However, it is recognized that the initial development and related studies might be performed in different ways.

Stability studies of generic pharmaceutical products differ from the studies of products containing new chemical entities (NCE).** The manufacturer of a generic product will have access to a body of experience with the original product. The stability of the drug substance is usually well known by the time the patent of the product has expired and therefore it is possible to reduce stability tests for the active ingredient. WHO intends to continue to provide information on more easily degradable drug substances and dosage forms since these require more attention from the viewpoint of stability in the development stage, registration, in routine production and distribution.

The manufacturer of a NCE has ample time for stability studies which are carried out in parallel with clinical trials and other R & D activities. The manufacturer of a generic product may therefore concentrate his attention on the development of an adequate formulation and on the assessment of its stability, because of the absence of time-consuming clinical trials and sometimes bioequivalence studies in his abridged application. Tests must also be made to study the possible interaction of the drug product with the packaging material in which it will be delivered, transported and stored throughout its shelf-life. The drug regulatory authority in these circumstances should be able to establish a tentative shelf-life on the basis of initial (before registration) stability data, e.g. as outlined in section 3.2 below. These, however, have to be confirmed by data generated through an on-going stability programme as required by GMP rules.

At the pre-marketing stage the manufacturer of a generic product is advised to concentrate its attention on the development of an adequate formulation from the viewpoint of its stability. Tests must also be made to study the possible interaction of the drug product with the packaging material in which it will be delivered, transported and stored throughout its shelf-life.

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

The storage conditions recommended by manufacturers on the basis of stability studies are meant to guarantee the maintenance of quality, safety, and efficacy throughout the shelf-life of a product. Importation of products into countries with extreme adverse climatic conditions should be given special consideration (see section 6).

For the safety of the patient 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.

* WHO Expert Committee on Specifications for Pharmaceuticals Preparations. *Thirty-first Report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).

** *Stability testing of New Drug Substances and Products*, ICH Harmonized Tripartite Guideline October 1993.

DEFINITION OF TERMS

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.

These data, in addition to real-time stability studies, may be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Batch

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

Climatic zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions (see section 2).

Expiry date

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

Mean kinetic temperature

The single test temperature corresponding to the effects on chemical reaction kinetics of a temperature-time distribution in each of the four world climatic zones and according to the formula developed by Haynes J.D. *Journal of Pharmaceutical Sciences*, 1971, 60:927-929. It is a higher value than that of the arithmetic mean temperature.

Real-time (long-term) stability studies

Evaluation of experiments for physical, chemical, biological and microbiological characteristics of a drug, during and beyond the expected time of shelf-life and storage of samples at expected storage conditions in the intended market. The results are used to establish shelf-life, to confirm projected shelf-life and recommend storage conditions.

* For the sake of consistency the definition is also quoted from the *WHO Expert Committee on Specifications for Pharmaceuticals Preparations. Thirty-first Report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790, p. 31):

Studies designed to increase the rate of chemical or physical degradation of a drug by using exaggerated storage conditions with the purpose of monitoring degradation reactions and predicting the shelf-life under normal storage conditions. The design of accelerated studies may include elevated temperature (e.g., 37-40 °C and up to 50-55 °C), high humidity and light.

Only a provisional shelf-life may be established on the basis of these studies. Therefore, accelerated studies should always be supplemented by real-time studies under expected storage conditions.

Shelf-life

The period of time during which a pharmaceutical product is expected, if stored correctly, to comply with the specification* 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 properties within specified limits throughout its shelf-life. The following aspects of stability are to be considered: chemical, physical, microbiological and biopharmaceutical.

Stability tests

Stability tests are 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, products presented in containers other than those proposed for marketing and other scientific rationale that support the analytical procedures, the proposed re-test period or shelf-life and storage conditions.

Utilization period

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

1. Purpose of Stability Testing

The main objectives of stability testing are:

Objective	Type of study	For use in
<ul style="list-style-type: none"> to select adequate (from the viewpoint of stability) formulations and container-closure systems 	accelerated	development of product
<ul style="list-style-type: none"> to determine shelf-life and storage conditions 	accelerated and/or real-time	development of product and registration dossier
<ul style="list-style-type: none"> to substantiate the claimed shelf-life 	real-time	registration dossier
<ul style="list-style-type: none"> 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

* "Shelf-life specification", i.e. requirements to be met throughout the shelf-life of the drug product (should not be confused with "release specification").

