9. Stability of the finished product

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Full details of stability testing conducted on the product together with associated validation must be included in the submission. The design of stability studies should be consistent with the relevant CPMP/ICH guidelines and associated TGA annotations (see 'Section 9.3 Stability study design').

At the time of submission, the data package should include sufficient stability data to justify a shelf life of at least 12 months.

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Stability of the finished product

9.1 General principles

The objective of a stability study is to determine the time during which a pharmaceutical product meets appropriate standards when stored under defined conditions. The product must be shown to remain, or be likely to remain, within its expiry specifications throughout the proposed shelf life when stored under the proposed storage conditions.

The requirement to remain within the expiry specifications applies to all batches, including those which may be released at the low end of the release limits. Therefore, the difference between release and expiry specifications must take into account the results of stability testing.

9.1.1 Formulation

The formulation (and the manufacturing process used to manufacture the formulation) used in the stability studies should be the same as that proposed for registration. Stability data on related formulations may be submitted as supporting evidence provided the differences between the formulation employed in the stability trial, and that proposed for registration are clearly stated and the relevance justified. A shelf-life will not normally be allocated for the purposes of registration if there are no data on the formulation to be registered.

9.1.2 Container

The stability of the finished product should be assessed in the container closure system proposed for registration. 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. Stability data in other types of container are of limited value, unless comparative studies 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.

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9.2 Data requirements

- A critical summary of the stability studies (see further details below).
- Full details and results of stability studies on the 'primary batches' (these studies should be designed in accordance with the relevant ICH guidelines).
- **Note:** 'primary batches' are those described under 'Section 9.4 Minimum data requirements'.
- Test methods and validation data, where required.

9.2.1 Critical summary of the stability studies

Where appropriate summary/s has/have already been provided under Module 2 and/or Module 3.2.P.8.1 in a CTD-formatted dossier, this does not need to be duplicated). The critical summary should include all of the following (for each of the submitted studies):

- A clear statement as to whether all (or some) of the batches tested were identical with the product intended for marketing in terms of formulation, container, method of manufacture and manufacturing equipment (if not, the differences should be justified and full details provided).
- Details of test methods and supporting validation data. If the stability study test methods are identical to those in the routine quality control specification it is sufficient to state this. Any change in test methods while the studies are in progress should be justified and validated.
- A table giving batch numbers, batch types (pilot or production), batch size or scale, storage conditions (temperature, humidity, lighting conditions, and storage upright or inverted for liquids), and storage durations. The controls applied to the storage conditions should be stated. For details of requirements for minimum number of batches, minimum study duration and storage conditions, see 'Section 9.4 Minimum data requirements' and 'Section 9.5 Storage conditions'.
- Brief details and a critical analysis of the results observed for each of the test parameters included in the studies. Separate comments should be provided for each test parameter, including the following:
    - a heading (parameter/test name, limits, and test technique) for example *Content of salicylic acid (HPLC - NMT 0.3%*).
    - an assessment and interpretation of the trends observed in the results of testing (numerical description is preferred). The variability in the

results and any anomalous results should be considered. If the results show excessive variability that prevents the assessment of the trends, this should be stated. It may be appropriate to discuss the results of any investigations into the loss of the active ingredient.

- The basis for selecting the proposed shelf life and storage condition should be discussed.

9.2.2 Critical summary of the stability studies for extension of shelf life

Where a sponsor applies to extend the shelf life of a registered product, the critical summary should address the above points and also state whether stability studies for the product have previously been evaluated by the TGA. If this is the case, the summary should:

- provide details of the date of the approval letter as well as file and reference numbers, if known
- state whether the stability data provided are a continuation of studies previously evaluated by the TGA (i.e. an extension of a study using the same batches, storage conditions and test methods).

