Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for prescription medicines

Appendix 14: Stability testing

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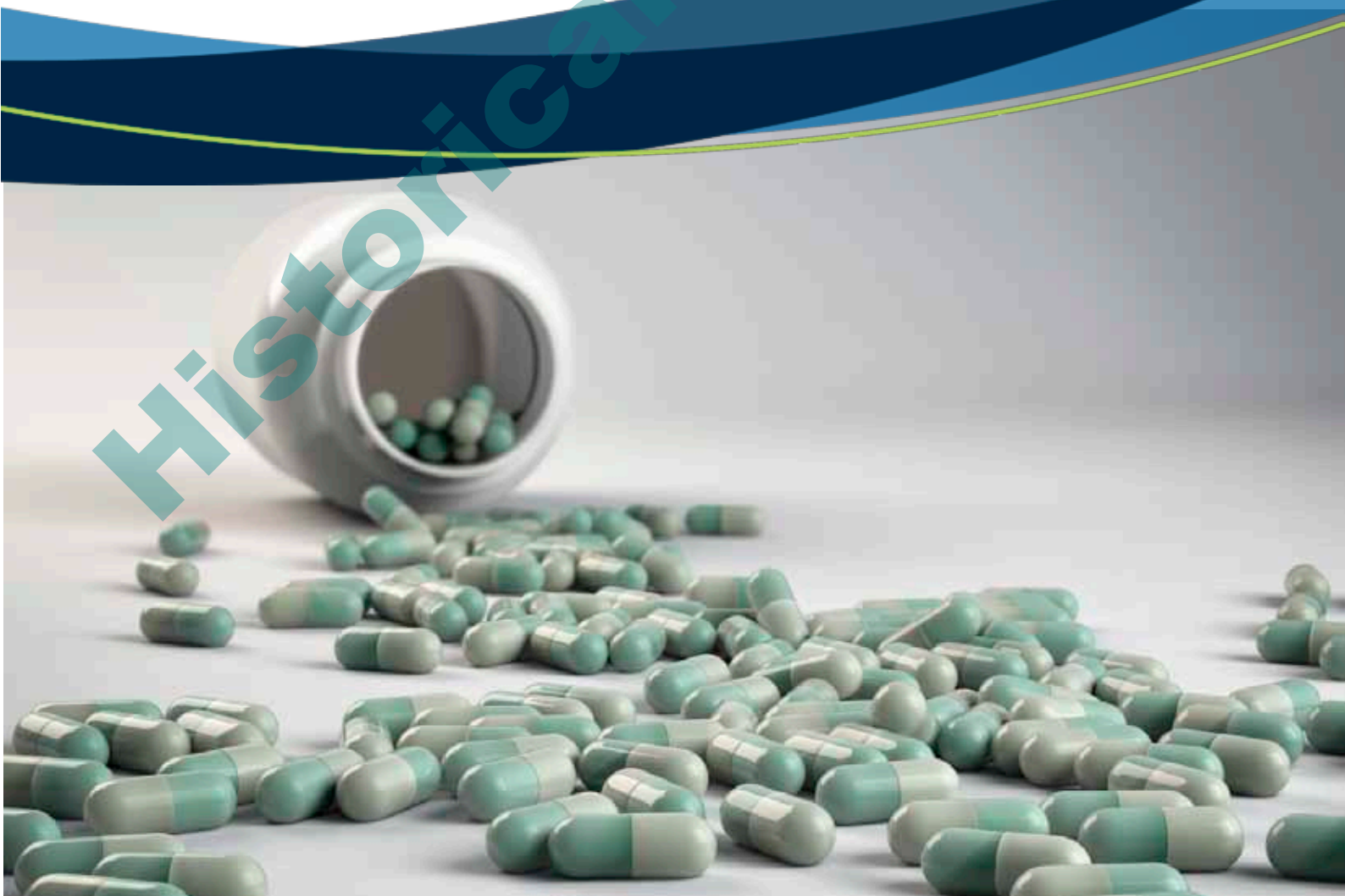
TGA Health Safety Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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Introduction

The Therapeutic Goods Administration (TGA) has adopted a number of Committee for Medicinal Products for Human Use (CHMP)/ International Conference on Harmonisation (ICH) guidelines relating to stability of active pharmaceutical ingredients (API) and finished products. The guidelines should be consulted for information regarding the design and conduct of stability studies. Copies are available on the TGA web site[1].

