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1 INTRODUCTION

This document specifies the minimum requirements for chemistry (and related manufacturing process requirements) submitted in support of an application to register veterinary medicines, or to vary the conditions on registered trade name products containing veterinary medicines. It also incorporates guidelines, which are intended to provide more detailed information and guidance to applicants to assist them in complying with the standard.

NB: This document does not apply to biological trade name products. Requirements for biological trade name products can be found in ACVM Registration Standard and Guideline for Biological Compounds (currently under construction).

The standard is compulsory for applications to register a trade name veterinary medicine, unless a waiver has been granted by the Agricultural Compounds and Veterinary Medicines (ACVM) Group of the New Zealand Food Safety Authority (NZFSA).

The requirements that form the standard are shown in this document in bold font and are mandatory, while the guidelines are in regular font and are non-mandatory.

Guidelines reflect principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. It is recognised that there are acceptable methods other than those described in these guidelines that are capable of achieving the principles of this document. At the request of applicants the ACVM Group will assess the appropriateness of alternative methods on a case-by-case basis.

Where the application is for a variation of an existing condition, an information waiver of all or part of the requirements of this standard may be granted.

Applicants should note that they are responsible for providing all information required by the ACVM Group to make a decision on the application. Applications that do not contain the required information will not be assessed. If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting the application.
1.1 **Scope**

This standard must be followed by all persons applying to register a veterinary medicine, or to vary the conditions on a registered veterinary medicine.

The standard provides specifications for:
- formulation and ingredient requirements;
- manufacturing requirements (of final product);
- specifications (of final product); and
- stability of final product.

1.2 **Definitions and abbreviations**

NB: Although some definitions given below include biologicals, the requirements for biological trade name products are in development. This document should be used for guidance.

**Accelerated stability testing**
Testing designed to increase the rate of chemical or physical degradation of a product by using exaggerated storage conditions.

**Active ingredient**
The substance(s) in a trade name product, which is primarily responsible for the biological or other effects that make the product a veterinary medicine.

**Active ingredient specification**
A statement (signed and dated by the manufacturer) of the description of the active ingredient, including the maximum and minimum limits of purity, the maximum levels of individual contaminants, test for identity and any other properties as applicable.  
**NB:** Certificates of analysis, certificates of conformance and material safety data sheets do not constitute a materials specification.

**Agricultural compound**
Any substance, mixture of substances, or biological compound, used or intended for use in the direct management of plants and animals, or to be applied to the land, place, or water on or in which the plants and animals are managed, for the purpose of:
- managing or eradicating pests, including vertebrate pests; or
- maintaining, promoting, or regulating plant or animal productivity and performance or reproduction; or
- fulfilling special nutritional requirements; or
- manipulating, capturing, or immobilising animals; or
- diagnosing the condition of animals; or
- preventing or treating conditions of animals; or
• enhancing the effectiveness of an agricultural compound used for the treatment of plants and animals; or
• marking animals;
and includes:
• any veterinary medicine, any substance, mixture of substances, or biological compound used for post-harvest pest control or disinfection of raw primary produce; and
• any substance, mixture of substances, or biological compound declared to be an agricultural compound.

**Batch**
A specific quantity of an active ingredient or other material 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.

**Biological (compound)**
A plant compound or veterinary medicine wherein the active ingredients, whether living or not, are derived from plants, animals, viruses or other micro-organisms, whether living or not, formulated either singly or in combination and where some essential characteristics of the source are retained in the preparation. A characteristic, though not universal, feature is the lack of precise chemical definition at the molecular level of the active ingredient.

**BPh**
*British Pharmacopoeia*

**BPh (vet)**
*British Pharmacopoeia (Vet)*

**CAS**
Chemical Abstracts Service

**Chemistry**
The chemical identity, properties, specifications, formulation details, manufacturing processes, methods of analysis of the active ingredients, impurities in the product, and storage stability data.

**Critical manufacturing control point**
A step at which control can be applied and is essential to prevent or eliminate an identified hazard or reduce an identified hazard to an acceptable level.

**Dermal veterinary medicine**
Any veterinary medicine that is applied topically to the exterior skin of any animal. Trade name products applied to the mucosal membranes, the eye or the ear (excluding the auricle/pinna) of an animal are not included in this category.
Systemic dermal veterinary medicine
Where the active ingredient(s) has the inherent property of transdermal absorption or where the formulation is designed to effect this process.

