



**Australian Pesticides &  
Veterinary Medicines Authority**

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**Guidelines for the Generation of Storage Stability Data of  
Veterinary Chemical Products**

**Veterinary Guideline no. 68**

**Version 3 June 2006**

APVMA  
PO Box E240 Kingston ACT AUSTRALIA 2604  
T: +61 2 6272 5158 F: +61 2 6272 4753 E: [EnquiryLine@apvma.gov.au](mailto:EnquiryLine@apvma.gov.au)  
<http://www.apvma.gov.au>

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## 1.0 INTRODUCTION

Veterinary chemical products can undergo physical, chemical and microbial changes on storage. The rate at which these changes occur depends on the nature of the active constituent(s), the formulation type, the packaging and, notably, the storage conditions (temperature, light and humidity). The stability of a veterinary chemical product may be defined as the capability of a particular formulation, in a specific container closure system, to remain within acceptable physical, chemical and microbiological specifications.

### 1.0.1 Objective

The purpose of stability testing is to provide evidence on how the quality of a veterinary chemical product, in its proposed marketing packaging, varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

### 1.0.2 Background

In June 2000 (NRA Gazette No. 6, June 2000), the APVMA adopted the following three Veterinary International Conference on Harmonisation (VICH) guidelines on stability testing for veterinary chemical products:

- Stability testing of new veterinary drug substances and medicinal products [VICH GL3 (Stability 1), adopted as APVMA Chemistry Guideline C3];
- Stability testing for new veterinary dosage forms [VICH GL4 (Stability 2), adopted as APVMA Chemistry Guideline C4]; and
- Stability testing: photostability testing of new veterinary drug substances and medicinal products [VICH GL5 (stability 3), adopted as APVMA Chemistry Guideline C5].

Guidelines C3 and C4 replaced Appendix 2-1 of the Vet Requirements Series, while guideline C5 was adopted as a new guideline.

The VICH guidelines C3 to C5 are primarily concerned with stability testing protocols for *new* veterinary drug substances and associated veterinary dosage forms. It is recognised that many formulations registered by the APVMA contain existing active constituents and related formulations and are not considered to be new drug substances and dosage forms as defined in guidelines C3 to C5. In addition, test requirements for particular dosage forms/packaging etc. are not covered in the VICH guidelines. The APVMA has now developed a comprehensive guideline for the stability testing of veterinary chemical products to replace APVMA Guidelines C3, C4 and C5. This guideline should be read in conjunction with guidelines C3 to C5 and is intended to provide more detailed information and guidance to the design, conduct and reporting of stability studies for veterinary chemical products. Alternate approaches to the principles and practices described in this guideline may be acceptable provided they are supported by adequate scientific justification.

These guidelines cover all veterinary chemical products (including ectoparasiticides) other than immunological products.

This guideline is divided into the following sections:

- Section 1.1 - Design of stability trials. Provides advice on the design of stability trial protocols and the details that should be provided in any report of stability testing.
- Section 1.2 - Recommended parameters to be tested for various dosage forms. Provides a consolidated list of recommended test parameters for different dosage forms.
- Section 1.3 - Additional tests. Provides a list of additional tests required for certain products, e.g., photostability testing for photosensitive products, high humidity testing for moisture sensitive products, in-use stability and sterility data requirements for parenteral and eye products, and cold temperature stability testing for liquid formulations.
- Section 1.4 - Interpretation of stability data. Outlines how the APVMA interprets the resultant stability data when establishing a product shelf life.
- Section 1.5 - Identifies circumstances where stability data may not be required and a default shelf life may apply.
- Section 1.6 - Definitions
- Section 1.7 - References

## **1.1 Design of stability testing trials**

Adequate stability data is required to demonstrate that the product will meet appropriate finished product expiry specifications when stored under specified temperature conditions throughout the proposed shelf life duration. The basic elements of the stability program are: description of the product, shelf life specifications, batch selection, containers, storage conditions, testing schedule, test parameters, test methods with validation data, test results and statistical analysis of the data.

### **1.1.1 Size and number of batches tested**

The overall quality of the product batches of the formulation used in stability testing should be representative of the quality of the formulation to be made on a production scale. Stability data from three (3) batches (preferably pilot and/or production scale) is considered by the APVMA to be the statistical minimum necessary to establish a shelf life for a product. Therefore when stability data from less than the minimum three batches are provided the applicant should include a valid scientific argument justifying the suitability of the data provided for establishing the proposed shelf life. Generally, the APVMA will not consider approving a shelf life greater than 12 months based on stability data generated from laboratory-scale batches alone. Stability data generated from related formulations may be submitted as supportive information. The batch identity, date of manufacture and batch size should be reported with the stability data.