9.3 Stability study design

The design of stability studies should be consistent with the following EMEA/CPMP/ICH documents (and any subsequent editions adopted by the TGA), taking into consideration the relevant TGA annotations and the following guidance, where appropriate. These documents and accompanying TGA annotation(s) can be found on the TGA website as updated from time to time:

- Stability Testing Guidelines: Stability Testing of New Drug substances and Products (Revision 2) [CPMP/ICH/2736/99 Revision 2 (Q1A)]
- Guideline on Stability Testing: Stability Testing of Existing Active substances and Related Finished Products (CPMP/QWP/122/02 Rev 1)
- Note for Guidance on Evaluation of Stability Data (CPMP/ICH/420/02)
- TGA annotated Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV- (CPMP/ICH/421/02)
- Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Medicinal Products (CPMP/ICH/4104/00)
- Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)

- Photostability Testing of New Drug substances and Medicinal Products (pp. 157-166 of Rules 1998 (3A) - 3AQ18a)

The stability data will be evaluated in accordance with all relevant CPMP/CHMP/ICH guidelines, therefore sponsors should also consult any other TGA adopted CPMP/CHMP/ICH guidelines which are of relevance to the sponsor's product.

The following sections are intended to assist applicants in applying the CHMP/ICH guidelines and in understanding how these guidelines are interpreted.

Transition period

There will be no requirement to justify submission of stability studies that were designed to meet the requirements of the previous ARGOM and were commenced prior to or within 12 months of the implementation of the current ARGOM. After this period a justification will be required. The sponsor should clearly state whether the stability studies were designed in accordance with the requirements.

9.4 Minimum data requirements

The Guideline on Stability Testing: Stability Testing of Existing Drug Substances and Related Finished Products (CPMP/QWP/122/02 Rev 1) distinguishes between two different types of product for which different minimum requirements are imposed for the dataset submitted with the application. These requirements can be briefly summarised as follows (sponsors must consult the guidelines for full details):

- **'Option a':** For conventional dosage forms such as immediate release solid dosage forms and solutions, when the active ingredient(s) are known to be stable, it is acceptable to provide a minimum of six months of long term, intermediate (if applicable) and accelerated stability data on a minimum of two batches of at least pilot scale.
- **Note:** Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (Revision 2) [CPMP/ICH/2736/99 (Q1A)] defines a pilot scale batch as one 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 least one tenth of a full production scale batch or 100,000 tablets or capsules, whichever is the larger.
- **'Option b':** For products which are likely to be unstable, or for which stability failure would be critical, data for three batches are required in the submission.

> Two of the three batches should be of at least pilot scale (the third batch may be smaller). The data must include at least 12 months of long term results, in addition to six months of accelerated data (and six months of intermediate data, if applicable).

Stability studies should be conducted on each individual strength and container size of the finished product unless bracketing or matrixing is applied [see Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Medicinal Products (CPMP/ICH/4104/00)].

9.4.1 Requirements for additional stability commitment

In cases where stability data have been provided only at pilot scale, or where full term production batch data have been provided for fewer than three production batches, the CPMP guideline states that a commitment should be made to conduct full term stability studies on production batches of the goods, up to a total of three. **However, for OTC medicine registrations, data for two production batches will generally be sufficient.**

In these cases, it will be made a condition of registration that stability trials are conducted on the first post-registration production batches of the goods, up to a total of two (see also 'Section 9.8 Post registration requirements').

9.5 Storage conditions

Selection of storage conditions for the stability studies should be appropriate for the storage conditions that are to be stated on the label of the finished product, and should be consistent with those described in the relevant CPMP/ICH guidelines tabulated in 'Section 9.3 Stability study design' (some departure from the ICH conditions is permissible where the conditions specified in the Australian Labelling Order are inconsistent with the ICH conditions, as detailed in the dot-points below).

Long term studies should be conducted at the maximum temperature stated on the finished product label, unless the guidelines prescribe differently. For example, where the labelled storage condition is 'Store at 2°C to 8°C (Refrigerate. Do not freeze)' the long term storage condition in stability trials should be 5°C±3°C.