1.1 In the development phase

Accelerated stability tests are carried out to compare in short-term experiments alternative formulations, packaging materials, and/or manufacturing processes. As soon as the final formulation and manufacturing process have been established, the manufacturer will carry out a series of accelerated stability tests which will permit prediction of the stability of the drug product, and determine its shelf-life and storage conditions. Real-time studies have to be started for confirmation. Suitable measures should be taken for the establishment of the utilization period for preparations in multidose containers, especially for topical use.

1.2 For the registration dossier

The drug regulatory authority will request the manufacturer to submit information on the stability of the product from tests made of the final dosage form in its final container and packaging. The data submitted result from both accelerated and real-time studies. Published and/or experimental supporting stability data may be submitted, e.g. on stability of active ingredients and related formulations.

"In use" stability data have to be submitted to support a recommended storage time and condition of diluted or reconstituted product in cases where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection and concentrate for oral suspension).

With the approval of the drug regulatory authority, a preliminary shelf-life is often established on condition that additional information from first production batches will be submitted after registration.

1.3 In the post-registration period

The manufacturer will carry out on-going real-time stability studies to substantiate the expiry date and the storage conditions previously projected. Data needed to confirm a tentative shelf-life have to be submitted to the registration body. Other results of on-going stability studies are verified in the course of GMP inspection. To ensure the quality and safety of products with particular reference to degradation, national health authorities will monitor the stability and quality of preparations on the market through a follow-up inspection and testing programme.

Once the product has been registered, additional stability studies are required whenever major modifications are made to formulation, manufacturing process, packaging or method of preparation. These results have to be communicated to the respective drug regulatory authorities.

2. Intended Market

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

Four climatic zones can be distinguished for the purpose of worldwide stability testing:

zone I:	temperate
zone II:	sub-tropical with possible high humidity
zone III:	hot/dry
zone IV:	hot/humid

The mean climatic conditions found in these zones are summarized in the tables below.

Climatic zone	Measured data in the open air		Measured data in storage room	
	[°C]	[% R.H.]	[°C]	[% R.H.]
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

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	[°C]*	[°C MKT]**	[%/R.H.]	[°C]	[%/R.H.]***
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

Since there are only few countries in zone I, the manufacturer would be well advised to apply climatic zone II conditions when he intends to market in temperate climates. For countries where certain regions are situated in zones III or IV, and also with the view to global market, it is recommended that stability testing programme be based on conditions corresponding to the climatic zone IV.

A stability study is based on varying degrees of temperature, time, humidity, light intensity and partial vapour pressure, and their application to the product in question. It should be pointed out that the effective or mean kinetic temperature reflects the actual situation better than measured mean temperature, i.e. there is a difference between a product being kept for 1 month at 20 °C and 1 month at 40 °C, or 2 months at 30 °C. Moreover, storage conditions often represent a higher temperature than the average meteorological data indicated for a country.

For some dosage forms, especially liquid and semi-solid dosage forms, the study design may also need to consider low temperatures, e.g. below zero, -10 to -20 °C (freezer), freeze-thaw cycles and temperatures between 2-8 °C (refrigerator). For certain preparations it may be important to observe effects caused by the exposure to light.

3. Design of Stability Studies

3.1 Test samples

For registration purposes test samples from products containing fairly stable active ingredients are taken from two different production batches, whereas three batches should be sampled from products containing easily degradable active ingredients. The batches to be sampled should be representative of the manufacturing process, of pilot plant or full production scale. Where possible, batches should be manufactured using different batches of active ingredients.

For on-going studies batches from current production should be sampled in accordance with a pre-determined schedule. The following approach may be suggested:

* Calculated by other means. All data measured below 19 °C were adjusted to 19 °C since drug products were stored in inside-facilities.

** Mean Kinetic Temperature

*** 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.

- one batch every other year may be tested for formulations considered to be stable, (otherwise one batch per year);
- one batch every 3-5 years may be tested for formulations when the stability profile has been established, unless a major product change has been made, e.g. to the formulation or the method of manufacture.

Details concerning the batches should be stated in the test records, i.e. packaging of the drug product, batch number, date of manufacture, batch size, etc.

3.2 Test conditions

3.2.1 Accelerated studies

Test conditions are determined by the intended climatic zone in which the drug products will be distributed and used, as well as by the type of dosage forms. As a rule, accelerated studies are less suitable for semi-solid and heterogeneous formulations, e.g. emulsions etc.

An example of accelerated stability testing is set out in the table below.