### **1.1.2 Containers**

The product should be packaged in the same containers (materials and size) that are proposed for the marketing of the final product. If the product will be marketed in containers of differing materials, then all proposed containers should be trialled. If the product is to be marketed in containers in which stability testing would be impractical (e.g., too large), then stability trials in smaller containers of the same materials and construction may be used to extrapolate to the larger containers.

### **1.1.3 Bracketing**

Bracketing design may be used if the product strengths are very closely related in composition, such as,

1. a tablet range made with different compression weights of a similar basic granulation, or
2. a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells, or
3. bottles containing 100 tablets and bottles containing 1000 tablets, or
4. bottles containing 100 mL of a product and bottles containing 500 mL of the product.

Bracketing can be applied to different container sizes or different fills in the same container closure system. For example, where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container closure system into the stability program.

An example of bracketing design is given in the table below:

**Table 1-1 Bracketing design**

| Strength       |        | 50 mg |   |   | 75 mg |   |   | 100 mg |   |   |
|----------------|--------|-------|---|---|-------|---|---|--------|---|---|
| Batch          |        | 1     | 2 | 3 | 1     | 2 | 3 | 1      | 2 | 3 |
| Container size | 100 mL | ✓     | ✓ | ✓ |       |   |   | ✓      | ✓ | ✓ |
|                | 250 mL |       |   |   |       |   |   |        |   |   |
|                | 500 mL | ✓     | ✓ | ✓ |       |   |   | ✓      | ✓ | ✓ |

### 1.1.4 Storage conditions

Storage stability programmes should include real time studies or a combination of real time and accelerated conditions. Conditions of storage likely to be encountered in Australia should be considered in designing the stability trial [Australia has climatic conditions encompassing International Conference on Harmonisation (ICH) Climatic Zones II-IV]. Recommended storage conditions from the Code of Practice for Labelling Veterinary Chemical Products are listed below:

- Store below  $-18^{\circ}\text{C}$  (deep freeze);
- Store below  $-5^{\circ}\text{C}$  (freeze);
- Store between  $2^{\circ}\text{C}$  and  $8^{\circ}\text{C}$  (refrigerate. Do not freeze);
- Store below  $8^{\circ}\text{C}$  (refrigerate);
- Store below  $25^{\circ}\text{C}$  (air conditioning);
- Store below  $30^{\circ}\text{C}$  (room temperature).

The temperature at which samples are stored at (e.g., real time and/or accelerated conditions) will impact on how the stability data are interpreted and the length of shelf life that can be recommended. Recommended storage conditions are as follows:

**Table 1-2 Recommended storage conditions (temperatures and relative humidities)**

| Proposed storage temperature (product label)    | Real time testing  | Accelerated testing   |
|---|--|---|
| Products intended for Storage in a freezer      | $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$                        | Accelerated trial probably not appropriate                              |
| Products intended for Storage in a refrigerator | $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$                          | $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 60% RH $\pm 5\%$ RH      |
| $25^{\circ}\text{C}$ (air conditioning)         | $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 60% RH $\pm 5\%$ RH | $35 - 40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 75% RH $\pm 5\%$ RH |
| $30^{\circ}\text{C}$ (room temperature)         | $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 65% RH $\pm 5\%$ RH | $40 - 45^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 75% RH $\pm 5\%$ RH |

RH = Relative Humidity

### 1.1.5 Testing intervals

Samples should be tested as soon as practicable following manufacture, and then every 3 months over the first year, every 6 months over the second year and at 12-month intervals thereafter. The dates of product testing should be recorded and reported with the stability data.

### 1.1.6 Test parameters

The stability study should cover those features susceptible to change during storage and likely to influence the quality, safety and efficacy of the product. Test parameters to be measured in a stability trial are determined by the dosage form/formulation type and may include:

- Physical properties of the product;
- Organoleptic properties (taste, odour, etc.);
- Active ingredient content and formation of toxic degradation products;
- The content of other important components of the formulation (e.g., antimicrobial preservatives);
- Microbial properties (where appropriate); and
- Properties of the container/closure system.