Non-systemic dermal veterinary medicine
Where the active ingredient has little or no dermal translocation and the formulation is not designed to effect this process. Systemic absorption may occur, however, through cuts and abrasions.

EuPh
European Pharmacopoeia

Excipient
All other intentionally added components of a veterinary medicine excepting those active ingredients upon which the biological activity is dependent as defined above. Also known as formulates, inerts and non-active ingredients.

Expiry specifications
These specifications are the limits within which the product must be maintained during its shelf life, e.g. pH 6.5-7.0

Formulation
A list of all the ingredients with their concentrations added together to give the end-use product. This will contain one or more active ingredient(s) and possibly excipient(s) (non-active ingredient[s]).

GLP
Good Laboratory Practice International Code: ISO/IEC 17025-
General Requirements for the Competence of Testing and Calibration Laboratories.

Impurity
Any constituent other than an active ingredient or an excipient. Impurities include intermediates, reaction products, degradation products, contaminants or chemicals added for purposes of extraction or purification.

INN
International Non-Proprietary Name

ISO
International Standards Organisation

IUPAC
International Union of Pure and Applied Chemistry

Manufacture
In relation to any veterinary medicine, ‘manufacture’ includes all the following aspects: acquiring materials, making up, preparing, producing or processing, and assessing the trade name product for release; it also includes the relabelling and repacking of a veterinary medicine for the purposes of sale.
Manufacturer
Any person who manufactures a veterinary medicine.

Materials specification
Details of the chemical or compound including the maximum and minimum limits of purity, the maximum levels of individual contaminants, test for identity and any other properties as applicable.

Overage
The excess of active ingredient deliberately added to a formulation to compensate for manufacturing loss or loss during storage.

Pharmacopoeia
An authoritative work containing descriptions of drugs that are used in the practice of medicine (or veterinary medicine) listing the specifications, their formulae and dosages, and directions for determining purity and strength.

Pilot batches
Pilot batch production should be identical to production batches (equipment, site, procedures and controls). There should be no significant changes with scale-up.

Plant compound
Any substance, mixture of substances, or biological compound used, or intended for use, in the direct management of a plant. It also includes compounds used in the post-harvest treatment of unprocessed agricultural commodities of plant origin.

Real time stability testing
Testing on the product stored in the container and closure system intended for marketing, under proposed storage conditions that support a proposed shelf life for that product.

Release specifications
These are the specifications for a product to meet before it is released for sale, e.g. pH 6.5-7.0

Shelf life
The time interval from date of manufacture that a product is expected to remain within the approved expiry specification, provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Specification
A broad term used for defining the identity and purity of the substance or material.

Stability
Stability of a trade name product is denoted by adherence to the active ingredient content, impurity specifications and physico-chemical characteristics as specified at the time of manufacture and maintained throughout the shelf life of the trade name product within the specified range.
Trade name product
A veterinary medicine identified and packaged under a trade name for a specified use or uses.

Validation
Confirmation by examination and provision of objective evidence that the particular requirements for a specified intended use are fulfilled.

Veterinary medicine
Any substance, mixture of substances, or biological compound(s) used or intended for use in the direct management of an animal.

VICH
International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

1.3 Units
All units should preferably be SI units.

1.4 References

- *ACVM Registration Information Requirements for Veterinary Medicines in New Zealand*
- *ACVM Standard for Good Manufacturing Practice*
- *ACVM Guideline for Good Manufacturing Practice*
- *ACVM Registration Standard and Guideline for Biological Compounds* (under construction – likely to be published under a changed title)
- *ACVM Guidelines for Information Waivers*
- VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) GL1 - Validation of Analytical Procedures: Definition and Terminology
- VICH GL2 - Validation of Analytical Procedures: Methodology
- VICH GL8 - Stability Testing for Medicated Premixes
- VICH GL10 - Impurities in New Veterinary Drug Substances
- VICH GL11 - Impurities in New Veterinary Medicinal Products
- European Agency for the Evaluation of Medicinal Products/Committee for Veterinary Medicinal Products: Notes for Guidance: In-Use Stability Testing of Veterinary Medicinal Products 1996.
2 FORMULATION AND INGREDIENT REQUIREMENTS

2.1 Formulation type/ pharmaceutical dosage form

2.1.1 The formulation type of the trade name product must be stated. Select from the list given in Annex 1.

2.1.2 For controlled-release devices, the rationale of the formulation and/or design principle (with technical drawing and/or technical description) of the device must be provided. The composition of the device components must be supplied. The applicant must document any procedures attendant upon reuse of the device that may impact on the risks to be managed under the ACVM Act 1997.