The CHMP/ICH stability guidelines primarily cover:

- products containing APIs that are prepared by chemical synthesis;
- products containing APIs that are pure chemical entities isolated from a natural source (for example, vincristine, digoxin);
- radiopharmaceuticals (however, see below);
- products containing APIs that are produced by microbial fermentation (for example, many antibiotics and some anticancer agents);
- materials of biological origin (however, see below).

The CHMP/ICH guidelines do not cover radionuclide generators. Information required on the stability of radionuclide generators varies with each case. Advice on requirements for a particular generator system may be obtained from:

Director
Medical Radiation Branch
Australian Radiation Protection and Nuclear Safety Agency (ARPANSA)
619 Lower Plenty Road
YALLAMBIE VIC 3085
Telephone (03) 9433 2211

The present document is designed to assist applicants in applying the CHMP/ICH guidelines and in understanding how the TGA interprets these guidelines and assesses stability data.

[1] http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm

Materials of biological origin

The principles described in this document also generally apply to stability studies on materials of biological origin, such as hormones, allergens, modified animal tissues, vaccines and the products of genetic engineering or other newer biological techniques. However some specific guidelines may not be appropriate for biologicals, in particular:

- references to chemical assay techniques, such as the preference stated in Section 3.3 for chromatographic methods for decomposition products, may not always be appropriate for biologicals;
- it may not always be possible to establish degradation pathways and identify decomposition products formed in significant amounts (see Sections 2.1 and 3.3 below);
- the degradation of biologicals is not usually amenable to kinetic analysis and extrapolation from *accelerated* testing (see Section 5). Unless specifically negotiated otherwise, all biologicals require real-time stability data.

Stability data for biologicals will be evaluated on a case-by-case basis, having regard to the nature of the product and the methods of analysis (physical, chemical, biological) that are appropriate for that product.

Sponsors should refer to the CHMP/ICH guideline (*Quality of Biotechnological Products: Stability of Biotechnological / Biological Products*[2]) on the stability of biological products adopted by the TGA for the specific requirements for these materials. In particular, sponsors should note the following:

- if a sponsor desires storage at two temperatures (for example, 1 month at <25°C and 23 months at 2-8°C) separate studies are not sufficient and a study using both temperatures in a worst-case scenario (that is, high temperature first then low temperature) is required;
- in stability studies a potency assay must be used. A content assay (HPLC, ELISA etc) is not sufficient unless the content assay is a pharmacopoeial assay (for example, insulin or somatropin);
- sponsors should ensure that cumulative stability is demonstrated. Intermediates and bulks for biological products may be stored for long periods and sponsors should demonstrate the worst-case scenario: finished product stability from intermediates held for the maximum time.

Extensions of shelf-life of biologicals are not self-assessable.

1. General principles

The objective of a stability study is to determine the period of time during which a medicine meets appropriate standards when stored under defined conditions. The following statement, which appears in the British Pharmacopoeia (BP), reflects a principle that should be familiar to any pharmaceutical manufacturer:

[2] http://www.tga.gov.au/industry/pm-euguidelines-biotechnology.htm

> A manufacturer must recognise that a product or material may be challenged at any time during its claimed period of use by the methods of the Pharmacopoeia and that it must then comply with the pharmacopoeial requirements. These requirements allow for acceptable levels of change that may occur during storage and distribution and reject articles showing unacceptable levels of change. Frequently a manufacturer will need to apply more stringent test limits at the time of release of a batch of the product or material in order to ensure compliance. (BP 2003, Supplementary Chapter 1)

Thus the difference between release and expiry specifications must take into account the results of stability testing. The release specification is that which the product must comply prior to the release of the product for sale. The expiry specification is that which the product must comply up to the expiry date of the batch. Release limits are commonly tighter than those at expiry, to allow for changes in the product with time.

The maximum permitted shelf life is normally five years.

2. Stability trial design

2.1 Active pharmaceutical ingredient

An assessment of the stability of the API is required for new medicines not previously registered in Australia. Where changes are made to the manufacture of an API, stability studies should be carried out in line with Good Manufacturing Practice (GMP) requirements. Such data would not generally be required for evaluation, but may be requested in certain circumstances. Such information provides a useful guide to the problems that may be encountered during stability studies on finished products and allows an appropriate re-test period to be assigned for the material

Studies should establish the inherent stability characteristics of the molecule, in particular the degradation pathways, the identity of degradation products formed in significant amounts and the suitability of proposed analytical procedures for quantification of both the API and degradation products. The nature of the studies will depend on the API, but is likely to include the effect of elevated temperature, the effect of acidic or alkaline conditions, susceptibility to moisture and oxidation, and the effect of light. The effect of pH may be important when the finished product is an aqueous solution or suspension, in the latter case by means of effects on the fraction of API actually dissolved, however small.

