GUIDELINE FOR STABILITY DATA

The purpose of stability testing is to provide evidence on how the quality of a 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. 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 2 current batches (preferably pilot and/ or production scale) is considered by the DCA to be the statistical minimum necessary to establish a shelf life for a product.

Therefore when data from less than the minimum two batches are provided the applicant should include a valid scientific argument justifying the suitability of the data provided for establishing the proposed shelf life.

The batch identity, date of manufacture and batch size should be reported with the stability data.

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.

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	√	√	√	√				√	√

4. Storage condition

Storage stability programmes should include real time studies or a combination of real time and accelerated conditions. Recommended storage conditions from the labelling of Veterinary Products are listed below:

Store below –18°C (deep freeze);

Store below –5°C (freeze);

Store between 2°C and 8°C (refrigerate. Do not freeze);

Store below 8°C (refrigerate);

Store below 25°C (air conditioning);

Store below 30°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 (Minimum 2 batches)	Accelerated testing (Minimum 2 batches)
Products intended for Storage in a freezer	-20°C±5°C	Accelerated trial probably not appropriate
Products intended for Storage in a refrigerator	5°C ±3°C	25°C ±2°C and 60% RH ±5% RH
25°C (air conditioning)	25°C ±2°C and 60% RH±5% RH	35 – 40°C ±2°C and 75% RH ±5% RH
30°C (room temperature)	30°C ±2°C and 75% RH	40 – 45°C ±2°C and 75% RH

	±5% RH	±5% RH

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.

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;
- Organolepticproperties (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

Relevant test parameters for each type of dosage form are given in Attachment C. 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.

7. Expiry specification

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”.

8. Duration of stability trials

(i) Locally manufactured product

At point of submission, 3 months accelerated data (45-50℃/75% RH ±5% RH) or 6 months accelerated data (40℃/75% RH ±5% RH)and a commitment letter to submit real time stability data once available is required to claim for 3 years shelf life.

(ii) Imported product

A minimum of 12 months realtime stability data with a complete accelerated data are required during submission to claim for 2 years shelf life.

9. 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 substance.

(ii) Intramammary products

Intramammary products are solutions, emulsions, suspensions or semi-solid preparations containing one or more active substances 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 substance 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.

10. Additional Tests

i) Parenteral products

(a) Stability of reconstituted products

The in-use stability of parenteral veterinary 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”.

(b) 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.

ii) 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.

iii) 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.

- **Injectables**

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

- **Ophthalmic products**

Sterility should be demonstrated for all ophthalmic products.

- **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.

- **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.

iv) Dissolution testing

The dissolution test for solid dosage forms is a physical quality control test designed to ensure the consistency of active substance release from the dosage form and

assure consistent batch-to-batch behavior. Dissolution data should be generated on at least 6 individual units at each test station.

11. 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 applicants 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.

i) 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℃, 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℃.

ii) 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℃ 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℃ (room temperature)’. Stability data for 3 batches stored for 12 months at 30℃ and 40 – 45℃ are provided in the application. The maximum shelf life that the NPRA will recommend for the product on the basis of the submitted data is 24 months when stored below 30℃ (room temperature).

Example 2: The proposed storage condition for a product is store ‘below 30℃ (room temperature)’. Stability data for 3 batches stored for 18 months at 30℃ and 40 – 45℃ are provided in the application. The maximum shelf life that the NPRA 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).

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

Veterinary products that are the subject of an individual monograph in a recognized pharmacopoeia [BP, BP (Vet), PhEur 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 withconsideration for safety of the analyst).

Dosage form	**Recommended Test Parameters**
Aerosols (pressurised pharmaceutical preparations)	Identification of the Active substance Active substance assay Preservative content (where appropriate) Delivered dose or dose per actuation Particle size distribution (suspensions only) Number of metered doses
Capsules	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Impurities (where appropriate) Disintegration time Dissolution profile (where appropriate)
Collars/ear tags	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Dissolution profile (release of active substance from the inert matrix)
Emulsions	Appearance (including phase separation) Identification of the active substance Active substance assay Preservative content (where appropriate) pH Viscosity Microbial Limit (where appropriate)

Dosage form	Recommended Test Parameters
Granules	Appearance Identification of the active substance Active substance assay Moisture content Uniformity of content/mass (for single dose preparations only) Dissolution profile (where appropriate)
Implants (sub-cutaneous, intravaginal)	Appearance Identification of the active substance Active substance assay Uniformity of content/mass Hardness Friability Moisture content (where appropriate) Dissolution profile (release of the active substance from the inert matrix)
Injectables	Appearance, colour, clarity Identification of the active substance Particulate matter Active substance assay Impurities (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Bacterial endotoxins –Pyrogens pH (aqueous preparations only)
Oral powders	Appearance Identification of the active substance Active substance assay Moisture content (where appropriate) Microbial Limit(where appropriate)
Paste	Appearance Identification of the active substance Active substance assay Viscosity Microbial Limit (where appropriate)
Powders for injection	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) pH of reconstituted solution Sterility testing for reconstituted solutions (where appropriate) **Note: 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.**

Dosage form	Recommended Test Parameters
Soluble powders in drinking water	Appearance Identification of the active substance Active substance assay pH of solution **Note: In-use shelf life of medicated drinking water should not exceed 24 hours unless justified by providing stability data to show that the active substance is stable for the length of time stated on the label**
Solutions	Appearance (e.g. cloudiness, precipitation, clarity of solution) Identification of the active substance pH (aqueous solutions only) Active substance assay Impurity content (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Viscosity (where appropriate) Specific gravity (where appropriate) Microbial Limit (where appropriate)
Suppositories	Appearance Identification of the active substance Active substance assay Microbial Limit (where appropriate) Dissolution
Suspensions	Appearance Identification of the active substance pH (aqueous suspensions only) Viscosity (where appropriate) Active substance assay Particle size distribution (where appropriate) Preservative content (where appropriate) Microbial Limit (where appropriate)
Tablets	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) Tablet hardness Friability (uncoated tablets) Disintegration time Dissolution profile (where appropriate) Uniformity of content/mass Uniformity of weight **Note: For chewable tablets, testing for disintegration time and dissolution profile is not required.**

Dosage form	Recommended Test Parameters
Topical, ophthalmic and otic products (e.g., powders, ointments, creams, lotions, gels and pastes)	Appearance, colour, clarity and odour Identification of the active substance Active substance assay Preservative content (where appropriate) pH Microbial limits/sterility (where appropriate) **Note: For ophthalmic products (creams, solutions, suspension and ointments), testing for sterility is required.**

Reference: Guidelines For The Generation of Storage Stability Data of Veterinary Chemical Products, Veterinary Guideline No 68, APVMA