Relevant test parameters for each type of dosage form are given in Section 2. It is expected that all relevant parameters will be addressed in a stability trial. If certain parameters are not addressed relevant scientific argument should be provided as to why testing was not required.

### 1.1.7 Expiry specifications

An expiry specification is the combination of physical, chemical, biological and microbiological test requirements that a veterinary chemical product must meet throughout its shelf life. The range of values that each test parameter must fall within throughout the shelf life of the product should be provided. These are often referred to as “check specifications” or “expiry specifications”.

### 1.1.8 Duration of stability trials

A minimum of 6 months data should be submitted for products with storage period of greater than 6 months. For those with less than 6 months, the amount of data should be determined on a case-by-case basis. The maximum shelf life that will be considered is dependent on the duration that the stability data are collected over. Full details are given in Section 4.

### 1.1.9 Analytical methods

A key factor in a stability study is the use of analytical methods, which will provide meaningful and reliable data.

Analytical methods used for the assay of the active constituent in the product should be stability indicating. A stability-indicating assay is one that accurately measures the active constituent without interference from degradation products, process impurities and excipients.

Full details of the analytical methods used to monitor the product during stability trials must be provided, except where collaboratively tested standard methods (BP, EP, USP etc) for the analysis are used since these are regarded as validated and do not require full revalidation (for further details of the necessary degree of method validation see the APVMA’s *Guidelines for the Validation of Analytical Methods for Active Constituent, Agricultural and Veterinary Chemical Products*). Details of all important operational parameters, such as instrumentation, sample preparation, method of extraction of the active constituent from the product, details of the reference standards and reagents preparation, validation data, copies of representative chromatograms and representative calculations should be provided (see [APVMA Guidelines for the Validation of Analytical Methods](#) for further details).

Analytical methods described in Collaborative International Pesticide Analytical Council (CIPAC) handbooks and Association of Official Analytical Chemists (AOAC) Manual for an agricultural active

constituent and agricultural chemical product (used as ectoparasiticides products for treatment of external parasites in animals), and in British Pharmacopoeia (BP), British Pharmacopoeia (veterinary) [BP (Vet)], European Pharmacopoeia (Ph Eur) and United States Pharmacopoeia (USP) for veterinary actives and veterinary chemical product are legally recognised as the regulatory methods, and these procedures (if one is available) are used by the APVMA for determining compliance with the Agricultural and Veterinary Chemicals Code Act. It is recommended that analytical methods described in official and recognized publications, such as pharmacopoeias [BP, BP (Vet), Ph Eur and USP], CIPAC handbooks and AOAC for a particular formulation be used, where available. Alternative analytical methods may be proposed by the registrants in place of regulatory methods.

The results obtained in the measurement of physical properties are highly dependent on the analytical procedures used. Wherever possible, it is recommended that standard pharmacopoeial methods be used to measure the physical properties of veterinary chemical products. If a standard method is not used then a full description of the procedure is required. Argument as to why the methodology is appropriate may also be required if the procedure deviates significantly from the accepted technique.

### **1.1.10 Validation of analytical methods**

#### **(i) Determination of active constituent content and impurities**

Validation data should be provided to confirm that the analytical procedures used in stability testing give reliable and accurate results. The type of validation data required is dependent on the analytical technique, but typically includes demonstration of linearity over a suitable concentration range, specificity, precision, accuracy and limit of quantitation (see [APVMA Guidelines for the Validation of Analytical Methods](#) for further information).

Analytical methods described in official and recognised publications, such as pharmacopoeias [BP, BP (Vet), Ph Eur and USP] for veterinary actives and veterinary chemical products, and CIPAC handbooks and the AOAC manual for pesticidal products are regarded as validated and do not require revalidation. However, the suitability of these methods should be verified under actual conditions of use, i.e., the specificity and accuracy of the method should be demonstrated for the published method when applied to the relevant sample matrix and laboratory conditions.

#### **(ii) Determination of physical properties**

Validation of methods used to determine physical parameters will not normally be required provided that generally accepted methods {recognised pharmacopoeia [BP, BP (Vet), Ph Eur and USP] or equivalent} are used.

## 1.2 PARAMETERS/CHARACTERISTICS OF THE PRODUCT TO BE TESTED IN STABILITY TRIALS

Veterinary chemical products that are the subject of an individual monograph in a recognized pharmacopoeia [BP, BP (Vet), Ph Eur and USP] are required to comply with the requirements stated in the monograph. The following list of parameters for each dosage form is presented as a guide for the type of tests to be included in a stability study. In general, appearance and assay tests should be performed for all dosage forms.