The kinetics of degradation of the active raw material cannot be assumed to apply to reactions that occur in the finished product, and care should be exercised in extrapolating on the basis of such data.

2.2 Finished product

The formulation must be the same as that proposed for registration in Australia.

Stability data on related formulations may be submitted as **supporting** evidence provided that the differences between the formulation employed in the stability trial and that proposed for registration are clearly stated. A shelf life will not normally be allocated for the purposes of registration if there are no data on the formulation to be registered.

All manufacturing processes must have been carried out on the batches used in the stability trial (for example, filtration, packaging, sterilisation).

The product should be tested in the container closure system in which it will be registered in Australia. If the product is to be registered in more than one container closure system, stability data should normally be provided for each presentation unless a bracketing/matrixing approach can be adequately justified (however, see Section 6.2 below and Appendix 12 (*Changes to the quality information of registered medicines: Notification, Self-Assessment and prior Approval*) for information on changes that may be made to quality aspects of medicines without prior approval). Stability data in other types of pack are of limited value, unless comparative studies of the two types of pack are provided that clearly demonstrate the equivalence or superiority of the container closure system intended for registration over the system used in the stability trials.

For medicines containing new API, stability information should be generated on a minimum of three batches with a stability commitment as described in the CHMP/ICH guidelines on stability testing.

For products containing existing APIs, the selection of batches should follow the requirements of the relevant CHMP guidelines.

Where the product is to be registered in several strengths or pack sizes, bracketing or matrixing may be applied, as described in the relevant CHMP guidelines. It is recommended that, wherever possible, the batches of finished product used in stability trials be manufactured using more than one batch of API.

Conditions of storage likely to be encountered in Australia should be considered in designing the stability trial, since Australia has climatic conditions encompassing ICH Zones II-IV. If a storage temperature of 30˚C is intended for the product labels, then the full-term studies should be conducted at 30°C/65%RH. Storage conditions should be clearly defined. Lighting conditions should be specified – see CHMP guideline *Photostability Testing of New Active Substances and Medicinal Products*[3].

The use of uncontrolled temperature conditions in stability trials is unacceptable. Terms such as *room temperature* and *normal warehouse conditions* allow the product to be exposed to a wide range of conditions and make shelf life assessment difficult. Where a shelf life is based upon uncontrolled storage conditions, it will usually be shorter than the duration of the submitted study. If storage in a refrigerator is proposed without the caution *Do not freeze*, then stability, particularly physical stability (for example, no formation of a precipitate, no denaturation of a protein) must be demonstrated under frozen conditions. In general studies at -20°C as described in CHMP guidelines should be provided in this case.

Stability studies at elevated temperatures are useful in predicting longer-term shelf life periods from short term data (see Section 5 below). However, these predictions should be verified by studies on production batches in the pack intended for registration at the maximum recommended storage temperature for the full term proposed. For example, if the proposed storage temperature statement is *Store below 30 ℃*, long term studies should be carried out at 30°C/65%RH.

The cycling effect of night and day temperatures and humidity can be important, for example, for creams, suspensions and inhaler products where the API may be present partly in suspension and partly in solution. Cycling conditions may be simulated in environmental cabinets. The data are useful in confirming the stability of the product under conditions of stress. However it is difficult to derive accurate predictions for the shelf life of a product from this information and it is not a formal requirement

Where the product is to be registered in a moisture permeable material such as polyvinyl chloride (PVC) or lower density grades of polyethylene, or where the closure system allows moisture transfer, the stability of the product should be determined under conditions of high humidity at the recommended temperature (see Section 3.7 below).

[3] http://www.tga.gov.au/industry/pm-euguidelines-quality.htm

Loss of moisture by transpiration can be important for some products, such as injections in plastic packs and water-based creams in PVC tubes. The extent of loss can be assessed by accurate weighing of marked individual packs over time. If severe it may also be apparent as an increase in API concentration in the product.

