

STABILITY TESTING OF NEW ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS *)

Guideline Title	Stability Testing of New Active Substances and Medicinal Products*)
Legislative basis	Directive 75/318/EEC as amended
Date of first adoption	October 1993
Date of entry into force	Compulsory for applications submitted after 1/1/1998
Status	Last revised 1993
Previous titles/other references	ICH Q1A: <i>Stability Testing of New Drug Substances and Products</i>, III/3352/92, CPMP/ICH/380/95
Additional Notes	This note for guidance concerns the application of Part 2, sections C and F of the Annex to Directive 75/318/EEC as amended, with a view to the granting of a marketing authorisation for a new medicinal product. This guideline replaces those sections of the CPMP guideline entitled <i>Stability tests on Active Ingredients and Finished Products</i> which refer to new active substances and medicinal products containing new active substances.

CONTENTS

PREAMBLE

OBJECTIVE

SCOPE

ACTIVE SUBSTANCE

PRODUCT

ANNEX I

STABILITY TESTING OF NEW ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS *)

PREAMBLE

The following guideline sets out the stability testing requirement for a marketing authorisation within the three areas of the EC, Japan and the USA. It does not seek necessarily to cover the testing that may be required for registration in or export to other areas of the world.

The guideline seeks to exemplify the core stability data package required for new active substances and medicinal products. It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches.

The guideline provides a general indication on the requirements for stability testing, but leaves sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the materials being evaluated.

The principle that information on stability generated in any one of the three areas of the EC, Japan and the USA would be mutually acceptable in both of the other two areas has been established, provided it meets the appropriate requirements of this guideline and the labelling is in accord with national/regional requirements.

Details of the specific requirements for sampling, test requirements for particular dosage forms/packaging etc., are not covered in this guideline.

OBJECTIVE

The purpose of stability testing is to provide evidence on how the quality of a an active substance or medicinal product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established.

SCOPE

The guideline primarily addresses the information required in marketing authorisations for new active substances and associated medicinal products.

This guideline does not currently seek to cover the information required for abbreviated or abridged applications, variations, clinical trial applications, etc.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three areas of the EC, Japan and the USA. The mean kinetic temperature in any region of the world can be derived from climatic data (Grimm, W. *Drugs Made in Germany*, 28, 196-202, 1985 and 29, 39-47, 1986).

ACTIVE SUBSTANCE

General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

Formal Studies

Primary stability studies are intended to show that the active substance will remain within specification during the re-test period if stored under recommended storage conditions.

Selection of Batches

Stability information from accelerated and long term testing is to be provided on at least three batches. The long term testing should cover a minimum of 12 months duration on at least three batches at the time of submission.

The batches manufactured to the minimum of pilot plant scale should be by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of active substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale.

Supporting information may be provided using stability data on batches of active substance made on a laboratory scale.

The first three production batches of active substance manufactured post approval, if not submitted in the original marketing authorisation application, should be placed on long term stability studies using the same stability protocol as in the approved marketing authorisation application.

Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability-indicating testing methods must be applied. The need for the extent of replication will depend on the results of validation studies.

Specification

Limits of acceptability should be derived from the profile of the material as used in the pre-clinical and degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials.

Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage shipment and subsequent use. Application of the same storage conditions as applied to the medicinal product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature sensitive active substances should be stored under an alternative, lower temperature condition which will then become the designated long term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15°C above this designated long term storage temperature (together with the appropriate relative humidity conditions for that temperature). The designated long term testing conditions will be reflected in the labelling and re-test date.

	Conditions	Minimum Time Period at Submission
Long term testing	25°C±2°C/ 60% RH±5%	12 months
Accelerated Testing	40°C±2°C/ 75% RH±5%	6 months

Where 'significant change' occurs during six months storage under conditions of accelerated testing at 40°C±2°C/75 percent RH±5 percent, additional testing at an intermediate condition (such as 30°C±2°C/60 percent RH±5 percent) should be conducted for active substances to be used in the manufacture of dosage forms tested long term at 25°C/60 percent RH and this information included in the marketing authorisation application. The initial marketing authorisation application should include a minimum of 6 months data from a 12 months study.

'Significant change' at 40°C/75 percent RH or 30°C/60 percent RH is defined as failure to meet the specification.

The long term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate re-test periods, and the further accumulated data can be submitted to the Authorities during the assessment period of the marketing authorisation application.

The data (from accelerated testing at an intermediate condition) may be used to evaluate the impact of short term excursions outside the label storage conditions such as might occur during shipping.

Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the active substance. Testing under the defined long term conditions will normally be every three months, over the first year, every six months over the second year and then annually.