The list of test parameters presented for each dosage form is not intended to be exhaustive, nor it is expected that every listed test be included in the design of a stability protocol for a particular veterinary chemical product (for example, a test for odour should be performed only when necessary and with consideration for safety of the analyst).

**Table 1-3 Dosage forms**

| <b>Dosage form</b>                                    | <b>Recommended Test Parameters</b>   |
|---|--|
| Aerosols<br>(pressurised pharmaceutical preparations) | Active constituent assay<br>Preservative content (where appropriate)<br>Delivered dose or dose per actuation<br>Particle size distribution (suspensions only)<br>Number of metered doses<br>Loss in weight<br>Valve corrosion  |
| Capsules  | Appearance<br>Capsule integrity (leakage for soft-gelatin capsules, brittleness for hard-gelatin capsules)<br>Uniformity of content/mass<br>Active constituent assay<br>Impurities (where appropriate)<br>Disintegration time<br>Dissolution profile (where appropriate) |
| Collars/ear tags                                      | Appearance<br>Uniformity of content/mass<br>Active constituent assay<br>Dissolution profile (release of active constituent from the inert matrix)  |
| Emulsions   | Appearance (including phase separation)<br>Homogeneity (extent of separation, ease of reconstitution)<br>Active constituent assay<br>Preservative content (where appropriate)<br>pH<br>Viscosity<br>Effect of freezing   |
| Granules  | Appearance<br>Active constituent assay<br>Particle size distribution/dustiness<br>Moisture content<br>Uniformity of content/mass (for single dose preparations only)   |

|  |   |
|--|---|
|  | Dissolution profile (where appropriate)   |
| Implants<br>(sub-cutaneous,<br>intravaginal) | Appearance<br>Active constituent assay<br>Uniformity of content/mass<br>Hardness<br>Friability<br>Moisture content (where appropriate)<br>Dissolution profile (release of the active constituent from the inert matrix)   |
| Injectables                                  | Appearance, colour, clarity<br>Particulate matter (see Point 1)<br>Active constituent assay<br>Impurities (where appropriate)<br>Preservative content (where appropriate)<br>Sterility (where appropriate)<br>Bacterial endotoxins -Pyrogens (see Point 2)<br>pH (aqueous preparations only)<br>Syringeability (where appropriate)<br>Effects of freezing<br>Interactions with the closure (store some container in the inverted position)<br><b>Note:</b> For formulations packaged in multi-dose containers, in-use (broached vial) testing is required unless the in-use shelf life is 24 hours or less. |
| Injections formulated as suspensions         | In addition to the tests for Injectables, test for sedimentation rate and ease of resuspendability  |
| Medicated feed                               | Appearance<br>Active constituent assay<br>Homogeneity (uniformity of distribution of the active constituent)  |
| Oral powders                                 | Appearance<br>Active constituent assay<br>Completeness of solution/ or dispersion<br>Moisture content (where appropriate)   |
| Paste  | Appearance<br>Active constituent assay<br>Homogeneity (uniformity of distribution of the active constituent)<br>Palatability (where appropriate)<br>Viscosity   |
| Powders for injection                        | Appearance<br>Active constituent assay<br>Impurities (where appropriate)<br>pH of reconstituted solution<br>Sterility testing for reconstituted solutions (where appropriate)<br>Completeness of solution/or dispersion<br><b>Note:</b> In-use shelf life of reconstituted product should not exceed 24 hours unless justified by providing stability data to show that the reconstituted product is stable for the length of time stated on the label.   |
| Soluble powders in drinking water            | Appearance<br>Active constituent assay  |