The following additional points should be noted:

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- For products labelled 'Store below -18°C (Deep Freeze)', the storage conditions -20°C±5°C detailed in sub-section 2.2.7.5 of the Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 Rev 1) are acceptable.
- For products labelled 'Store below 8°C (Refrigerate)', without the caution Do not freeze, stability must be demonstrated both at 5°±3°C and at -20°±5°C. This is particularly important for products that may have physical stability issues (e.g. segregation, formation of precipitates, or denaturation of proteins).
- Similarly, for products labelled with the condition 'Store below -5°C (Freeze)', which also allows for storage in a deep freezer, stability must be demonstrated at -20°±5°C, as well as under controlled conditions at -5°C (ideally, the temperature control for stability trials at -5°C should be within ±3°C, as for refrigerated storage; but, as this is not a standard ICH temperature for stability studies, this will be evaluated on a case-by-case basis).
- Where products are packaged in potentially moisture permeable materials, studies under high or low humidity may be required, as discussed below.

Australia has climatic conditions encompassing ICH zones I-IV, therefore conditions of storage likely to be encountered in Australia should be considered in designing the stability trial. However, as described in the CHMP/ICH stability guidelines, stability data for products stored in impermeable containers may be conducted under any humidity condition.

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

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

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

In this section: 9.5.1 High humidity studies | 9.5.2 Low humidity studies | 9.5.3 Cycling of temperature and humidity | 9.5.4 In-use data

9.5.1 High humidity studies

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The use of moisture-permeable containers and/or closures 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 and physical stability (e.g. 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:

- Plastic blister packs such as polyvinyl chloride blisters,
- Low density polyethylene bottles,
- Glass or high density polyethylene bottles when fitted with closures made of moisture-permeable polymers.

The Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 Rev 1) require 6 months of data at 40°C/75%RH to be provided in applications to register products that are to be stored at 25°C or 30°C. These data, if satisfactory, would also be generally 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. The TGA annotation to the Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV (CPMP/ICH/421/02)provides useful guidance in this case. Relevant parts of the annotation are reproduced below.

If a product does not show satisfactory stability for at least 3 months at 40°C/75% RH, there are several acceptable options:

- argue that, as the container is designed to provide a barrier to water vapour, further investigation of stability under conditions of high humidity is not necessary
- demonstrate, by testing at least 3 batches, that the product is stable for 3-6 months at 30°C/75% RH
- package the product in a container/closure system that is less permeable to water vapour
- label the product 'Store below 25°C'.

If a product is labelled 'Store below 25°C', the TGA will accept:

- long term stability testing at 25°C/60% RH in place of 30°C/65% RH

- 6 months testing at 25°C/80% RH or 30°C/65% RH (at least 3 batches) in place of 40°C/75% RH. Nevertheless, initial testing of the product should be conducted in accordance with the guideline, that is, at 30°C/65% RH and 40°C/75% RH. If stability is inadequate under these conditions (and, if tested, the alternative condition of 30°C/75% RH) the use of more protective packaging should be considered before the option of labelling the product 'Store below 25°C'.

Generally, if a product shows satisfactory stability for at least 3 months at a high humidity test condition (40°C/75% RH, 30°C/75% RH, 30°C/65% RH or 25°C/80% RH, as appropriate), then the TGA will consider a shelf life of up to 2 years, subject to satisfactory long term stability data. If a product is stable for 6 months under these conditions then a shelf life in excess of 2 years will be considered.

[Any of these four storage conditions would be acceptable for high humidity testing of a product labelled 'Store below 25°C', but only 40°C/75% RH or 30°C/75% RH would be acceptable for a product labelled 'Store below 30°C'.]

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.

9.5.2 Low humidity studies

Aqueous solutions, suspensions and emulsions supplied in permeable plastic containers may lose water by evaporation on storage. Stability studies consistent with those described in section 2.2.7.3 Finished products packaged in semi-permeable containers in the Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 Rev 1) should be carried out for products in this category.

9.5.3 Cycling of temperature and humidity

The cycling effect of night and day temperatures and humidity can be important in certain cases, such as creams, suspensions and inhaler products where the active ingredient may be present partly in suspension and partly in solution. Where relevant, the cycling effect of temperatures and humidity should be considered in the design of stability studies.

Temperature cycling study(s) should be designed to mimic the likely conditions of actual marketplace storage, and should take into account product-specific chemical

and physical degradation properties. The most common period of cycle is 24 hours, reflecting the normal diurnal rhythm.