2.2 Formulation

2.2.1 The formulation of the trade name product must include:

• composition
  Concentrations* must be expressed in g/L or g/kg (milligrams or micrograms may be substituted for grams as appropriate).

  For vaccines a recognisable international unit is sufficient.

  Where the product contains separate formulations (e.g. coatings) these should be shown as a separate distinguishable formulation.

* Discrete concentration values of ingredients must be given. For excipients, variations of ±5% in practice is considered acceptable.

• mass(es) or volume(s) of the trade name product to be administered as a ‘single dose’ at any one time (e.g. tablet weight). The related concentrations of active ingredients must also be stated.

NB: The formulation declared in the chemistry and manufacturing dossier, and on the product data sheet, must be a complete and accurate account of the ingredients and their concentrations in the trade name product.

2.2.2 Where an overage (small excess) of active ingredient has been deliberately added, the actual concentration (nominal plus overage) must also be stated. It must be noted whether the overage is intended to cover losses during manufacture, storage, or both.
2.3 **Active ingredient requirements**

The following information must be provided for each active ingredient.

2.3.1 Identification of the active ingredient(s)
- chemical or IUPAC, ISO and common (INN) or proposed name*
  and Chemical Abstracts Service (CAS) registry number*;
- empirical molecular formula and molecular weight
  or molecular weight range and median;
- two-dimensional chemical structure;
- three-dimensional spatial configuration.

* If not assigned then a unique identifying code will suffice.
# If assigned the CAS number must be supplied.

2.3.2 Active ingredient specification

The active ingredient specification must include:

2.3.2.1 Pharmacopoeial standards
- nomination of the national and/or international standard(s) with which each
  active ingredient complies;
  This includes pharmacopoeial standards, ISO, and any other internationally
  recognised standards. Any variations from these nominated standards must be
  documented and the variations supported. The relevant pharmacopoeial
  monograph must be supplied. If the active ingredient complies with acceptable
  pharmacopoeial standards, then 2.3.2.2 does not apply and the reporting of those
  required elements is waived.

Internal methods for analysis different from those cited for pharmacopeial
standards are acceptable where these have been validated and all reference
materials used are traceable. Where internal methods (non-pharmacopeial)
are used or referenced, authorised copies of these validated methods must be
provided.

- If the active ingredient is produced to a more exact specification, this must be
  provided.

2.3.2.2 Where the active ingredient is non-pharmacopoeial the following is required:
- manufacturer’s specifications including minimum content of pure active
  ingredient, isomeric ratio where applicable and maximum impurity content.
  Where the active substance is produced at more than one plant, this must be
  provided for each plant separately;
- in-house analytical methods;
  Details of a validated analytical method of the active ingredient must be provided,
  including any in-house analytical tests that were used to determine the identity
  and proportion (true active ingredient content) of active ingredients. Any data
  obtained by measurement must meet the required specificity, precision and
  accuracy;
• description of chemical and physical characteristics — see list below;
• impurities related to the active ingredient and the nature of the relationship;
• particle size (sieve tests, median and range).

2.3.2.3 Chemical and physical characteristics relevant to the active ingredient(s) must include the appropriate characteristics from those listed below:

Physical characteristics
• state;
• colour;
• melting point/range for solids;
• boiling point/range (atmospheric pressure) for liquids;
• specific gravity;
• particle size (sieve tests, median, range);
• viscosity (liquids only);
• odour.

Chemical characteristics
• isomeric content (enantiomeric, rotational, diastereomeric and/or geometric);
• solubility (in water and organic solvents);
• hydrolytic properties;
• photolytic properties;
• polymorphism;
• pKa and (aqueous) pH values;
• hygroscopicity;
• n-octanol/water partition coefficient;
• chelating and/or encrypting properties.

2.3.2.4 The applicant must address the issue of impurities present in the active ingredient(s):
• Any impurities present at a concentration of 1 g/kg or more, with reference to their CAS numbers, if available, must be documented.
• Impurities present at less than 1 g/kg that may be toxicologically significant (e.g. dioxins, heavy metals, persistent organo-carbon compounds, primary aromatic amines PCBs or nitrosamines), or those specified compounds subject to international treaty or bilateral or multilateral agreement (e.g. certain hormones/growth promotants) must be identified, quantified and reported.

Details of the impurities must include:
• name(s);
• content (S.I. units);
• maximum allowable limits.