|  |   |
|--|---|
|  | <p>pH of solution</p> <p><b>Note:</b> In-use shelf life of medicated drinking water should not exceed 24 hours unless justified by providing stability data to show that the active constituent is stable for the length of time stated on the label.</p>   |
| Solutions  | <p>Appearance (e.g. cloudiness, precipitation, clarity of solution)</p> <p>pH (aqueous solutions only)</p> <p>Active constituent assay</p> <p>Impurity content (where appropriate)</p> <p>Preservative content (where appropriate)</p> <p>Sterility (where appropriate)</p> <p>Viscosity (where appropriate)</p> <p>Specific gravity (where appropriate)</p> <p>Effects of freezing</p>   |
| Suppositories  | <p>Appearance</p> <p>Active constituent assay</p> <p>Softening range</p> <p>Dissolution</p>   |
| Suspensions  | <p>Appearance</p> <p>pH (aqueous suspensions only)</p> <p>Re-suspending ability</p> <p>Viscosity (where appropriate)</p> <p>Active constituent assay</p> <p>Effects of freezing</p> <p>Particle size distribution (where appropriate)</p>   |
| Tablets  | <p>Appearance</p> <p>Active constituent assay</p> <p>Impurities (where appropriate)</p> <p>Moisture content</p> <p>Tablet hardness</p> <p>Friability (uncoated tablets)</p> <p>Disintegration time</p> <p>Dissolution profile (where appropriate)</p> <p>Uniformity of content/mass</p> <p><b>Note:</b> For chewable tablets, testing for disintegration time and dissolution profile is not required.</p>  |
| Topical, ophthalmic and otic products (e.g., powders, ointments, creams, lotions, gels and pastes) | <p>Appearance, colour, clarity and odour</p> <p>Homogeneity (extent of separation, ease of reconstitution)</p> <p>Product consistency</p> <p>Active constituent assay</p> <p>Preservative content (where appropriate)</p> <p>pH</p> <p>Deliverable mass or volume (eye and ear preparations in single dose containers only)</p> <p>Container leakage (paste syringes)</p> <p>Resuspendability (lotions)</p> <p>Microbial limits/sterility (where appropriate)</p> <p>Effect of freezing (where appropriate)</p> <p><b>Note:</b> (1) For ophthalmic products (creams, solutions, suspension and ointments), testing for sterility is required.</p> <p>(2) For sterile eye and ear preparations packaged in</p> |

|  |  |
|--|--|
|  | multi-dose containers, in-use (broached container) testing is required if the product is not used within four weeks after opening the container. |
|--|--|

**Point 1:** Particulate contamination: sub-visible particles [ref: BP (Vet) – Parenteral preparations]

Veterinary chemical products when supplied in containers with a nominal content of more than 100 mL and when the content is equivalent to a dose of more than 1.4 mL per kilogram of body mass, solutions for infusion or solutions for injections must be tested for particulate contamination: sub-visible particles at the beginning and the end of stability period.

**Point 2:** Bacterial endotoxins or pyrogens [ref: BP (Vet) – Parenteral preparations]

When the volume to be injected in a single dose is 15 mL or more and is equivalent to a dose of 0.2 mL or more per kilogram of body mass, the product must be tested for pyrogens or bacterial endotoxins at the beginning and the end of stability period.

### **1.2.1 Testing requirements for specific veterinary chemical product types**

**(i) Controlled-release dosage forms**

In addition to the specific stability tests that are required for the particular dosage form, the stability study should include the dissolution test to determine the rate of release of the active constituent.

**(ii) Intramammary products**

Intramammary products are solutions, emulsions, suspensions or semi-solid preparations containing one or more active constituents in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, a test for sterility must be performed.

**(iii) Oral drenches**

Drenches for oral administration are available as powders or concentrated solutions or suspensions. They are also available as solutions or suspensions ready for use. Parameters relevant to particular dosage forms should be monitored in the stability study.

**(iv) Veterinary liquid products for cutaneous applications**

Veterinary liquid products for cutaneous applications are liquid preparations intended to be applied to the skin to obtain a local and/or a systemic effect. Veterinary liquid products for cutaneous applications include dip concentrates, pour-on, spot-on, sprays, teat dips, teat sprays and udder-washers. These preparations may be supplied as concentrates or ready-to-use products. They are solutions, emulsions or suspensions containing one or more active constituent in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, stability data on diluted dipping/jetting and teat sprays products are required.

## 1.3 ADDITIONAL TESTS

### 1.3.1 Photostability testing for photosensitive products

Veterinary chemical products that may be prone to degradation on exposure to light must be tested for photostability. One batch of the product should be tested for light stability. Further information about the data required can be found in the VICH guidelines on stability testing: photostability testing of new veterinary drug substances and medicinal products VICH GL5 (stability 3).

**Note:** for the products packaged in opaque packaging, which does not permit entry of light, photostability testing is not required.