The possibility of leaching of substances from containers into the product should be considered for the following types of product:

- any product where this could occur and may be a hazard. This includes any parenterals, ophthalmics and inhalation products. Particular attention should be paid to:
- containers manufactured from semipermeable materials and the possibility of extractables leaching from outside the primary container, in particular the ink, solvents or adhesives of the secondary packaging;
- the additives in plastics and elastomers and their possible degradation products that may form during manufacturing steps, especially during filling and sterilisation steps and storage;
- injectables and ophthalmics supplied in non-glass containers or with plastic or rubber stoppers;
- plastic components of metered dose aerosols (see Appendix 19: *Metered Dose Aerosols (Pressurised and Non-Pressurised)*).

The possibility of the absorption of radiopharmaceutical radioactivity on the glass or closure of the vial should be considered. This may occur in the case of some types of high specific activity radiopharmaceuticals.

In-use stability data should be generated where relevant, for example:

- where the product must be reconstituted or diluted prior to use;
- where the product is claimed to be stable when mixed with other products;
- where the product may be labile once the container is opened.

The stability of the in-use form of the product should be established for the period of time and under the conditions for which storage is recommended.

Published papers may be submitted as evidence of in-use stability provided they can be shown to be relevant to the formulation proposed for registration, and they include sufficient detail to allow independent evaluation.

Where it is claimed (on the label or in the Product Information, PI) that the product may be diluted with a range of solutions, the most common example being parenteral medicines diluted in large volume intravenous infusions, stability data should establish compatibility with each recommended diluent at the extremes of the recommended dilution ratios for the permitted duration of storage.

Tests on reconstituted and/or diluted solutions should normally include pH, clarity/particulate matter, assay and, if assay sensitivity allows, degradation products. Sponsors should note however, that, regardless of chemical stability (unless this requires a shorter time), the PI for injections intended to be reconstituted or diluted should include the direction:

> *To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours* (or words to that effect).

Where storage at 2-8°C is not possible because of adverse effects on the product, the maximum time for storage at room temperature (not more than 6 hours) should be specified and justified. If there are valid reasons why the reconstituted and/or diluted product may be kept for longer than

24 hours at 2-8°C (or 6 hours at >8°C), appropriate data should be generated and included in the application.

Where the product sponsor recommends that the product be used with a delivery device such as an infusion pump, then compatibility should be demonstrated. This may include data on whether substances are extracted from the device into the product and, if so, whether they are toxic.

Where a precipitate may form during normal storage (for example, in an intravenous injection where the API may precipitate because of borderline solubility) directions for redissolving must be included in the PI and should be supported by appropriate stability data.

Studies of container closure interaction with the product should be considered where this is a risk. For example, liquids in containers other than ampoules should be stored inverted to determine whether contact with the closure affects stability.

3. Appropriate tests

3.1 General

The CHMP guidelines on specifications, test procedures and acceptance criteria provide guidance in the selection of appropriate tests and limits for stability studies.

All test methods used in stability studies should be appropriately validated. The CHMP/ICH guidelines on analytical method validation should be consulted for typical method validation requirements.

It is very important that test method details are provided. Where test methods are identical to those in the routine quality control specifications, this should be explicitly stated and not left to the evaluator to assume. Alternative test methods may be used in stability studies, but they should be fully described and appropriately validated.

Dissolution procedures other than those in finished product specifications are discouraged (except to add extra test points for the generation of dissolution profiles).

As it may be difficult to compare results before and after a change, test methods should not be changed during stability studies. If a change to a test method is required, it should be justified and the amended method should be fully described and validated. Both procedures should be conducted at several stations to allow the results to be compared, unless another approach can be justified.

Changes to dissolution test methodology during stability studies are strongly discouraged.

3.2 Assay

Quantitative results for assay should be provided so that any trends over time can be observed. Qualitative results such as *Complies* are unacceptable.

Where multiple assay results are provided at one time-point, it should be clear what these represent (for example, repeat injections of analytical solution or replicate sampling from a defined number of dosage units).

As well as assay of the API, it may be necessary to assay other components, for example, preservatives or antioxidants.

It should be noted that loss of the API may be due to factors other than degradation, such as complexing with excipients, adsorption onto or absorption into the container wall, volatilisation, etc.

3.3 Degradation products

Trends in the formation of degradation products, as well as assay, will be considered in the evaluation of the stability data and in assigning of a shelf life to a product. Therefore the levels of degradation products should be quantified as far as possible.