Storage temperature [°C]	Humidity [%]	Length of period [months]
<i>Zone IV</i> - For hot climatic zones or global market: 40±2%	75±5%	6
<i>Zone II</i> - For temperate and subtropical climatic zones: 40±2%	75±5%	3

Alternative storage conditions may be used, in particular, six months testing carried out at a temperature of at least 15 °C above the expected long-term storage temperature (together with the appropriate relative humidity conditions). Storage at higher temperatures for shorter time periods may be applied, e.g. 3 months at 45-50 °C and 75% R.H., especially for zone IV or global market.

Where changes outside the specification limits occur in the course of accelerated studies, additional testing at intermediate conditions should be conducted, e.g. 30±2 °C/60±5% R.H. The initial registration application should include a minimum of 6 months data from one year study.

Storage under test conditions of high relative humidity applies particularly to solid dosage forms in semi-permeable packaging. For products in primary containers designed to provide a barrier for water vapours, storage conditions of high relative humidity are not necessary.

3.2.2 Real-time studies

Experimental storage conditions should be as close to the projected actual storage conditions in the distribution system, as practicable.

As for the length of studies - for registration purposes - results of at least 6 months (alternative 12 months) studies should be available at the time of registration. It should be possible to submit the registration dossier before the end of this 6-months period.

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 is considered to be a time period of:

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

For ongoing studies samples may be tested less frequently, e.g. at 6-months intervals for the confirmation of provisional shelf-life, or every 12 months for well established products. Highly stable formulations may be tested after the first 12 months and at the end of the shelf-life.

Test results are considered to be positive when no significant degradation nor changes in the physical, chemical, and if relevant, in the microbiological and biological properties of the product have been observed, and the product stays within its specification.

4. Analytical Methods

A systematic approach should be adopted in the presentation and evaluation of stability information. This 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 tests for products of decomposition, physicochemical tests (hardness, disintegration, particulate matter, etc.), should be determined, and for solid or semi-solid oral dosage forms dissolution test should be carried out.

Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Assay methods should be chosen to be stability indicating. Tests for related compounds or products of decomposition used, should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity.

Test methods to prove the efficacy of additives, such as antimicrobial agents, should be foreseen to see if they remain effective and unchanged throughout the projected shelf-life.

A check-list, similar to the one used for the WHO Survey on Stability of Essential Drugs (Annex 1), could be used to identify other stability characteristics of the product.

5. Stability Report

A stability report must be established for internal use, registration purposes etc. detailing the design, and the concept of the study, as well as results and conclusions.

The results should be presented as a table and a graph. For each batch, results of testing should be given both at the time of manufacture and at different moments during storage. A standard form should be prepared containing a summary of the results for each pharmaceutical preparation. A form is given in Annex 2, as one possible example.

The evaluation of stability for a given product, thus the definition of a proposed shelf-life and storage condition, must be based on these results.

6. Shelf-life and Recommended Storage Conditions

Shelf-life is always determined in relation to storage conditions. If batches of a product demonstrate different stability profiles, the shelf-life proposed should be based on the stability of the least stable, unless there are other justifiable reasons.

A tentative shelf-life of 24 months may be established provided the following conditions are satisfied:

- the active ingredient is considered to be stable (not easily degradable);
- stability studies as outlined under 3.2 have been performed with positive results;
- supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more;
- the manufacturer will continue to perform the real-time studies until the proposed shelf-life is covered, and the results, as received, will be submitted to the registration authority.

Products with less stable active ingredients and formulations not suitable for experimental studies for storage at elevated temperature (e.g. suppositories) will need more extensive real-time stability studies. The proposed shelf-life in this case should not exceed twice the time period covered by real-time studies.

After evaluation of the stability, the product may be prominently labelled with the following storage conditions:

- store at normal storage conditions,*
- store between 2-8 °C under refrigeration, no freezing,
- store below 8 °C under refrigeration,
- store in a freezer at -5 to -20 °C,
- store below -18 °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 °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. In these cases *"normal conditions"* may be defined at a national level. Recommended storage conditions have to be determined with regard to the conditions that are 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 cover up stability problems.

If applicable, recommendations should also be given regarding the utilization period and storage conditions, if different from previous, after opening and dilution, or reconstitution of a solution, e.g. antibiotic powder for reconstitution.

* This statement is often missing for products destined for areas with temperate climate.

** WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Thirty-first Report*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).