Such data may be 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 routine requirement.

9.5.4 In-use data

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

- Where chemical and microbiological deterioration occurs once a multidose product container is opened (e.g. for antacids, and sterile preparations such as those intended for ophthalmic use), in-use testing should be performed to justify the proposed storage period and conditions after the container is opened.
- **Note:** For sterile products that are intended for multiple use the preservative efficacy must be demonstrated over the open shelf life period (for eye preparations this is 4 weeks) – see 'Section 9.6.6 Preservative efficacy' further information)
- Where the product must be reconstituted or diluted prior to use (e.g. oral powders for suspension), and is claimed or implied to be stable when stored for a certain period or mixed with other products (e.g. food or beverages), in-use testing should justify the claimed or implied storage period and conditions including diluent.

The Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99) should be consulted for products requiring in-use stability data. 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.

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9.6 Appropriate tests

9.6.1 General

The TGA-adopted CPMP/ICH guidelines Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 Rev 1) and Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99) provide guidance in the selection of appropriate tests and limits for stability studies.

All test methods used in stability studies should be appropriately validated, and test method and validation data should be provided, in line with the requirements set out in 'Section 7.9 Analytical procedures and validation'. If test methods and validation data have been included elsewhere in the dossier they do not need to be duplicated in the Stability section.

Where test methods are identical to those in the finished product specifications, this should be explicitly stated. 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).

Test methods should not be changed during stability studies, as it may be difficult to compare results obtained before and after a change. If a change to a test method is required, the change should be justified 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.

Where a test gives quantitative results these should be provided instead of indicating 'complies' or 'passes'. However, if 'complies' refers to a limit that is tighter than the specification limit (e.g. to a limit of '< 100' in microbial testing where the specification limit is '< 1000') this may be acceptable provided it is unambiguously indicated in the stability reports.

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9.6.2 Assay

For assays it is particularly important that quantitative results are provided, so that any trends over time can be observed. Where multiple assay results are provided at one time-point, it should be clear what these represent (e.g. repeat injections of analytical solution or replicate sampling from a defined number of dosage units).

For tablets and capsules it is vital that an adequate number of individual dose unit results are sampled to minimise the effect of individual dose unit variations. The number sampled (and pooled or averaged) should be consistent with that required under TGO 78 Standard for Tablets and Capsules.

The active ingredient assay method should be stability indicating (refer to 'Section 7.9 Analytical procedures and validation'). Where a loss of the active ingredient is observed in the stability studies, the fate of the active ingredient may require investigation. It should be noted that loss of the active ingredient may be due to factors other than degradation, such as complexing with excipients, adsorption onto or absorption into the container wall and volatilisation.

In addition to assay of the active ingredient, it may be necessary to assay other components, such as preservatives or antioxidants.

9.6.3 Degradation products

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

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

More information regarding control of degradation products is included in 'Section 7.4 Related substances' and 'Section 7.9.1 Stability indicating assays'.

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

9.6.4 Physical properties

It is necessary to monitor the physical properties of the product during storage. The physical tests that are appropriate to include in the stability study will vary with the formulation in question. Some important physical attributes of the major dosage forms are outlined in the following table.

Table 9.1 Physical attributes of the major dosage forms.

Dosage form	Physical tests
Tablets and capsules	Dissolution, disintegration (if dissolution is not required), appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules)
Liquid formulations	Appearance, colour, odour, pH, clarity (solutions) and particle size distributions (suspensions), 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, phase separation (emulsions)
Aerosols	Leak test, particulate contamination, valve function and appearance, weight loss. For metered dose aerosols refer to the BP monograph Preparations for Inhalation - external site and also to the specific product monographs. Metered dose aerosols and some pump actuated aerosols will also require measurements of active ingredient mass aerodynamic particle size distribution on ageing
Suppositories and pessaries	Appearance, softening temperature (moulded products), dissolution rate (compressed products), disintegration testing
Freeze-dried material (including materials for reconstitution)	Appearance of both freeze dried and reconstituted material, pH, water content, rate of solution
Medicated soap bars	Appearance, odour, weight loss and pH

Loss of moisture by transpiration can be important for some products, such as water based creams in moisture permeable containers. 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 the concentration of the active ingredient or other components in the product.