Results should be given for total and all individual degradants detected, even where the identity of the degradant is unknown. Where appropriate, relative retention times should be given for unidentified degradation products to aid correlation and interpretation of data.

If reference standards for degradants are unavailable, response factors should be taken into account in the calculation of results. If response factors cannot be determined, the method used to calculate the level of the degradant should be justified.

Synthetic impurities that are not also degradants need not be reported, provided they are adequately controlled in the API specification. Retention times of synthetic impurities should be determined to ensure that they do not interfere with measurement of the degradation products.

Chromatographic techniques are preferred for the separation and detection of degradation products, but validated alternative methods of quantification may be acceptable.

Degradation products should be reported, identified and/or qualified if they are present at levels above those described in the CHMP/ICH guidelines on impurities in new active substances and medicines or Appendix 18 (*Impurities in active pharmaceutical ingredients and finished products*).

3.4 Physical properties

In addition to content of active ingredient(s) and degradation products, it is also necessary to monitor the physical properties of the product during storage. The physical tests will vary with the formulation in question but important attributes of various dosage forms may include the following:

***Tablets and capsules*:** Dissolution rate (or dissolution profiles for sustained-release products), appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules).

***Liquid formulations and injections*:** Appearance, colour, odour, pH, clarity (solutions) and freedom from visible particulate contamination, sub-visible particulate contamination (large volume parenterals), particle size distribution (suspensions), micelle size distribution (micellar solutions), resuspendibility (suspensions), viscosity, moisture content (powders for reconstitution), phase separation (emulsions).

***Ointments and creams*:** Appearance, odour, viscosity, softening range, loss of water, physical and chemical homogeneity, particle size distribution, particle formation, pH.

***Freeze-dried material (including materials for reconstitution)*:** Appearance of both freeze-dried and reconstituted material, pH, water content, reconstitution time.

***Aerosols*:** See *Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products* (CPMP/QWP/2845/00)[4].

***Suppositories and pessaries*:** Appearance, softening temperature (moulded products), dissolution rate (compressed products).

[4] http://www.tga.gov.au/industry/pm-euguidelines-quality.htm

***Transdermal patches*:** Appearance, *in vitro* release rate, adhesive strength.

3.5 Preservative efficacy

Because chemical assays do not necessarily indicate antimicrobial efficacy, if a product, such as eye drops or a multidose oral solution, contains an antimicrobial preservative, it will usually be necessary to conduct a microbial challenge test at the end of the shelf life in addition to chemical assay of the preservative during the study, as described in the CHMP/ICH guidelines on stability of new and existing products.

Appropriate studies would include preservative efficacy testing using repeated microbial challenges, and preservative efficacy testing after simulated in-use or microbial limit testing of containers that have been used by patients.

The chemical stability of the preservative over the open shelf life should also be demonstrated.

Further information is contained in Appendix 16 (*Preservative efficacy testing*).

3.6 Dissolution rate

The behaviour of dissolution rate over time should be examined for all solid oral dosage forms and other compressed products (suppositories, implants etc.). Dissolution data should be generated on at least six individual units at each test station and should be reported as both mean data and either individual data or ranges. Test conditions should be those used in routine quality control or, if dissolution is not a part of routine quality control, any reasonable, validated method.

It is normally necessary to generate dissolution profiles (percent of nominal content dissolved at a number of time points at appropriate intervals to almost complete dissolution) for certain products, for example:

- modified release products;
- certain immediate release products, for example carbamazepine tables where it has been shown that tablets that release the API rapidly lead to a higher incidence of adverse effects;
- in cases where there is uncertainty about the validity of the dissolution test method;
- in cases where single-point data suggest there may be a problem with the dissolution rate of the product (especially with aging).

3.7 High humidity studies

Temperature and relative humidity data available from the Australian Bureau of Meteorology have established that a number of major centres in Australia experience a combination of high humidity and high temperature during the summer months. These centres can therefore be classed as Zone IV regions as defined in CHMP/ICH guidelines.

The use of moisture-permeable containers for the packaging of pharmaceuticals raises questions concerning the stability of the contents when stored under conditions of high humidity. High relative humidity can affect chemical stability (for example, some antibiotics are readily hydrolysed) and physical stability (for example, altered dissolution rate).