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ANNEX 1

SURVEY ON STABILITY OF PHARMACEUTICAL PREPARATIONS INCLUDED IN THE WHO MODEL LIST OF ESSENTIAL DRUGS			
ANSWER SHEET			
Name of reporting person	Address	Country Climatic zone	
NAME OF ESSENTIAL DRUG :			
Description of product			
<i>Dosage form</i>			
1. tablet	coated <input type="checkbox"/>	uncoated <input type="checkbox"/>	
2. capsule	hard <input type="checkbox"/>	soft <input type="checkbox"/>	
3. injection	liquid <input type="checkbox"/>	powder <input type="checkbox"/>	
4. oral liquid	solution <input type="checkbox"/>	suspension <input type="checkbox"/>	
5. topical semi-solid	cream <input type="checkbox"/>	ointment <input type="checkbox"/>	
6. eye preparations	liquid <input type="checkbox"/>	semi-solid <input type="checkbox"/>	
7. other (please state)			
<i>Packaging (material and type)</i>			
1. glass	bottle <input type="checkbox"/>	vial <input type="checkbox"/>	ampoule <input type="checkbox"/>
2. plastic	bottle <input type="checkbox"/>	vial <input type="checkbox"/>	ampoule <input type="checkbox"/>
3. paper	box <input type="checkbox"/>	bag <input type="checkbox"/>	
4. metal	<input type="checkbox"/>		
5. blister pack	<input type="checkbox"/>		
6. other (please state)			
<i>State of packaging</i>			
	intact <input type="checkbox"/>	damaged <input type="checkbox"/>	
<i>Storage conditions</i>			
according to the manufacturer's indications?	yes <input type="checkbox"/>	no <input type="checkbox"/>	
<i>Shelf-life (if available)</i>			
claimed by the manufacturer years months	
percentage elapsed when tested %		
<i>Source of product tested</i>			
1. manufactured in country of use	<input type="checkbox"/>		
2. imported from neighbouring country(s)	<input type="checkbox"/>		
3. imported from distant country(s)	<input type="checkbox"/>		
Problems encountered			
<i>Occurrence</i>		<i>Pharmacopoeial non-compliance</i>	
1. very frequent	<input type="checkbox"/>	1. identification <input type="checkbox"/>	
2. occasionally, but important	<input type="checkbox"/>	2. assay <input type="checkbox"/>	
3. rarely	<input type="checkbox"/>	3. purity tests <input type="checkbox"/>	
		4. other pharmacopoeial test(s) <input type="checkbox"/>	
<i>Organoleptic</i>		<i>Microbial</i>	
1. change of colour	<input type="checkbox"/>	1. microorganisms visible <input type="checkbox"/>	
2. visible changes, i.e. capping, cracking, foam	<input type="checkbox"/>	2. tests for bacteria positive <input type="checkbox"/>	
3. unhomogeneous appearance	<input type="checkbox"/>	3. tests for fungi positive <input type="checkbox"/>	
4. crystallization	<input type="checkbox"/>	4. tests for pyrogens positive <input type="checkbox"/>	
5. particles, turbidity, precipitation	<input type="checkbox"/>	5. other (please state) <input type="checkbox"/>	
6. sedimentation, caking, agglomeration	<input type="checkbox"/>		
7. smell, i.e. gas formation	<input type="checkbox"/>		
8. rancidity	<input type="checkbox"/>		
9. phase separation of emulsion	<input type="checkbox"/>		
10. interaction with packaging material	<input type="checkbox"/>		
11. other (please state)	<input type="checkbox"/>		
<i>Additional information</i>			
.....			
.....			
.....			
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	methyldopa
aminophylline	nifedipine
ampicillin	paracetamol
benzylpenicillin	phenoxymethylpenicillin
chloramphenicol	propranolol
chloroquine	spironolactone
chlorpromazine	sulfamethoxazole+trimethoprim
epinephrine	suxamethonium bromide
ergometrine	tetracycline
ethinylestradiol	warfarin
thiamin	
glyceryl trinitrate	
ibuprofen	
indometacin	
isosorbide dinitrate	

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., *Pharmazeutische Zeitung*, 1974, 119:321-324):

zone I	-	temperate
zone II	-	sub-tropical with possible high humidity
zone III	-	hot and dry
zone IV	-	hot and moist

**STABILITY TESTING
SUMMARY SHEET**

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	Pressure

RESULTS

- 1) Chemical findings:.....
.....
.....
- 2) Microbiological and biological findings.....
.....
.....
- 3) Physical findings.....
.....
.....
- 4) Conclusions.....
.....
.....

Responsible officer Date ../19..