### 1.3.2 High humidity studies

Stability data for products that are to be registered in moisture-permeable containers (e.g., containers made from polyvinyl chloride or low density polyethylene), and products that are potentially labile to moisture, must be generated under conditions of high humidity.

### 1.3.3 Parenteral products

#### (i) Storage in inverted position

Parenteral veterinary chemical products (except ampoules) should be stored both upright and inverted position in order to determine whether contact of the product with the closure system affects product integrity.

#### (ii) Multiple dose containers

For parenteral products supplied in multi-dose containers, broached vial stability data are required to justify a shelf life of the product after it has been punctured for the first time. The purpose of such testing is to establish a period of time during which the product may be used following removal of the first dose of product from the container without adversely affecting the integrity of the product.

In order to properly conduct the test for multiple entry, the container stopper should be entered with a needle and withdrawn the maximum number of times as stated on the label. The physical (e.g., colour, clarity, closure integrity, presence of particulate matter), chemical [e.g., active constituent level(s), antimicrobial and chemical preservative efficacy level(s), pH] and microbiological properties (e.g., total viable count) of the product should be monitored. The container contents should also be checked for visual particles as the penetration of the rubber septum with the needle may generate rubber particles. Further information about the data required can be found in the CVMP's Note for Guidance, 'In use Stability Testing of Veterinary Medicinal Products' (The European Agency for the Evaluation of Medicinal Products, EMEA/CVMP 127/95).

#### (iii) Stability of reconstituted products

The in-use stability of parenteral veterinary chemical products that are reconstituted prior to administration, or diluted prior to use, or claimed to be stable when mixed with other products, or where the product may be labile once the container is opened, must be demonstrated,

**Note:** the in-use stability data for reconstituted products and for parenteral products supplied in multi-dose containers is not required if the product label contains a disposal statement to the effect "To avoid

microbial contamination, unused portions of the product must be discarded within 24 hours after reconstitution or first broaching of the container”.

**(iv) In-use stability testing**

The in-use stability test should be designed to simulate the use of the product in practice. The product should be stored as recommended on the product label throughout the duration of the test. A storage condition recommendation for the product after first use may be specified on the label that is different to the unopened container storage conditions.

### **1.3.4 Sterile eye and ear preparations in multiple dose containers**

For sterile eye and ear preparations packaged in multi-dose containers, in-use (broached container) testing is required if the product is not used within four weeks after opening the container.

**Note:** the in-use testing is not required if the product label states that the product be used within 4 weeks of opening the container.

### **1.3.5 Sterility requirements for product stated to be sterile**

Sterility should be considered as part of the shelf life of a veterinary chemical product stated to be sterile. The samples should be tested on the initial date and at the proposed expiration date.

**(i) Injectables**

Sterility testing should be demonstrated for all injectable veterinary chemical products (including intramammary products) except euthanasia products and ear implants for bovine and ovine species.

**(ii) Ophthalmic products**

Sterility should be demonstrated for all ophthalmic products.

**(iii) Ampoules**

Sterility should be demonstrated on sealed ampoules only on the date of manufacture. Since the ampoules are hermetically sealed, this type of seal prevents microbial contamination.

**(iv) Sterile products with microbial inhibitors**

Veterinary chemical products containing preservatives (microbial inhibitors) to control microbial contamination should be tested for preservative contents at reasonable intervals in the stability trial. This may be accomplished by microbial challenge test (e.g., Efficacy of Antimicrobial Preservation of the BP or Antimicrobial Preservative Effectiveness Test of the USP) and by performing chemical assays for the preservatives during the regular stability testing schedules. If a lack of or low levels are found, testing for sterility should be carried out.

### **1.3.6 Cold temperature stability testing**

Liquid formulations [e.g., solutions, suspensions, emulsions, and semi-solid products (*e.g., creams, ointments and pastes*)] may be adversely affected by storage at low temperature. Storage at low temperature may result in crystallisation of the active constituent(s), sedimentation, significant changes in viscosity or phase separation of emulsions.

In some places in Australia, night temperatures regularly approach 0°C or lower. Therefore, the liquid formulations should be subjected to stability testing at 0 ±2°C or lower for 7 days. Physical properties (e.g., precipitation, phase separation) of the product should be monitored to determine the physical stability of the product.

**Note:** stability data generated at lower temperatures is not required if the product label contains a warning against exposure to low temperatures.