Data should be generated to establish the effect of high humidity on solid dosage forms packaged in containers that are likely to be permeable to moisture. Examples of containers that would generally be considered moisture-permeable include:

- polyvinyl chloride blisters

- low density polyethylene bottles
- glass or high density polyethylene bottles when fitted with polypropylene closures.

Containers that are generally considered to be moisture-impermeable include:

- glass ampoules
- Al/Al blisters
- HDPE or glass bottles fitted with HDPE or metal closures

As described in the CHMP/ICH stability guideline, stability data for products stored in impermeable containers may be conducted under any humidity condition.

If a sponsor believes that high humidity data are not needed for a product that is packed in a particular material, this view should be supported by, for example, information on the composition, thickness, density and moisture transmissibility of the packaging materials.

The CHMP/ICH guidelines on stability data require 6 months data at 40C/75%RH to be provided in applications to register products to be stored at room temperature. These data, if satisfactory, would also generally be sufficient to establish the adequacy of the packaging to protect the product from moisture. However, some products may be adversely affected by the high temperature used in such studies. As described in the CHMP/ICH stability guidelines, if significant changes are observed at 40C/75%RH, stability studies should be undertaken at 30C/65%RH. In particular cases other conditions, such as 25C/80%RH, may be more appropriate. The decision to use such conditions should be justified in the application.

These short term high humidity data provide support for stability data accumulated at the maximum recommended storage temperature at lower relative humidity, but do not remove the need for studies for the duration of the shelf life.

3.8 Low humidity studies

Aqueous solutions supplied in permeable plastic containers may lose water by evaporation on storage. Stability studies in line with those described in the relevant CHMP/ICH guidelines should be carried out for products in this category.

4. Presentation of results

Results obtained at the commencement of the trial and at nominated time intervals throughout the trial should be provided. This will allow any trends to be detected and will enhance the predictive value of the trial. Data that do not include initial results (that is at the start of the trial) are of limited value.

If more than one assay result is available for any particular time interval, all results should be quoted rather than, or in addition to, an average figure. Where bioassays are employed to study antibiotics, the accompanying fiducial limits of error (p = 0.95) of each assay should be provided.

Assay results obtained during the study should be recorded either as absolute values (for example, as a particular number of milligrams of API per capsule) or as a percentage of the nominal (labelled) content.

Care should be taken that individual dose unit variations, such as between individual tablets or between individual vials of a freeze-dried powder, are allowed for in stability studies. For freeze-

dried vials, this may be achieved by assaying the content of active per unit weight of powder. For tablets and capsules, an average content may be obtained by conducting the assay on pooled samples (normally 20 tablets or capsules), or by averaging individual dose unit results.

Wherever possible, quantitative results should be quoted rather than a statement that the product complies with a particular specification.

All results obtained should be discussed and explanations given where necessary, for example for anomalous or unusual results, change in assay method, change in appearance, and whether mass balance has been achieved with respect to assay and degradation products.

5. Prediction of shelf life from stability data

One of the more difficult steps in a stability trial is to assign appropriate storage conditions and a shelf life from the accumulated data. The difficulty is reduced and the reliability of extrapolation is enhanced if the data include frequent intermediate stations, are derived from several batches, consider a range of conditions, are of high precision, include analysis for breakdown products, and consider the physical properties of the formulation.

The accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict a probable shelf life for a product stored at a defined temperature from stability data obtained at an elevated temperature. This *accelerated* stability testing is useful in providing information from which to assess the probable stability of a new product but it should be conducted in conjunction with long term stability studies at the maximum recommended storage temperature for the duration of the nominated shelf life.

In theory, the stability of the API is directly related to the kinetics of the various degradation reactions. However the relevant physico-chemical equations are strictly applicable only when a single reaction occurs by a single mechanism. Because medicines are usually mixtures of substances and may be in the solid state (for example, powders and tablets), these theoretical models do not necessarily hold and cannot be relied upon as predictive tools. The issue of physical stability (for example, dissolution rate and particle formation) adds a further complication. There is therefore no substitute for the shelf life being determined empirically, ultimately over the full shelf life.

Where appropriate, shelf lives may be predicted for quantitative attributes (for example, assay and degradation products) by calculation of the time at which the one-sided 95% confidence interval intersects the acceptance criterion as described in the CHMP/ICH guidelines on stability studies. This type of analysis should take into account the worst-case situation at batch release. For example, if the lower assay release limit is 95% and the lower assay expiry limit is 90%, a maximum decrease in assay of 5% should be allowed over the shelf life.