The relationship of the impurity to the active ingredient must be explained and the origin of the impurity must be documented.
2.3.3 Batch analysis
Batch analysis must include the date of manufacture, batch size, place of manufacture, results for appropriate parameters (e.g. active content and impurities as specified above) from appropriate determinative analytical methods (including counter ions when present). Where the active substance is produced at separate plants, this must be provided for each plant separately.

2.3.4 Any additives (e.g. stabilisers) must be identified.

2.3.5 Laboratory accreditation
Where analytical data is supplied from a laboratory in support of a particular specification or an element of an active ingredient, excipient or impurity requirement, then documentation outlining any accreditation or recognised expertise in that area for the laboratory is required.

2.3.6 Manufacturer of active ingredient(s)
The following details for each producer of the active ingredient(s) must be provided:
• name;
• postal address;
• physical address;
• telephone and fax numbers.

The ACVM Group reserves the right to enquire into the manufacturing process of active ingredient(s) where it needs to satisfy issues relating to suitability of the process or adequacy of Quality Assurance procedures that may impact on the risks under the ACVM Act 1997.

2.4 Excipient (non-active ingredient) requirements

For each excipient in a trade name product, identification must include:

2.4.1 Non-systemic dermal veterinary medicine only:
• approved chemical name;
• common name (INN); and
• CAS registry number*.

* For any non-active ingredient (i.e. excipient/inert), where no CAS number has been assigned (or a CAS number is not applicable), full details of the ingredient must be supplied. The details on such ingredients must include:
• name;
• percentage of each component in the ingredient (and CAS number if available)#;
• the material safety data sheet (MSDS) for the ingredient.

# Where the ingredient is composed of a mixture of individually non-quantifiable substances, then a statement and a MSDS must be supplied.
2.4.2 All other veterinary medicines (e.g. systemic dermal, oral and parenteral veterinary medicines):
- approved chemical name;
- common name (if known);
- (CAS) registry number*;
- nomination of the standard with which each non-active ingredient complies.

2.4.2.1 Acceptable standards include pharmacopoeial standards, ISO, and other internationally recognised standards. Any variations from the nominated standards must be provided. The relevant pharmacopoeial monograph must be supplied. If ingredients are not to pharmacopoeial standard, then section 2.4.2.2 applies.

Internal methods are acceptable where these have been validated and all reference materials used are traceable. Where internal methods are used or referenced, validated copies of the methods must be provided.

2.4.2.2 If the excipient is non-pharmacopoeial then this section applies (if section 2.4.2.1 is not applicable).
Applicants must supply:
- a description of chemical and physical characteristics (see below for guidance);
- impurities related to non-active ingredient(s) (see section 2.4.4 for guidance).

* For any excipient where no CAS number has been assigned (or a CAS number is not applicable), full details of the ingredient must be supplied. The details on such ingredients must include:
  - name;
  - percentage of each component in the ingredient (and CAS number if available)*;
  - the material safety data sheet (MSDS) for the ingredient.

  * Where the ingredient is composed of a mixture of individually non-quantifiable substances then a statement and a MSDS must be supplied.

2.4.3 Chemical and physical characteristics
Required chemical and physical characteristics relevant to the non-active ingredient(s) must include the appropriate characteristics from those listed below:

Physical characteristics
- state;
- colour;
- melting point range/boiling point range;
- specific gravity;
- particle size (sieve tests, median, range);
- odour.
Chemical characteristics
- isomeric content (enantiomeric, rotational, diastereomeric and/or geometric);
- solubility (in water or organic solvents e.g. methanol, hexane, toluene, etc);
- hydrolytic properties;
- photolytic properties;
- polymorphism;
- pKa and pH values;
- hygroscopicity;
- n-octanol/water partition coefficient;
- chelating and/or encrypting properties.

2.4.4 The applicant must address the issue of impurities present in the non-active ingredient(s):
- Any impurities present at a concentration of 1 g/kg or more, preferably with reference to their CAS numbers, if available, must be documented.
- Impurities present at less than 1 g/kg that may be toxicologically significant (e.g. dioxins, heavy metals, persistent organo-carbon compounds, primary aromatic amines PCBs or nitrosamines), or those specified compounds subject to international treaty or bilateral or multilateral agreement (e.g. certain hormones/growth promotants) must be identified, quantified and reported.

Details of the impurities must include:
- name(s);
- content (S.I. units);
- maximum concentration.

