2003-06-10

NOTICE

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Health Canada is pleased to announce the finalization of the Guidance for Industry ***Stability Testing of Existing Drug Substances and Products***. This guidance is an extension of the previously released ICH[1] / Health Canada guidance document entitled *Stability Testing of New Drug Substances and Products* (also referred to as the "parent guidance") and defines the stability data package in submissions for "existing" drug substances and associated products. In the interests of international harmonization, wherever possible, this guidance conforms to the principles of the ICH parent <guidance>, with changes necessary to reflect the recommendations for existing drugs indicated by "<text>".

A draft version of this document of the same title was released for Stakeholder consultation in 1997. This finalized version has been to updated include revisions as a result of the maintenance of the parent guidance, additional clarification as a result of comments that have been received (where appropriate), as well as to promote consistency with other Health Canada guidance documents. A summary of the notable updates is provided in Attachment 1 to this *Notice*.

The effective date (with the exception of the Intermediate Storage Condition) of this guidance document is April 1, 2004. The stability data package for submissions *received* after this date should follow the recommendations of this guidance. Mid-stream switch of the intermediate storage condition from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application. **It is recommended that submissions contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65% RH ± 5% RH, if applicable, by April 1, 2006.**

This guidance document makes reference to another Health Canada guidance document entitled *Impurities in Existing Drug Substances and Products.* Health Canada is in the process of finalizing this document which will replace the draft version released in 1999 entitled *Identification, Qualification, and Control of Related Impurities in Existing Drugs*.

This and other Guidance documents are available on the **Therapeutic Products Directorate/Biologics and Genetic Therapies Directorate/ Marketed Health Products Directorate Website (s)** (**http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/**). The availability of

[1] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

printed copies of guidance documents may be confirmed by consulting the *Guidelines and Publications Order Forms* (available on the TPD/BGTD/MHPD Website) or by contacting the Publications Coordinator[2].

Should you have any questions regarding the content of the guidance, please contact:

Bureau of Pharmaceutical Sciences
Therapeutic Products Directorate, Health Canada
Finance Building (A/L 0202A2)
Ottawa, Ontario
K1A 1B9

Internet: bps_enquiries@hc-sc.gc.ca
Phone: (613) 941-3184
Fax: (613) 957-3989

[2] Tel: (613) 954-6466; E-mail: publications_coordinator@hc-sc.gc.ca

Attachment 1 - Summary of Notable Updates

(1) Revisions as a result of the maintenance of the parent guidance:

- text to reflect the changes from ICH Q1A to Q1A(R) to Q1A(R2);
- recommendations for drug substances and products intended for storage at low temperature conditions and for drug products packaged in semi-permeable containers;
- guidance for the stability testing and specification of drug products containing antimicrobial preservatives;
- revisions to the storage conditions as per ICH Q1A(R2) have been incorporated (as result of Q1F) (e.g., the Intermediate storage condition has been changed from 30°C ± 2°C/60% ± 5% to 30°C ± 2°C/65% ± 5%);
- references have been made to Q1D, Q1E (and Health Canada Impurity) <guidances>;
- the Glossary from the Q1A <guidance> has been incorporated.

(2) Additional clarification:

- guidance has been provided on examples of various scenarios for stability designs (e.g., multiple strengths of identical or closely related formulations);
- clarification on approaches for "release and shelf life specifications" versus "regulatory acceptance criteria";
- guidance on the establishment of storage statements for labelling purposes.

(3) Consistencies with other Health Canada guidance documents:

- the Scope of the guidance has been clarified to include Supplemental New Drug Submissions (SNDSs), Supplemental Abbreviated New Drug Submissions (SANDSs), and Notifiable Changes (NCs);
- description on the definition of the start of a retest date;
- the selection of batches has been revised to correspond with ICH Q1A (e.g., including the definition for *pilot scale*), with changes to accommodate existing drugs (e.g., One of the two batches should be at least pilot scale batches and the second one can be smaller, if justified (e.g., for solid oral dosage forms, 25 000 or 50 000 tablets or capsules);
- the evaluation of the stability data should follow the recommendations of the ICH Q1E <guidance> (including the amount of extrapolation beyond the available long term data);
- guidance on the Continuing Stability Programme;
- the minimum time period covered by data at the time of submission at the accelerated storage condition was revised from 3 months to 6 months with a testing frequency having a minimum of three time points (e.g., 0, 3, and 6 months) to be consistent with the Q1C guidance.

Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Stability Testing of Existing Drug Substances and Products

Published by authority of the
Minister of Health

Date Adopted	2003/04/23
Effective Date	2004/04/01
Effective Date for the intermediate storage condition of 30°C ± 2°C/65% RH ± 5% RH, if applicable	2006/04/01

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Guidance Document

Canada

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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1 INTRODUCTION

1.1 Objectives of the Guidance

<This guidance is an extension of the previously released ICH[3] /Health Canada guidance document entitled *Stability Testing of New Drug Substances and Products* and defines the stability data package in submissions for existing drug substances and associated products. An "existing drug" is one that is not a new active substance but requires the filing of a New Drug Submission (NDS), an Abbreviated New Drug Submission (ANDS) or a Supplement for which a Notice of Compliance has been previously issued pursuant to Division C.08 of the *Food and Drug Regulations* (e.g., generic products). This could also include submissions for new dosage forms, new strengths[4]. This guidance may also be used when determining stability requirements for Notifiable Changes.>

1.2 Scope

<This guidance addresses the stability information to be included on existing drug substances and associated drug products in new drug submissions (NDSs) and abbreviated new drug submissions (ANDSs), Supplements and Notifiable Changes.

For determination of stability requirements to Notifiable Changes, this guidance may be used in conjunction with the Health Canada policy *Stability Requirements for Changes to Marketed New Drugs.*

This guidance applies to pharmaceutical drugs, including synthetic drugs and semi-synthetic drugs. This guidance does not apply to biologics or radiopharmaceuticals.

The ICH harmonised tripartite guidance *Stability Testing of New Drug Substances and Products* was originally adopted as a Health Canada guidance in the fall of 1994. This guidance defines the stability data package in submissions for new molecular entities and associated products. The scope of the guidance further states that “This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, ...”. The present guidance serves to delineate the stability data package for existing drug substances and products.

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3 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

4 Note: The term “new drug”, as defined in section C.08.001 of the *F&DR*, is broader than the corresponding ICH definition, which is restricted to new molecular entities (new active substances).

In the interests of international harmonization, wherever possible, this guidance conforms to the principles of the ICH Guidance Document Q1A(R2) *Stability Testing of New Drug Substances and Products*, with changes necessary to reflect the recommendations for existing drugs indicated by "<text>".>

1.3 General Principles

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 to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

<Alternate approaches to the principles and practices described in this guidance may be acceptable provided they are supported by adequate scientific justification. However, submission sponsors are encouraged to discuss significant variations with Health Canada in advance to avoid rejection or withdrawal of the submission.>

2 GUIDANCE

2.1 Drug Substance

2.1.1 General

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

<The retest period is based on the results of long term stability studies performed by the drug substance manufacturer or the submission sponsor using validated analytical procedures.

The start of the retest period should begin at the date of manufacture of the drug substance. The retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

In certain cases, information available in the public domain may be sufficient to establish an appropriate retest period, e.g., if the synthetic route and manufacturing process are identical and a substantial body of evidence exists that establishes that the drug is inherently stable. In all instances, sponsors are encouraged to provide all relevant information available on the stability of the drug substance.

Submission sponsors should either:

a) assign a retest period for the drug substance based on the available stability data, after which any batch should be retested for compliance with specification and then used immediately (e.g., within 30 days of testing),

or

b) certify that the drug substance will be tested for compliance with specification immediately prior to use in the manufacture of the drug product. In this case, formal stability studies on the drug substance will not be necessary.

When available, relevant stability data available in the public domain, including information in official pharmacopoeias, or from drug substance (active pharmaceutical ingredient) manufacturers should be provided.>

2.1.2 Stress Testing

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10˚C increments (e.g., 50˚C, 60˚C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions.

Results from these studies will form an integral part of the <submission>.