Packaging/Containers

The containers to be used in the long term, real time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution

Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the active substance and evaluating the stability information (covering as necessary the physical, chemical and microbiological test characteristics), a retest period applicable to all future batches of the bulk substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally unnecessary to go through the formal statistical analysis but merely to provide a full justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data etc.

Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes.

Statements/Labelling

A storage temperature range may be used in accordance with relevant national/regional requirements. The range should be based on the stability evaluation of the active substance. Where applicable, specific requirements should be stated, particularly for active substances that cannot tolerate freezing. The use of terms such as 'ambient conditions' or 'room temperature' is unacceptable.

A re-test period should be derived from the stability information.

PRODUCT

General

The design of the stability program for the finished product should be based on the knowledge of the behaviour and properties of the active substance and the experience gained from clinical formulation studies and from the stability studies on the active substance. The likely changes on storage and the rationale for the selection of product variables to include in the testing programme should be stated.

Selection of Batches

Stability information from accelerated and long term testing is to be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. Two of these three batches should be at least pilot scale. The third one may be smaller (e.g., 25,000 to 50,000 tablets or capsules for solid oral dosage forms). The long term testing should cover at least 12 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large scale batches for marketing. The process should provide medicinal product of the same quality intended for marketing, and meeting the same quality specification as to be applied for release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of active substance.

Data on the laboratory scale batches is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information. The first three production batches manufactured post approval, if not submitted in the original marketing authorisation application, should be placed on accelerated and long term stability studies using the same stability protocols as in the approved marketing authorisation.

Test procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated and the assays should be stability-indicating. The need for the extent of replication will depend on the results of validation studies.

The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties and characteristics, organoleptic properties and where required, microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives.

Specifications

Limits of acceptance should relate to the release limits (where applicable), to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable derivations from the release specification based on the stability evaluation and the changes observed on storage. It will need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials. The justification for the limits proposed for certain other tests such as particle size and/or dissolution rate will

require reference to the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use (e.g., reconstitution or dilution as recommended in the labelling).

See Table below for accelerated and long term storage conditions and minimum times. An assurance that long term testing will continue to cover the expected shelf life should be provided.

Other storage conditions are allowable if justified. Heat sensitive finished products should be stored under an alternative lower temperature condition which will eventually become the designated long term storage temperature. Special consideration may need to be given to products which change physically or even chemically at lower storage conditions e.g., suspensions or emulsions which may sediment or cream, oils and semi-solid preparations which may show an increased viscosity. Where a lower temperature condition is used, the six months accelerated testing should be carried out at a temperature at least 15°C above its designated long term storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25°C±2°C/60 percent RH±5 percent RH. The designated long term testing conditions will be reflected in the labelling and expiration date.

Storage under conditions of high relative humidities applies particularly to solid dosage forms. For products such as solutions, suspensions etc., contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary but the same range of temperatures should be applied. Low relative humidity (e.g., 10-20 percent RH) can adversely affect medicinal products packed in semi-permeable containers (e.g. solutions in plastic bags, nose drops in small plastic containers etc.) and consideration should be given to appropriate testing under such conditions.

	Conditions	Minimum Time Period at Submission
Long term testing	25°C±2°C/60% RH±5%	12 months
Accelerated Testing	40°C±2°C/75% RH±5%	6 months

Where 'significant change' occurs due to accelerated testing, additional testing at an intermediate condition e.g. 30°C±2°C/60 percent ±5 percent RH should be conducted.

'Significant change' at the accelerated condition is defined as:

1. A 5 percent potency loss from the initial assay value of a batch;
2. Any specified degradant exceeding its specification limit;
3. The product exceeding its pH limits;
4. Dissolution exceeding the specification limits for 12 capsules or tablets.
5. Failure to meet specifications for appearance and physical properties e.g., colour, phase separation, resuspendibility, delivery per actuation, caking, hardness, etc.

Should significant change occur at 40°C/75 percent RH then the initial marketing authorisation application should include a minimum of 6 months data from an ongoing one year study at 30°C/60 percent RH; the same significant change criteria shall then apply.

The long term testing will be continued for a sufficient time beyond 12 months to cover shelf life at appropriate test periods. The further accumulated data should be submitted to the authorities during the assessment period of the marketing authorisation application.

The first three production batches manufactured post approval, if not submitted in the original marketing authorisation application, should be placed on accelerated and long term stability studies using the same stability protocol as in the approved marketing authorisation.

Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the medicinal product. Testing will normally be every three months over the first year, every six months over the second year and then annually.

The use of matrixing or bracketing can be applied, if justified.(See Glossary).

Packaging Materials

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected finished product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover as necessary physical, chemical, biological, microbiological quality characteristics, including particular properties of the dosage form (for example dissolution rate for oral solid dose forms).

The design of the stability study is to establish, based on testing a minimum of three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear,

quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data shows so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability and degradation performance.