The relationship of the impurity to the active ingredient must be explained and the origin of the impurity must be documented.
3 MANUFACTURING OF THE TRADE NAME PRODUCT

3.1 Manufacturer of trade name product

The following details of every site of manufacture# of the trade name product must be provided:

- name of organisation;
- postal address;
- physical address;
- telephone and fax numbers;
- name of contact person.

# includes repackers and relabellers. Refer to section 1.2 for definitions of ‘manufacturer’ and ‘manufacture’ as they relate to the ACVM Act.

3.2 Manufacturing process

A description of all stages involved in the manufacture of the trade name product, in the form of a simple flow diagram with explanations, must be provided. This description must identify the manufacturing process from the starting materials through to the packaged and labelled product.

Sufficient detail must be provided to cover at least the essential steps and processes, e.g. when the product or its ingredients are exposed to heat or processes likely to lead to toxic impurities.

3.3 Identification and management of critical manufacturing control points

Critical manufacturing control points must be identified on the process flow diagram.

The critical control points identified should be those that are controlled during the manufacturing process by objective measurement and are relevant to risk management.

3.4 Quality control

Full details of the quality control procedure including relevant analytical techniques (see section 5.5) must be provided.

This is required to ensure that batches produced will be of a consistent quality by meeting the release specifications (see section 4.1).
4 SPECIFICATIONS

4.1 Release specifications

The release specifications are the specifications within which the product must be before it is released for sale, e.g. pH 6.5-7.0

The release specifications of the trade name product must be listed.

Specifications must include (but are not limited to) the relevant chemical and physical characteristics from the following list:

- colour;
- odour;
- melting point/range for solids;
- boiling point/freezing point/range (atmospheric pressure) for liquids
- specific gravity;
- viscosity;
- particle size (sieve tests, median, range);
- physical dimensions;
- solubility and dissolution properties;
- decomposition products where these are of significance;
- pH;
- identification and assay of active(s), including definition of the range of the tolerable analytical results;
- identification and assay of required excipient(s), e.g. antimicrobials, preservatives, including definition of the range of the analytical results;
- tests on pharmaceutical form;
- sterility (where applicable);
- other characteristics, e.g. withdrawal volume for injectables;
- for controlled-release devices, final specifications must include a parameter indicative of drug release, e.g. a dissolution assay with analytical validation;
- impurities (where applicable refer to VICH Guideline 11: Impurities in New Veterinary Medicinal Products);
- pyrogenicity.
4.2 Expiry specifications

These specifications are the limits within which the product must be maintained during its shelf life. These will usually be justifiably wider than the release specifications. The appropriate specifications would usually include the parameters outlined above and any appropriate limits for degradation products.

If the product is released at the low end of a specification and the release and expiry specifications are the same, there is a likelihood that the expiry specification will be exceeded during the product’s shelf life.

4.2.1 The expiry specifications for the trade name product must be provided and justified. These must include (but are not limited to):

- those impurities and degradation products present in the product at the end of its proposed shelf life subject to the impurity criteria listed in section 2.3.2.4 and section 2.4.4;
- limits on acceptable levels of each impurity and degradation product;
- chemical characteristics, e.g. colour, active ingredient concentration(s);
- physical characteristics, e.g. density, freezing point, phase separation;
- active ingredient specifications;
- analytical methods used (previously cited methods may be referenced).

This includes pharmacopoeial standards, ISO, and other internationally recognised standards. Any variations from the nominated standards must be provided. Internal methods are acceptable where these have been validated and all reference materials used are traceable. Where internal methods are used or referenced, validated copies of the methods must be provided.

4.2.2 It is the responsibility of the applicant to set the specifications and the quantitative limits that define each impurity present having regard to any specifications in Annex 2. The expiry specifications must include (but are not limited to):

- sterility status (where applicable);
- a statement of all impurities present in the product including those resulting from degradation;
- limits on acceptable levels of impurities (as described above);
- any chemical property (including toxicity) that is consequential to the stability of the product over the proposed shelf life, e.g. oxidation products, organoleptic products, hydrolytic products, photolytic products and polymerisation products;
- characteristics of packaging, e.g. container/closure interaction with product, ingress or egress of water, leaching of containers into product (where applicable);
- pyrogenic status.

4.2.3 The expiry specifications must not be set to justify degradation where the degradation may have a negative impact on the efficacy, safety or residue profile of the product.
4.3 Packaging specifications

4.3.1 Details of size, shape, construction material and lining of all packaging to be marketed must be supplied.

New component packaging materials must be used unless approval for the use of secondhand materials, for the packaging of the trade name product, has been granted by the ACVM Group.