### 1.3.7 Dissolution testing

The dissolution test for solid dosage forms is a physical quality control test designed to ensure the consistency of active constituent release from the dosage form and assure consistent batch-to-batch behaviour. Dissolution data should be generated on at least 6 individual units at each test station.

- Apparatus: The dissolution apparatus should be one of those described in the BP, Ph Eur or USP. The use of methods other than the official method should be justified.
- Composition of dissolution medium: The test medium should preferably be aqueous-based; organic or aqueous-organic media should be avoided. For poorly soluble active constituent(s), a minimum content of an appropriate surfactant (e.g., sodium lauryl sulfate) may be added.
- Volume of dissolution fluid: The volume of the dissolution medium used should ensure sink conditions such that the solubility of the active constituent is not a limiting factor in the dissolution process. The sink conditions mean that when all of the active constituent in the test sample is fully dissolved, the concentration will not exceed 20% of the saturation concentration.
- Speed of agitation: The choice of rotation speed should be justified (the standard rotation speed is 50 rpm for the paddle apparatus and 100 rpm for the basket apparatus).

## 1.4 INTERPRETATION OF STABILITY DATA AND RECOMMENDATION OF PRODUCT SHELF LIFE

This section clearly defines the maximum shelf life that can be recommended on the basis of a given stability data set. The information will be of benefit to registrants developing stability testing programs for veterinary chemical products and it will give added transparency and consistency to the assignment of product shelf lives.

Real time studies, or a combination of real time and accelerated studies, should be provided to support the proposed shelf life.

### 1.4.1 Real time stability data

The real time stability data should be generated by storing the product under the proposed (label) storage conditions for the product. The maximum shelf life that will be recommended based on evaluation of real time data is as follows: Where product samples exhibit adequate stability when stored for Y months at temperature X°C, then a shelf life of Y months may be recommended where the normal (label) storage conditions of the product specify storage at or below X°C.

### 1.4.2 Accelerated stability data

Accelerated stability testing studies are designed to increase the rate of chemical degradation or physical change of a veterinary chemical product by using exaggerated storage conditions. In general, accelerated stability trials should be conducted at a storage temperature 10 – 15°C above the proposed storage temperature. The accelerated data should be supported by real time data of the same stability trial duration. Where no significant change occurs at the accelerated condition, the maximum shelf life that will be recommended based on evaluation of real time plus accelerated data is as follows:

**Table 1-4 Shelf life based on accelerated stability data**

| Stability data type     | Duration of stability trial | Maximum shelf life              |
|-------------------------|-----------------------------|---------------------------------|
| Real time + accelerated | Up to 12 months             | Twice the duration of the trial |
| Real time + accelerated | X* months                   | X + 12 months                   |

\* X = Greater than 12 months

Example 1: The proposed storage condition for a product is ‘store below 30°C (room temperature)’. Stability data for 3 batches stored for 12 months at 30°C and 40 - 45°C are provided in the application. The maximum shelf life that the APVMA will recommend for the product on the basis of the submitted data is 24 months when stored below 30°C (room temperature).

Example 2: The proposed storage condition for a product is store ‘below 30°C (room temperature)’. Stability data for 3 batches stored for 18 months at 30°C and 40 - 45°C are provided in the application. The maximum shelf life that the APVMA will recommend for the product on the basis of the submitted data is 30 months (i.e., 18 + 12 months) when stored below 30°C (room temperature).

## **1.5 SITUATIONS WHERE STABILITY DATA ARE NOT REQUIRED**

### **1.5.1 Repacks and currently registered products**

Repack products are identical in formulation and are sold in containers made of the same material as the currently registered product nominated as the reference product and made by the same manufacturer. In general, repack products are supported with a letter held on the APVMA file which has been provided by the reference product registrant and/or formulator to confirm that the product is a repack of the reference product.

### **1.5.2 Vitamins and minerals**

#### **(i) Minerals only**

For products (excluding parenteral products) containing minerals as the only active constituents, a shelf life of 18 months for liquid products and 24 months for solid products may be approved without evaluation of any supporting stability data in the submission, provided the label advice indicates the product should be stored at room temperature (below 30°C).

#### **(ii) Vitamins and Minerals**

In the case of products (excluding parenteral products) which contain vitamins, or vitamins and minerals as the only active constituents a shelf life of 12 months may be approved without evaluation of any supporting stability data in the submission, provided the label advice indicates the product should be stored under air conditioning (below 25°C) and protected from light, and provided there is no information available suggesting interactions occur between constituents which are likely to shorten the stability of the vitamin(s), e.g., iron and vitamin E interaction.