2.1.3 Selection of Batches

Data from formal stability studies should be provided on at least <two> primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

<When differences are identified in the production of the drug substance, e.g., owing to the use of different drug substance manufacturers, stability studies may not be necessary on material from each source provided that the same synthetic route is used and batch analyses **conducted by the submission sponsor** confirms that material from all sources or production methods meet the sponsor's specifications, including purity, potency and when relevant, crystal form and moisture. In such instances, the potential impact on retest periods of differences in the container closure system to be used by different drug substance manufacturers should be assessed.>

2.1.4 Container Closure System

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

2.1.5 Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, is addressed in ICH Q6A. In addition, specification for degradation products in a drug substance is discussed in Q3A <and Health Canada's *Impurities in Existing Drug Substances and Products.*>

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

2.1.6 Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

2.1.7 Storage Conditions

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long term testing should cover a minimum of <6> months' duration on at least <two> primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case applies if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.1.7.1 General Case

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25˚C ± 2˚C / 60% RH ± 5% or 30˚C ± 2˚C/65% RH ± 5% RH	<6> months
Intermediate**	30˚C ± 2˚C/65% RH ± 5% RH	6 months
Accelerated	40˚C ± 2˚C / 75% RH ± 5%	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2˚C/60% RH ± 5% RH or 30˚C ± 2˚C/65% RH ± 5% RH.
** If 30˚C ± 2˚C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25˚C ± 2˚C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

"Significant change" is defined as failure to meet the specification.

2.1.7.2 Drug Substances Intended for Storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5˚C ± 3˚C	<6> months
Accelerated	25˚C ± 2˚C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3 Drug Substances Intended for Storage in a Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20˚C ± 5˚C	<6> months

For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5˚C ± 3˚C or 25˚C ± 2˚C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

2.1.7.4 Drug Substances Intended for Storage below -20˚c

Drug substances intended for storage below -20˚C should be treated on a case-by-case basis.

2.1.8 Stability Commitment

When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

Where the submission includes long term stability data on <two> production batches covering the proposed retest period, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least <two> production batches, a commitment should be made to continue these studies through the proposed retest period.

2. If the submission includes data from stability studies on fewer than <two> production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least < two>, on long term stability studies through the proposed retest period.

3. If the submission does not include stability data on production batches, a commitment should be made to place the first <two> production batches on long term stability studies through the proposed retest period.

The stability protocol used for long term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.1.9 Evaluation

The purpose of the stability study is to establish, based on testing a minimum of <two> batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the 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 throughout the assigned retest period.

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 these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. 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 (e.g., 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 should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed 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.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the retest period can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

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

<Sponsors should consult ICH Q1E for details on the evaluation of stability data. In addition to providing complete stability information in submission volumes, sponsors should produce an accurate summary of the stability data as part of the Quality Overall Summary (QOS).>

2.1.10 Statements/Labelling

A storage statement should be established for labelling. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

<This would normally include a storage temperature range specified in degrees Celsius. Where applicable, specific precautions should be stated, e.g., "Protect from light", "Protect from freezing". Note: The use of precautionary statements should not be a substitute for selecting the appropriate container closure system for the bulk drug substance.>

A retest period should be derived from the stability information, and a retest date should be displayed on the container label, if appropriate.

2.2 Drug Products

2.2.1 General

The design of the formal stability studies for the drug product should be based on knowledge of the behaviour and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2.2.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

2.2.3 Selection of Batches

Data from stability studies should be provided on at least <two> primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. <One> of the <two> batches should be at least pilot scale batches and the <second> one can be smaller, if justified <(e.g., for solid oral dosage forms, a smaller batch is generally 25 000 or 50 000 dosage units). The larger of the two batches would be the batch used for comparative bioavailability studies, if applicable.>. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

<Note: In order to qualify under the Health Canada policy on *Extension of Expiration Dates*, sponsors need to have complete long term data on **three** production scale batches.>

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

<ICH Q1D should be consulted for details on bracketing and matrixing designs. The use of any reduced design should be justified.

Justification should include a discussion of factors which could affect the stability profile of the drug product (e.g., qualitative and/or quantitative differences in formulation, differences in batch size, and impact of manufacturing process parameters (such as equipment capacity and load, residence time in a humid phase)). Supporting documentation, such as results of drug/excipient compatibility studies or stability studies conducted on laboratory scale batches, should be provided.

Examples of stability designs include:

Scenario 1 *- a single strength:*

A minimum of two batches should be placed on stability.