In addition to the pack sizes to be marketed, approval for a pack size range may be sought. In such cases it must be demonstrated that the trade name product will remain stable in the smallest and largest pack size requested. All pack sizes with the equivalent hazard profile (e.g. same plastic type) that fall within the approved range will be considered approved. Registrants are required to notify the ACVM Group in writing when compliant pack sizes are to be marketed, if not specifically stated in the current approval.

4.3.2 Comments on the packaging must be included when the inherent chemical characteristics of the formulated product are such that the packaging must be designed to manage the associated risks, e.g. high acidity.

The comments could include notes on inherent chemical or physical characteristics that impact on packaging, for example:

- porosity;
- permeability;
- impact strength;
- closure type;
- stability (photolytic and hydrolytic stability of biodegradable packaging).
5 STABILITY TESTING OF THE FINISHED PRODUCT

Applicants who supply data that conform with this standard are deemed to have complied with the requirements of the VICH GL3 (Stability 1) document from the ‘International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products’ expert working group. This guideline is entitled STABILITY TESTING OF NEW VETERINARY DRUG SUBSTANCES AND MEDICINAL PRODUCTS.

‘Finished product’ in this context means that trade name product for sale at any time between compounding and the time of expiry (of the shelf life). The purpose of stability testing is to provide evidence on how the quality of a veterinary medicine 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.

A shelf life would not normally, excepting exemptions requested under section 5.3.10 and compounds listed in Annex 3, be approved for the purposes of registration if there is no stability data provided on the formulation to be registered. There should be a direct linkage between the trade name product label statement and the demonstrated stability characteristics of the product.

5.1 Proposed shelf life

5.1.1 A proposed shelf life must be nominated.

This is the length of time after which the product cannot be guaranteed to meet the supplied expiry specifications.

Unless a waiver has been requested, the proposed shelf life should not exceed the shelf life that is directly supported by the data. This means that if data from all three batches submitted as part of the stability study meet all the specifications, then a shelf life equivalent to the length of time all batches support would be appropriate. For example, for a real time stability study where 2 batches are tested to 36 months and 1 batch is tested to 24 months, a 24 month shelf life would be appropriate providing all the specifications are met.

5.1.2 Where the application is for a variation to an existing shelf life, the shelf life currently assigned to the product must be stated.

5.1.3 Extensions on the shelf life of individual batches may be requested. The stability data provided with such an application must be from the applicable batch with appropriate parameters and time points tested.

A justification for the extension of the shelf life of the individual batch should also be provided.
5.2 Proposed storage conditions

5.2.1 The proposed storage conditions of the product (i.e. label and product literature storage directions) must be stated.

5.2.2 The proposed temperature range for storage must be stated together with any other special conditions.

Where applicable, specific storage requirements must be stated. This is particularly important for products where the risk characteristic inherent in the product is one that is affected by storage conditions, e.g. freezing, high temperatures or, more likely, exposure to water, light or oxygen (air).

5.3 Stability study requirements

5.3.1 Stability study reports are required for all veterinary medicines unless specifically exempted by waiver or listing in Annex 3 (see section 5.3.12).

5.3.2 Stability studies must be conducted on the trade name product.

This means the formulation of the product used in the stability studies must be the same formulation as stated on the registration application form and the same as that used for any studies submitted in support of the registration application. Confirmation that this is the case must be given.

5.3.3 A minimum of three batches must be tested to support the proposed shelf life, one of which must be representative of a production batch, i.e. scaled up from a laboratory batch.

5.3.4 Each batch tested must be uniquely identified.

5.3.5 Stability studies must cover the chemical and physical parameters that are likely to impact on the safety, efficacy and/or residue profiles of the trade name product when used as directed. Recommended parameters based on dosage form are given in Annex 4. Additional parameters, such as photostability testing, may be appropriate. Any deviation from conducting trials determining the recommended parameters must be addressed.
5.3.6 Stability studies on trade name products must be conducted on the smallest pack size to be sold. Any variations must be fully justified. Additionally, for heterogeneous liquid formulations (e.g. suspensions), stability studies should also be conducted on the largest pack size to be sold. If stability testing on the largest size packaging would be impractical, then proof of phase stability must be provided.

If the product is to be marketed in packaging of different types, e.g. high density polyethylene and glass, then stability trials should be conducted on each packaging type.

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

This is also the case for an application for an extension of a previously approved shelf life.

5.3.8 The length of the stability study and the storage conditions must be sufficient to cover storage, shipment and subsequent use.