For other dosage forms not included in the above table, the sponsor should define the appropriate tests.

9.6.5 Microbial content testing

As defined in TGO 77 Microbiological standards for medicines sterile OTC dosage forms must comply with the Test for sterility of a default standard. TGO 77 also includes bacterial endotoxin test requirements, but these are not relevant to OTC products.

For non-sterile dosage forms, microbial content testing should be carried out at the end (and preferably at the beginning) of shelf life during stability studies to demonstrate that the product remains within product specifications until expiry; unless the absence of limits for microbial content in the expiry specifications have been justified (see 'Section 10.2 Non-sterile medicines').

9.6.6 Preservative efficacy

Products that are intended for multi-dose use should be adequately preserved for the duration of the claimed shelf life. This applies to both non-sterile products (e.g. aqueous creams, lotions, and oral liquids) and sterile products (e.g. eye preparations). It is necessary to prevent microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use.

During product development, preservative efficacy testing should be performed at the beginning and end of the claimed shelf life to demonstrate that the antimicrobial activity of the product as such or, if necessary, with the addition of a preservative(s), has not been impaired by storage. Data must be specific to the formulation and the container. If the requested shelf life is based on data generated under accelerated conditions, preservative efficacy tests should be performed on samples that have been stored at the higher temperature.

The TGO 77 Microbiological standards for medicines specify the minimum microbiological requirements with which a medicine must comply throughout its shelf life. In relation to preservative efficacy Clause 8 of TGO 77:

1. requires a multidose medicine, other than a liquid oral antacid medicine, to comply with the requirements of Appendix XVI.C of the

British Pharmacopoeia or Chapter 5.1.3 of the European Pharmacopoeia.

2. permits a multidose liquid oral antacid medicine to comply with the requirements of Chapter <51> of the United States Pharmacopoeia-National Formulary.

Chemical assays of the level of preservative are not accepted as substitutes for biological tests.

Note: Chemical tests and limits for content of preservatives are acceptable for routine quality control, provided the limits have been justified on the basis of preservative efficacy studies over the shelf life. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually also include requirements for pH which will ensure preservative efficacy (the limits should have been justified on the basis of preservative efficacy studies over the shelf life).

For sterile products (e.g. eye preparations), that are intended for multiple use, the preservative efficacy of the product over the open shelf-life period (e.g. 4 weeks for eye preparations) must also be demonstrated. Such testing should involve repeated microbial challenges over the open shelf-life period as this most closely mimics the in-use situation. Alternatively, microbial content testing may be carried out on partially used containers that have been used by patients for the full open shelf life.

Modifications of a pharmacopoeial preservative efficacy test (preferably the Ph. Eur. /BP test) that include a rechallenge with reduced numbers of organisms could be used. Guidance may also be obtained from the normative part of the international standard ISO 14730 Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard dating which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days.

Note: This reference is not being supplied as a standard that must be applied to a product. It is supplied solely to demonstrate the elements of the type of tests that would be required to support an open shelf life period.

9.6.7 Dissolution

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Test conditions should be those applied in the finished product specification (refer to 'Section 7.5 Tablets and capsules'). If different test conditions and/or limits are used, this should be justified, and validation data should be provided.

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.

For certain products, dissolution profiles should be generated showing the percent of nominal content dissolved at a number of time points (at appropriate time intervals). Products for which it is relevant to generate dissolution profiles include:

- modified release products
- certain immediate release products where it has been shown that rapid release of the active ingredient leads 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).

9.6.8 Extractables

The possibility of leaching of substances from container-closure systems into the product should be considered in the design of stability studies and data should be generated for any product where this could occur (e.g. liquid preparations in containers that have component/s made of plastic or rubber materials that are not covered by relevant default standard monographs), and particularly where this may be a hazard, for example:

- ophthalmics supplied in non-glass containers or with plastic or rubber stoppers
- plastic components of liquid products intended for inhalation.

