Health Canada Santé Canada

Stability Testing of New Drug Substances and Products

ICH Harmonised Tripartite Guideline

International Conference on
Harmonisation of Technical Requirements for the
Registration of Pharmaceuticals for Human Use

Canada

DRUGS DIRECTORATE GUIDELINES

ICH HARMONISED TRIPARTITE GUIDELINE

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

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FOREWORD

The ICH harmonised tripartite guideline: "Stability Testing of New Drug Substances and Products" has been developed by an ICH Expert Working Group and has been subject to consultation by the regulatory parties that include Canada. The ICH Steering Committee has recommended to the Regulatory Agencies adoption of the guideline. This guideline does not become an official Tripartite requirement until January 1, 1998.

The guideline primarily addresses the information required in submissions for new molecular entities and associated drug products. The stability requirements specific to generic drugs, clinical trial supplies, or biologicals were not considered in the development of this guideline. These issues will be dealt with through the revisions of existing Drugs Directorate Guidelines.

Until January 1, 1998, stability data generated for any New Drug Submission other than that for a biological, that is in accordance with either the Chemistry and Manufacturing Guidelines: New Drugs, or this ICH Guideline, will be accepted for review.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Preamble

The following guideline sets out the stability testing requirement for a Registration Application within the three areas of the European Community (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 package of stability data required for new drug substances and products. It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches.

This 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 accordance with national/regional requirements.

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

1.2 Objective

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug 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 life to be established.

1.3 Scope

The guideline primarily addresses the information required in Registration Applications for new molecular entities and associated drug 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).

2 DRUG SUBSTANCES

2.1 General

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

Stress Testing

Stress testing helps to determine the intrinsic stability of a molecule by establishing degradation pathways. Such tests are performed 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 a drug substance will remain within specification during the re-test period if stored under recommended storage conditions.

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

The overall quality of the batches of drug 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 drug substance made on a laboratory scale.

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

2.3 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.

2.4 Specifications

Limits of acceptability should be derived from the profile of the material as used in the pre-clinical and clinical batches. It must include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials.

2.5 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 drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature-sensitive drug substances should be stored under an alternative, lower temperature condition which will then become the designated long-term testing storage temperature. The six-month 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-month storage under conditions of accelerated testing at 40°C ±2°C/75% RH ±5%, additional testing at an intermediate condition (such as 30°C ±2°C/60% RH ±5%) should be conducted for drug substances to be used in the manufacture of dosage forms tested long-term at 25°C/60% RH, and this information included in the Registration Application. The initial Registration Application should include a minimum of 6 months data from a 12-month study.

"Significant change" at 40°C/75% RH or 30°C/60% 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 Registration Application.

The data (from accelerated testing or from 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.

2.6 Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug 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.

2.7 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.

2.8 Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the drug 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 drug 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. 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 supporting data, etc. Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes.

2.9 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 drug substance. Where applicable, specific requirements should be stated, particularly for drug 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.

3 DRUG PRODUCTS

3.1 General

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

3.2 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 the three batches should be at least pilot scale. The third batch 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 a product of the same quality intended for marketing, and meeting the same quality specifications as to be applied for release of the material. Where possible, batches of the finished product should be manufactured using identifiably different batches of drug substance.

Data on 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 Registration Application, should be placed on accelerated and long-term stability studies using the same stability protocols as in the approved drug application.

3.3 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.

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

3.5 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).

The table below shows 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 drug products should be stored under an alternative lower temperature condition that will eventually become the designated long-term storage temperature. Special consideration may need to be given to products that change physically or chemically at lower storage conditions (e.g., suspensions or emulsions that may sediment or cream, oils and semi-solid preparations which may show an increased viscosity). Where a lower temperature condition is used, the six-month 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% RH ±5% 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 to 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers, etc.). 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% ±5% RH) should be conducted. "Significant change" at the accelerated condition is defined as:

1) 5% 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% RH, the initial Registration Application should include a minimum of 6 months data from an ongoing one-year study at 30°C/60% 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 Registration Application.

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

3.6 Testing Frequency

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

Matrixing or bracketing can be applied, if justified. (See Glossary).

3.7 Packaging Materials

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected drug 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).

3.8 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover, as necessary, physical, chemical, biological and 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 drug 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 drug products after reconstituting or diluting according to labelling, should be addressed to provide appropriate and supportive information.

3.9 Statements/Labelling

A storage temperature range may be used in accordance with relevant national and regional requirements. The range should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated, particularly for drug 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 characteristics of the drug product.

4 GLOSSARY

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

Accelerated Testing

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

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.

Active Substance; Active Ingredient; Drug Substance, Medicinal Substance

The unformulated drug substance which may be subsequently formulated with excipient to produce the drug product.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes (e.g., 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 is 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, (e.g., tablet, capsule, solution, cream, etc.) that contains a drug ingredient generally, but not necessarily, in association with excipient.

Drug Product; Finished Product

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

Excipient

Anything other than the drug substance in the dosage form.

Expiry/Expiration Date

The date placed on the container/labels of a drug product designates 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 undertaken to a pre-approval stability protocol that embraces the principles of these guidelines.

Long-term (Real Time) Testing

Stability evaluation of the physical, chemical, biological and microbiological characteristics of a drug product and a drug 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% 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 drug 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

A substance that has not previously been registered as a new drug substance with the national or regional authority.

Pilot Plant Scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that 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 drug substance stored in the proposed packaging under storage conditions that support the proposed re-test date.

Data on the drug 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 drug substance should be re-examined to ensure that material is still suitable for use.

Re-test Period

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

Shelf Life; Expiration Dating Period

The time interval that a drug 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 whether a drug 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 drug substance must meet up to its re-test date or that a drug 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 ±2°C and Relative Humidity to ±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 (±2°C and/or ±5% RH) for more than 24 hours should be described in the study report and their impact assessed.

Stress Testing (Drug 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 drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of drug 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 drug substance and type of drug 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% or greater), oxidation and photolysis on the drug 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 still under discussion and will be considered in a further ICH document.)

It is recognized that some degradation pathways can be complex and that under forcing conditions, decomposition products may be observed that 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 (Drug Product)

Light testing should be an integral part of stress testing.

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 drug 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.

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