5.3.9 Each batch tested must include initial (time = 0 days) readings and final readings.

The frequency of testing will normally be every three months over the first year, every six months over the second year and then annually thereafter.

5.3.10 Non-compliance with the stated stability conditions must be fully addressed and justified.

5.3.11 In-use stability for reconstituted and multi-dose products must be addressed.

In-use stability for reconstituted and multi-dose products must be addressed where the formulation is such that microbiological contamination or product degradation may occur following opening or broaching of the pack. This includes trade name products intended for use in feed or water.

The test must be designed to simulate the use of the product in practice.

Throughout the period of the test, the product must be stored as recommended by the manufacturer, i.e. on labelling/product literature.

5.3.12 Exemption from conducting a stability study will be considered by the ACVM Group. See Annex 3 for applicable compounds. Applications for the exemption must be fully supported and accompanied by the completed form as per the Appendix. Analysis from two production/pilots batches must be provided (time zero analytical samples).
5.4 Stability study conditions

5.4.1 The stability trials must be conducted as either real time studies or a combination of real time and accelerated studies:

(a) Real time studies
Real time room temperature study conditions, unsupported by accelerated data, must be 25-30°C / 60±5% relative humidity. Where the applicant can show the packaging enclosure is non-permeable, then the relative humidity requirement will be waived.
If the trade name product is intended for storage in a refrigerator, then 5°C would be considered an appropriate testing temperature.

If data from all three batches submitted as part of the real time stability study meet the expiry specifications, then a shelf life equivalent to the length of time all three batches are tested to will be deemed applicable.

(b) Combination of real time and accelerated studies
Studies incorporating both real time and accelerated study conditions must conform to:
1) Accelerated 40±3°C / 75±5% relative humidity
2) Real time 25±5°C / 60±5% relative humidity
Where the applicant can show the packaging enclosure is non-permeable, then the relative humidity requirement will be waived.

Accelerated stability data may be used to support real time stability data where the results indicate that the product is within the given specifications during and on completion of the stability studies. For example, stability data from 3 batches studied for 6 months under both real time data and accelerated conditions (where the results indicate that the product is within the given specifications during and on completion of the stability studies) will equate to a shelf life of 1 year.

As a matter of ACVM Group policy, accelerated data will not support a shelf life beyond twice that supported by the real time studies. For example, 6 months of real time data + 9 months of accelerated data (where the results indicate that the product is within the given specifications during and on completion of the stability studies) will support a shelf life of no more than 1 year. In general accelerated data greater than 18 months must be accompanied by a justification as to why this will be a direct reflection of the trade name product’s stability.

5.4.2 Freezing stability studies: Freezing study conditions must be not more than -5±3°C.

The use of freezing stability study conditions should reflect the nature of the product and its use patterns, and these are only applicable to veterinary medicines that are subject to practical sub-ambient storage conditions. This applies to any veterinary medicine that may be exposed to low storage temperatures during its shelf life. At least one complete freeze-thaw cycle is required.
5.5 Analytical methods

It must be demonstrated that all assay methods used to determine the concentration(s) of the active ingredient(s) are specific to the active ingredient(s). Where an active ingredient is a stereoisomer or geometrical isomer of a molecule, then the method must demonstrate the required specificity.

5.5.2 The assay methods used must determine the concentration of each active ingredient in its active form (i.e. the active isomer). Non-active isomers and degradation products of the active ingredient(s) must be analysed as impurities.

Where the proportion and identity of non-active isomers and degradation products from a well known active ingredient of veterinary medicines is documented in published papers, and is known to be unaffected by the other ingredients or characteristics of the formulation, then this information and any other relevant information supporting this claim (including analytical methods or references to analytical methods) obtained from public domain sources may be used to fulfill the requirements of this element (5.5.2) under an ACVM Group information waiver.

5.5.3 Discussion of the methods of analysis and how they are used to resolve the active isomers, non-active isomers and degradation products (how the analytical methods separate and show the presence or absence of any isomers and degradation products) must be included.

5.5.4 Analytical methods employed in stability testing (those methods used to test the product to ensure it meets the given specifications) must be described.

5.5.5 The analytical methods must be validated within the testing laboratory. Copies of validation need not be supplied when pharmacopoeial standards, ISO, and other internationally recognised standards are employed. Any variations from the nominated standards must be documented and validated.

Internal methods are acceptable where these have been validated and all reference materials used are traceable. Where internal methods are used or referenced, an authorised copy of the methods and the validation itself must be provided. Citation to ‘in-house’ methods is not acceptable – an abstract description must be provided.