9.7 Prediction of shelf life from stability data

Prediction of shelf life is facilitated if the data include frequent intermediate stations (in line with the CPMP/ICH recommendations), 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 Note for guidance on Evaluation of Stability Data (CPMP/ICH/420/02) provides detailed guidance on evaluation of the data from formal stability studies.

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The guideline presumes that the required amount of 'minimum data' are available, as outlined under 'Section 9.4 Minimum data requirements'.

For products intended for storage in a freezer no extrapolation beyond the period covered by the long term data is permitted (and testing of a single batch at an appropriate elevated temperature should also be conducted to address the effect of short term excursions outside the proposed label storage condition, such as during shipping or handling).

For other products, the assessment should begin with any significant change under accelerated conditions and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long term data. Based on the outcome of this assessment, the guideline describes rules for the amount of extrapolation that can be permitted beyond the period covered by the long term data and Appendix A of the guideline provides a decision tree. In the case of products labelled 'Store below 25°C' or 'store below 30°C' where the accelerated and long-term data show little change or variability, the maximum extrapolation of shelf life is up to twice, but should not be more than 12 months beyond the period covered by long-term data [as per Note for Guidance on Evaluation of Stability Data (CPMP/ICH/420/02) section 2.4.1.1 and Appendix A of Note for Guidance on Evaluation of Stability Data]. In the case of products labelled 'store below 8°C' the maximum extrapolation of shelf life is up to one and a half times but should not be more than 6 months beyond the period covered by long-term data.

The maximum permitted total shelf life is normally five years.

9.8 Post-registration stability requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to details contained in the Code of GMP - Chapter 6 Quality control, or for additional advice contact the TGA).

Where a shelf life has been allocated on the basis of anything less than full-term data on two production batches, it will be made a specific condition of registration of the product that a stability testing program be initiated on the first production batches of the goods (to a total of two), and that any adverse results be immediately reported to the TGA.

Data may be requested for review at any time or followed up by the TGA's auditors during GMP audits of the manufacturer. If it is found that the required testing has

not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken which may include cancellation of the product's registration.

9.9 Product modifications that require stability data

Applications to make certain changes to a product may require supporting stability data. For example:

- Change in composition of a product
- Change of container
- Extension of shelf life.

9.10 Requirements for a proposed stability testing protocol for self assessable shelf life extension

A product's shelf life may be extended on the basis of stability testing conducted according to a protocol that was specifically approved by the TGA for this purpose. For a stability protocol to be considered for the purpose of self assessable shelf life extensions, it is necessary for at least 12 months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing, or one which is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a stand alone document which includes:

- a statement of the intended purpose (e.g. '*This protocol is intended for notification of shelf life increases of up to x years following self assessment of stability data*').
- a statement of the criteria for notifying a shelf life increase (e.g. 'full term stability data will be generated using two production batches stored at y°C, all analytical results obtained will comply with the protocol acceptance criteria'):
    - the precise formulation of the product (if overages are included, this should be stated).
    - the immediate container specifications.

- the storage conditions to be included on the label.
- the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test).
- a statement of the proposed tests and validated test methods (validation data should be included, unless referenced to elsewhere in the application).
- a matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study.

9.10.1 Shelf life extensions according to an approved protocol

The sponsor may submit an application to the TGA for shelf life extension without submitting additional data for assessment, if a protocol for self assessable shelf life extensions has been approved by the TGA for a particular product, and provided that:

- all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol.
- no other changes to quality related aspects of the product have been made, or are currently proposed to be made.
- a copy of the approval letter for the stability testing protocol is attached to the notification.
- at least two full production batches of the approved formulated product packed in the approved container have been used in the studies.
- the shelf life is not longer than the time for which stability data meeting the approved protocol are available.
- the shelf life is not longer than 5 years.

9.11 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. The prerequisites are:

- the existing shelf life should be at least 2 years;
- stability data are available to the TGA which validate the existing shelf life;
- a recent (less than 2 months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release; and

Stability of the finished product

- the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is purely intended as a one off required to ensure continued supply.

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