The stability of the medicinal products after reconstituting or diluting according to labelling, should be addressed to provide appropriate and supportive information.

Statements/Labelling

A storage temperature range may be used in accordance with relevant national/regional requirements. The range should be based on the stability evaluation of the medicinal product. Where applicable, specific requirements should be stated particularly for medicinal products that cannot tolerate freezing.

The use of terms such as 'ambient conditions' or 'room temperature' is unacceptable.

There should be a direct linkage between the label statement and the demonstrated stability of the medicinal product.

ANNEX 1

Glossary and Information

The following terms have been in general use and the following definitions are provided to facilitate interpretation of the guideline.

Accelerated Testing

Studies designed to increase the rate of chemical degradation or physical change of an active substance or medicinal product by using exaggerated storage conditions as part of the formal, definitive, storage programme.

These data, in addition to long term stability studies, may also 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.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples are represented by those at the extremes.

Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of immediate containers are to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.

Climatic Zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.

Dosage Form; Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream etc. that contains an active substance generally, but not necessarily, in association with excipients.

Medicinal Product; Finished Product

The dosage form in the final immediate packaging intended for marketing.

Excipient

Anything other than the active substance in the dosage form.

Expiry/Expiration Date

The date placed on the container/labels of a product designating the time during which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal (Systematic) Studies

Formal studies are those undertaken to a pre-approval stability protocol which embraces the principles of these guidelines.

Long Term (Real Time) Testing

Stability evaluation of the physical, chemical, biological and microbiological characteristics of a product and an active substance, covering the expected duration of the shelf life and re-test period, which are claimed in the submission and will appear on the labelling.

Mass Balance; Material Balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision.

This concept is a useful scientific guide for evaluating data but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing

The statistical design of a stability schedule so that only a fraction of the total number of samples are tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure and possibly in some cases different container/closure systems.

Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the Regulatory Authority, where this is possible. In every case it is essential that all batches are tested initially and at the end of the long term testing.

Mean Kinetic Temperature

When establishing the mean value of the temperature, the formula of J. D. Haynes (J. Pharm. Sci. 60, 927-929, 1971) can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes derived his formula.

New Molecular Entity; New Active Substance

An active substance which has not previously been registered as a new active substance with the national or regional authority concerned.

Pilot Plant Scale

The manufacture of either active substance or product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale.

For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full production or 100,000 tablets or capsules, whichever is the larger.

Primary Stability Data

Data on the active substance stored in the proposed packaging under storage conditions that support the proposed re-test date.

Data on the product stored in the proposed container-closure for marketing under storage conditions that support the proposed shelf life.

Re-Test Date

The date when samples of the active substance should be re-examined to ensure that material is still suitable for use.

Re-Test Period

The period of time during which the active substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given product, provided that it has been stored under the defined conditions; after this period, the batch should be retested for compliance with specification and then used immediately.

Shelf life; Expiration Dating Period

The time interval that a product is expected to remain within the approved shelf life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Specification - Release

The combination of physical, chemical, biological and microbiological test requirements that determine a product is suitable for release at the time of its manufacture.

Specification - Check/Shelf life

The combination of physical, chemical, biological and microbiological test requirements that a active substance must meet up to its re-test date or a product must meet throughout its shelf life.

Storage Conditions Tolerances

The acceptable variation in temperature and relative humidity of storage facilities.

The equipment must be capable of controlling temperature to a range of $\pm 2^{\circ}\text{C}$ and Relative Humidity to $\pm 5\%$ RH. The actual temperatures and humidities should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed these ranges (i.e., $\pm 2^{\circ}\text{C}$ and/or $\pm 5\%$ percent RH) for more than 24 hours should be described in the study report and their impact assessed.

Stress Testing (Active substance)

These studies are undertaken to elucidate intrinsic stability characteristics. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated tests.

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the active substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of active substance.

These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual active substance and type of product.

This testing is likely to be carried out on a single batch of material and to include the effect of temperatures in 10°C increments above the accelerated temperature test condition (e.g., 50°C , 60°C , etc.) humidity where appropriate (e.g., 75 per cent or greater); oxidation and photolysis on the active substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.

Results from these studies will form an integral part of the information provided to regulatory authorities.

Light testing should be an integral part of stress testing. [The standard conditions for light testing are discussed in the note for guidance *Photostability Testing of New Active Substances and Medicinal Products*.]

It is recognised that some degradation pathways can be complex and that under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated or long term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products, if it has been demonstrated that in practice these are not formed.

Stress Testing (Product)

Light testing should be an integral part of stress testing (see note for guidance on *Photostability Testing of New Active Substances and Medicinal Products*).

Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Supporting Stability Data

Data other than primary stability data, such as stability data on early synthetic route batches of active substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed re-test period or shelf life and storage conditions.