Scenario 2 *- multiple strengths of identical formulations:*

Identical formulations are those where a common blend containing identical components in identical proportions is manufactured by the same process and is compressed to multiple strengths. If a coating is present, the composition of the coating is identical for all strengths. Bracketing or matrixing designs may be acceptable if scientifically justified. A minimum of two common blends should be manufactured. These can be compressed to each of the proposed strengths. If bracketing is proposed, batches of the highest and lowest strengths, resulting from the two common blends, should be placed on stability.

Scenario 3 *- multiple strengths of closely related formulations:*

Closely related formulations are considered different strengths with formulations that differ only in minor excipients (e.g., colourants or flavourings); or that differ by minor amounts of the same excipients.

If closely related formulations differ in the relative amount of excipients, bracketing may be acceptable if justified. A minimum of two batches of the highest strength and two batches of the lowest strength should be placed on stability. One batch of each of the intermediate (bracketed) strengths should be manufactured and certificates of analyses should be provided.

For formulations which differ in the composition of minor excipients (e.g., colourants, flavourings), supporting stability data should be provided to demonstrate excipient compatibility and justify bracketing. Stability data on the intermediate (bracketed) strengths may not be necessary if formulations are closely related.

Scenario 4 *- formulations are not identical or closely related (e.g., different excipients, significant changes in concentrations):*

A minimum of two batches of each strength should be placed on stability, bracketing is not permissible.

The Health Canada policy *Bioequivalence of Proportional Formulations* should be used in the assessment to establish if the formulations are considered proportional (e.g., closely related). This policy outlines acceptable variations depending on the function of the excipient (e.g., fillers, disintegrants, lubricants).>

2.2.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.5 Specifications

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A. In addition, specification for degradation products in a drug product is addressed in Q3B <and Health Canada's *Impurities in Existing Drug Substances and Products.*>

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

<The concept of "release and shelf life specifications" versus "regulatory acceptance criteria" is described in ICH Q6A. Health Canada would consider either approach acceptable. More stringent release acceptance criteria may be necessary in certain cases in order to ensure that shelf life acceptance criteria are met throughout the labelled shelf life of the drug product.>

2.2.6 Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

2.2.7 Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at <6> months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long term testing should cover a minimum of <6> months' duration on at least <two> primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

2.2.7.1 General Case

Study	**Storage conditions**	**Minimum time period covered by data at submission**
Long-term*	25˚C ± 2˚C / 60% RH ± 5% or 30˚C ± 2˚C/65% RH ± 5% RH	<6> months
Intermediate**	30˚C ± 2˚C/65% RH ± 5% RH	6 months
Accelerated	40˚C ± 2˚C / 75% RH ± 5%	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2˚C/60% RH ± 5% RH or 30˚C ± 2˚C/65% RH ± 5% RH.
** If 30˚C ± 2˚C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25˚C ± 2˚C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;

2. Any degradation product's exceeding its acceptance criterion;

3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;

   and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH; or

5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2 Drug Products Packaged in Impermeable Containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

2.2.7.3 Drug Products Packaged in Semi-Permeable Containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25˚C ± 2˚C/40% RH ± 5% RH or 30˚C ± 2˚C/35% RH ± 5% RH	<6> months
Intermediate**	30˚C ± 2˚C/65% RH ± 5% RH	6 months
Accelerated	40˚C ± 2˚C/not more than (NMT) 25% RH	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2˚C/40% RH ± 5% RH or 30˚C ± 2˚C/35% RH ± 5% RH.
** If 30˚C ± 2˚C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25˚C ± 2˚C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30˚C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25˚C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40˚C/NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40˚C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity

and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g., 40˚C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	**Reference relative humidity**	**Ratio of water loss rates at a given temperature**
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

2.2.7.4 Drug Products Intended for Storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5˚C ± 3˚C	<6> months
Accelerated	25˚C ± 2˚C/60% RH ± 5%RH	6 months

If the drug product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

2.2.7.5 Drug Products Intended for Storage in a Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20˚C ± 5˚C	<6> months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5˚C ± 3˚C or 25˚C ± 2˚C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

2.2.7.6 Drug Products Intended for Storage below -20˚c

Drug products intended for storage below -20˚C should be treated on a case-by-case basis.