For example, if the actual release assay result for the stability batch is 101% (determined from the intercept of the regression line), then the shelf life should be determined by the time the confidence interval reaches 96%, rather than the expiry limit (90%). This takes into account the possibility of batches being released right on the lower release limit and ensures they will comply with the expiry limit throughout the shelf life.

The maximum extrapolated shelf life permitted by the TGA is normally 3 years. Shelf lives longer than 3 years should be supported by data on production batches stored under the appropriate storage conditions for the duration of the proposed shelf life.

6. Product modifications

Manufacturers may not implement changes to quality data for registered medicines without prior approval from the TGA, except in accordance with Appendix 12 (*Changes to the quality information of registered medicines: Notification, Self-Assessment and prior Approval*), and then only in accordance with the specified conditions. Applications to make other changes should provide details of the proposed change and relevant quality data. Whether or not stability data are required will be a matter of judgement in each case.

Examples of changes that would normally require supporting stability data include:

- significant change in composition of a product;
- change of tablet container from less permeable container such as a glass or HDPE bottle to a more permeable container such as a PVC blister pack;
- increase in the radioactive concentration at which a radiopharmaceutical is provided.

Examples of changes that would not normally require justification in terms of additional stability data provided that adequate stability data are available for the existing product (note however that data other than stability data may be required) include:

- tightening of existing specifications for the finished product consistent with existing stability data, for example narrowing of assay limits for a product;
- change of site of manufacture of the active raw material or finished product with no other change to quality data;
- an additional pack size for tablets stored in a blister pack with no change of packaging materials.

The following general comments may assist sponsors in the accumulation of stability data in particular circumstances.

6.1 Change in formulation

A proposal to change to a completely new formulation would be regarded as an application to register a new product and would require the accumulation of stability data in accordance with the general provisions of these guidelines. A proposal for a minor change such as the removal of a small amount of a dye may not require submission of additional stability data at the time of submission of the application (however, other data may be required). Between these two extreme situations, the amount of data required will depend upon the nature and extent of the proposed change to the formulation.

The new and old formulations should be listed side-by-side to facilitate assessment of the data.

6.2 Change in packaging

The major consideration in evaluating a proposal for a change in packaging is the relative protection afforded to the product by the new and old packs. If the new pack is known to be more protective, for example, an amber screw-capped glass bottle compared with a clear PVC bottle, it is

likely that no data would be required at the time of submission. However, a commitment should be given to place three production batches in the new packaging on stability trial at the recommended storage temperature to verify the shelf life. Where the pack is less protective or where some interaction with the container is possible, additional stability data will be required.

For solutions in new packaging, information on leaching is important. Appendix XIX of the BP (*Containers*) and General Tests and Assays <661> (*Containers*) of the United States Pharmacopeia (USP) provide an outline of some of the factors to be considered and appropriate test methods (equivalent test methods are acceptable).

Where the new pack has a greater permeability to moisture, the effects of high humidity on solid dosage forms or the extent of possible fluid loss from liquid preparations at low relative humidities should be considered.

6.3 Change in site of manufacture

Generally, no stability data are required at the time of submission. Refer to Appendix 12 (*Changes to the quality information of registered medicines: Notification, Self-Assessment and prior Approval*) for information on data requirements for changes that may be made to quality aspects of medicines with or without prior approval.

6.4 Older products

For many older products, shelf lives would have been based on the results of stability testing conducted under non-ICH conditions. However, subsequent testing under the current ICH conditions may reveal stability problems such that the approved shelf life or storage conditions may no longer be appropriate.

In such an event, the sponsor should contact the Pharmaceutical Chemistry Evaluation Section promptly to discuss appropriate action.

7. Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data that would normally be necessary. The prerequisites are as follows:

- the existing shelf life should be at least 2 years;
- stability data should be available to the TGA that validate the existing shelf life and show no significant deterioration of the product during this period;
- a recent (less than 2 months old) certificate of analysis showing compliance with specifications should be supplied for the batch near its expiry date, together with the results obtained at batch release;

- if relevant, the company should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life.

Prospective extensions of more than 6 months or to a shelf life of more than 5 years are not normally acceptable.