In any case where an applicant proposes a different shelf life, stability data and/or argument should be provided to support this.

### **1.5.3 New products based on existing active constituent(s), intended for use in non-food/fibre producing animals other than dogs, cats or horses (e.g., ornamental fish, aviary birds and rodents)**

A product may be given an approved shelf life of 18 months without stability data provided the active has had a historical basis of registration for use in a similar type of formulation, where no previous problems of stability have been reported and are considered unlikely to occur.

### **1.5.4 Therapeutic Pet Food Diets**

A product may be given an approved shelf life of 12 months (dry products) or 24 months (canned products) without supporting stability data.

## 1.6 DEFINITIONS AND ABBREVIATIONS

**Active constituent** the substance or substances in a formulated product, which is/are primarily responsible for the biological or other effects that make the product a veterinary chemical product.

**AOAC** Association of Official Analytical Chemists.

**APVMA Gazette** The *Commonwealth of Australia Agricultural and Veterinary Chemicals Gazette*, published monthly (with additional special gazettes published from time to time).

**Batch** A specific quantity of an active constituent or an agricultural or veterinary chemical product that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

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

**BP** British Pharmacopoeia.

**BP (Vet)** British Pharmacopoeia (Veterinary).

**CIPAC** Collaborative International Pesticide Analytical Council.

**Climatic zones** The four zones into which the world is divided based on the prevailing annual climatic conditions, as follows:

- Zone I: temperate;
- Zone II: subtropical, with possible high humidity;
- Zone III: hot/dry; and
- Zone IV: hot/humid.

**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 later are intended to provide additional protection to the product.

**Dosage form** A pharmaceutical product type (e.g., tablet, capsule, solution, cream etc) that contains the active constituent generally, but not necessarily, in association with excipients.

**Ph Eur** European Pharmacopoeia.

**Excipient** All other intentionally added components of an agricultural or veterinary chemical product except the active constituent(s).

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

**Laboratory batch** Any batch of formulated product where the total size of the batch is <10% of a normal production batch.

**Pharmacopoeia** An authoritative work containing descriptions of active drugs listing specifications, their formulae and dosage forms and directions for determining purity and strength.

**Pilot scale batch** A batch of a product manufactured by a procedure fully representative of and stimulating that to be applied to a full production scale batch. For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full production batch.

**Production batch** A batch of formulated product that is the same size (weight or volume) as would be manufactured under normal manufacturing conditions.

**Repack** A product which is identical to the currently registered product (the reference product) in every way except the product may be marketed under a different brand name, whether by the same company or different one.

**Shelf life** The shelf life is the length of time in years and months up to which the chemical product maintains its labelled potency, purity and physical characteristics.

**Specifications** A broad term used for defining the identity and purity of the active constituent and product.

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

**Specifications – shelf life/check/expiry** The combination of physical, chemical, biological and microbiological test requirements that a veterinary chemical product must meet throughout its shelf life.

**Stability indicating assays** The assay method that accurately quantitates the active constituent without interference from impurities, degradation products and excipients.

**USP** United States Pharmacopoeia.

**Veterinary chemical product** A substance or a mixture of substances that fits the legal definition in the Agricultural and Veterinary Chemicals Code Act 1994.

## 1.7 REFERENCES

1. Committee for Veterinary Medicinal Products (CVMP), Note for Guidance, 'In use Stability Testing of Veterinary Medicinal Products' (EMA/CVMP 127/95).
2. International Conference on Harmonisation (ICH), Harmonised Tripartite Guideline for Stability Testing of New Drugs Substances and Products 1993.
3. Australian Pesticides and Veterinary Medicines Authority, *Vet Labelling Code: Code of Practice for Labelling Veterinary Chemical Products*.
4. Veterinary International Conference on Harmonisation (VICH), International Cooperation on Harmonisation of Technical Requirements for registration of Veterinary Medicinal products:
  - 4.1 VICH GL 3 (Stability 1), Stability Testing of New Veterinary Drug Substances and Medicinal products.
  - 4.2 VICH GL4 (Stability 2), Stability Testing for New Veterinary Dosage Forms.
  - 4.3 VICH GL5 (stability 3), Photostability Testing of New Veterinary Drug Substances and Medicinal Products.