2.2.8 Stability Commitment

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life.

Where the submission includes long term stability data from <two> production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least <two> production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months.

2. If the submission includes data from stability studies on fewer than <two> production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least <two>, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

3. If the submission does not include stability data on production batches, a commitment should be made to place the first <two> production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

2.2.9 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of <two> batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show 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; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 one-sided confidence limit for the mean curve intersects the acceptance criterion. 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 (e.g., 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 should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed 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.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified. This justification should be based on what is known about the

mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

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

<Sponsors should consult ICH Q1E for details on the evaluation of stability data. In addition to providing complete study information in submission volumes, sponsors should to produce an accurate summary of stability data as part of the Quality Overall Summary (QOS).>

2.2.10 Statements/Labelling

A storage statement should be established for the labelling. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instructions should be provided, particularly for drug product that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

<Labelling would normally include a storage temperature range specified in degrees Celsius. Where applicable, specific precautions should be stated, e.g., “Protect from light”, “Protect from freezing”. Note: The use of precautionary statements should not be a substitute for selecting the appropriate container closure system for the drug product.

If the results from the stability studies demonstrate that the drug product is acceptable under the General Case (section 2.2.7), the following are examples of acceptable storage statements:

"Store between 15˚C - 30˚C"
"Store at Room Temperature (15˚C to 30˚C)"
"Store at 25˚C, with excursions permitted to 15˚C - 30˚C".

When only a maximum storage temperature is proposed (e.g., "Store up to 25˚C"), sponsors should provide stability data to demonstrate that the product is not adversely affected by low temperature storage conditions (e.g., 5˚C ± 3˚C).

<2.2.11 Continuing Stability Studies>

<A *Continuing Stability Programme* (i.e. ongoing stability studies) should be implemented to ensure compliance with the approved shelf life specifications. A minimum of one batch of every strength of the drug product should be enrolled into the continuing stability programme each year. Bracketing and matrixing can be applied, if scientifically justified.>

3 GLOSSARY

The following definitions are provided to facilitate interpretation of the guidance.

Accelerated Testing - Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect 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 such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or 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). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic Zones - The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm (Drugs Made in Germany, 28:196-202, 1985 and 29:39-47, 1986).

Commitment Batches - Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container Closure System - The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage Form - A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

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

Drug Substance - The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient - Anything other than the drug substance in the dosage form.

Expiration Date - The date placed on the container label of a drug product designating the time prior to 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 Stability Studies - Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable Containers - Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate Testing - Studies conducted at 30˚C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25˚C.

Long Term Testing - Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labelling.

Mass 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 error.

Matrixing - The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. 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 closure system, and, possibly in some cases, different container closure systems.

Mean Kinetic Temperature - A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.
When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (J. Pharm. Sci., 60:927-929, 1971) can be used.

New Molecular Entity - An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot Scale Batch - A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary Batch - A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, <one> of the <two> batches should be at least pilot scale batch, and the <second> batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production Batch - A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest Date - The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest Period - The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semi-permeable Containers - Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf Life (also referred to as expiration dating period) - The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification - See Q6A.

Specification – Release - The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification - Shelf life - The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage Condition Tolerances - The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) 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, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress Testing (drug substance) - Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress Testing (drug product) - Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting Data - Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

4 REFERENCES

<4.1 Health Canada Documents>

- *Food and Drugs Act*, *Food and Drug Regulations*, and *Medical Devices Regulations*
- Quality Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) for Pharmaceuticals
- Impurities in Existing Drug Substances and Products
- Extension of Expiration Dates
- Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms
- Stability requirements for changes to marketed new drugs

<4.2 ICH Documents>

- Q1A(R2): Stability Testing of New Drug Substances and Products
- Q1B: Photostability Testing of New Drug Substances and Products
- Q1C: Stability Testing of New Dosage Forms
- Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products
- Q1E: Evaluation of Stability Data
- Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV
- Q3A(R): Impurities in New Drug Substances
- Q3B(R): Impurities in New Drug Products

- Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- Q7A: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients
- M4: Common Technical Document (CTD)
- M4Q: The Common Technical Document - Quality (CTD-Q)