8. Self-assessable shelf life extensions according to an approved protocol

Shelf lives may be extended through the *self-assessable changes* procedure in accordance with a stability test protocol that was approved explicitly for this purpose. Such protocol may be submitted with the application for registration or subsequent to registration. All of the following conditions must apply:

- at least 12 months data are available or a 12 month shelf life has already been approved;
- the TGA has explicitly approved the protocol for the purpose of self-assessable shelf life extensions;
- all quality aspects of the product, including its immediate container and closure and labelled storage conditions, are identical to those approved at the time the stability test protocol was approved, except for any subsequent changes that were approved by the TGA;
- at least 3 production batches of the product have been tested in accordance with the approved stability test protocol;
- the total shelf life is not longer than the time for which stability data meeting the approved protocol are available on 3 production batches, and in any case is not longer than 5 years;
- any change in shelf life is notified and the date of implementation advised (standard condition of registration number 2);
- if the TGA requests copies of the additional stability data, these will be supplied within one month of the request.

Any stability test protocol proposed for this purpose should include:

- the number of batches to be tested;
- a statement of the proposed tests and test methods;
- a matrix indicating the time stations at which each of the tests will be conducted;
- acceptable limits for results for each test.

Sponsors should note that:

- the TGA may impose conditions on the implementation of an approved test protocol, such as a maximum total shelf life of less than 5 years;

- to provide a suitable safety margin, the acceptable limits for results should normally be somewhat tighter than expiry specifications. If results are outside these tighter limits but within expiry specifications, the sponsor has the option of submitting the data for evaluation with an argument as to why the shelf life should be extended.

Annex 1: Acceptable temperature storage conditions that may appear on labels

(From Therapeutic Goods Order No 69 *General requirements for labels for medicines*[5])

1. Store below -18°C (Deep freeze).
2. Store below - 5°C (Freeze).
3. Store below 8°C (Refrigerate).
4. Store at 2°C to 8°C (Refrigerate. Do not freeze.).
5. Store below 25°C.
6. Store below 30°C.

Note: In Australia, condition 5 represents air conditioned premises while condition 6 represents normal *room temperature* storage conditions.

[5] http://www.comlaw.gov.au/Details/F2009C00264

Annex 2: Common Deficiencies in Stability Data and Trial Design

To assist sponsors in the design and reporting of stability studies, TGA evaluators have compiled a list of deficiencies that are commonly encountered and lead to questions and delays in approval of a shelf life:

1. Failure to specify the formulations used in the trial, and to state which batches are identical to the formulation that will be registered in Australia.
2. Failure to state the size or scale of the batches used in the trial.
3. Failure to describe clearly the packaging used in the trial and to confirm whether it is identical to the pack that will be used in Australia.
4. Failure to accumulate stability data on more than one batch of the product.
5. Failure to define accurately the temperature, lighting and humidity conditions applied during the trial.
6. Failure to fully describe test methods and sample sizes.
7. Failure to provide validation of analytical methods.
8. Expression of results as *passes test* or similar when a quantitative figure would be available.
9. Failure to include quantitative or semiquantitative determinations of the content of degradation products, or to provide only total content rather than values for individual impurities.
10. Use of an HPLC assay procedure to detect impurities without validation for the purpose. HPLC assay procedures as used for determination of the active ingredient are often unsuitable for separation and detection of impurities as they use too short a run time. Such a procedure would be acceptable if validated for impurity detection. Note, however, that long run times do not in themselves ensure good separation.
11. Failure to comment or conduct additional tests when there is a lack of mass balance between the formation of degradation products and the loss of the active substance. For example, are the assay procedures sufficiently specific? Is the API volatile? Is it adsorbed on to the container wall?
12. Failure to conduct additional tests to investigate the significance of obvious alterations in the characteristics of the product. For example a distinct change in the colour of the product may necessitate additional investigation for degradation products.
13. Failure to include information on the physical characteristics of the product during storage, such as dissolution characteristics, homogeneity, particle size etc.
14. Failure to reconstitute radiopharmaceuticals at the activities and radioactive concentrations that would be used in a clinical situation.
15. Failure to include stability studies under conditions of high humidity for products that are to be registered in moisture-permeable containers, and especially for those which are potentially labile to moisture (for example, many antibiotics).
16. Failure to provide results from intermediate time stations to facilitate assessment of any trends in the parameters measured.
17. Failure to provide results for individual dosage units where these are available (for example, dissolution profiles).
18. Attempting to extrapolate data obtained in the trial beyond reasonable limits.

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