The applicant may wish to specify and provide certain critical performance characteristics that need to be maintained independently of composition and that would need to be maintained after any proposed formulation change to facilitate acceptance of future formulation changes without the requirement to repeat efficacy and residue studies.

5.5.6 As a study to GLP is not a mandatory requirement for stability studies, it is required that stability studies in support of shelf life must be accompanied by a signed declaration from a competent person that the results are true and accurate.

This declaration would preferably be signed by someone not involved in the study.
5.6 Discussion of stability study results

The applicant must provide discussion on observed variations from the expiry specifications and the likely impact of these variations on the proposed shelf life of the trade name product.

For example, if the formulated trade name product is altered before use (e.g. diluted or dissolved), the applicant must show that any changes occurring over the shelf life of the trade name product do not adversely affect that process.

6 FURTHER READING


APPENDIX

SAMPLE DECLARATION FOR EXEMPTION FROM STABILITY STUDIES FOR FORMULATIONS CONTAINING VETERINARY MEDICINES

<company letterhead>

<applicant name>
<applicant address>
<ph no>
<fax no>
<e mail>

I <name of signer> declare for the product <product name>, being a veterinary medicine for which an application for registration has been made, that the toxicity of neither the above-mentioned product nor any of its constituent parts shows an increase in human or animal toxicity over the claimed shelf life of <state years> such that the toxicity at the expiry of the claimed shelf life will be measurably greater than that attributable to the product or its constituents when first formulated for sale.

The conclusive nature of the evidence supplied in support of this claim is such as to absolve <applicant name> from supplying stability data as required in the ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines issued by the Agricultural Compounds and Veterinary Medicines Group of the New Zealand Food Safety Authority.

signed <name>

date <date>

<bibliography of references and attachments supplied>

For ACVM use only

Confirmed: Name signature date
# ANNEXES

## ANNEX ONE:
DEFINITIONS OF FORMULATION TYPES

<table>
<thead>
<tr>
<th><strong>Aqueous solution or suspension:</strong></th>
<th>A formulation of particles dissolved or suspended in water.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block (salt lick):</strong></td>
<td>A prepared mixture of salt and minerals formed into blocks for oral consumption by groups of animals as a feed supplement.</td>
</tr>
<tr>
<td><strong>Bolus:</strong></td>
<td>A rounded concentrated mass of pharmaceutical or nutritional preparation ready to be swallowed.</td>
</tr>
<tr>
<td><strong>Capsule:</strong></td>
<td>A soluble structure containing a dose of a pharmaceutical preparation.</td>
</tr>
<tr>
<td><strong>Cerate:</strong></td>
<td>A pharmaceutical preparation of wax-like consistency, usually for topical intramammary use.</td>
</tr>
<tr>
<td><strong>Cream:</strong></td>
<td>An oil in water emulsion generally used topically in the treatment of skin disease.</td>
</tr>
<tr>
<td><strong>Gel:</strong></td>
<td>A colloid of firm consistency, although containing much liquid.</td>
</tr>
<tr>
<td><strong>Granule:</strong></td>
<td>Solid formulation comprising small particles usually for administration without further dilution.</td>
</tr>
<tr>
<td><strong>Impregnated material:</strong></td>
<td>Any solid pharmaceutical preparation inserted into intact tissues or body cavity (includes HGPs and CIDRs). Also includes collars.</td>
</tr>
<tr>
<td><strong>Oily solutions or suspension:</strong></td>
<td>A colloid mixture of two immiscible liquids, one dispersed throughout the other in small droplets.</td>
</tr>
<tr>
<td><strong>Ointment:</strong></td>
<td>A semi-solid pharmaceutical preparation usually for topical application.</td>
</tr>
<tr>
<td><strong>Paste:</strong></td>
<td>A highly viscous pharmaceutical preparation containing a large amount of powder.</td>
</tr>
<tr>
<td><strong>Powder:</strong></td>
<td>An aggregation of fine particles usually obtained by grinding. Applies to freeze dried vaccines.</td>
</tr>
<tr>
<td><strong>Syrup:</strong></td>
<td>A viscous concentrated solution of a sugar used as a vehicle for medications.</td>
</tr>
<tr>
<td><strong>Tablet/pellet:</strong></td>
<td>A small solid pharmaceutical preparation usually for oral administration.</td>
</tr>
<tr>
<td><strong>Vapour releasing product:</strong></td>
<td>A formulated product containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation rate normally is controlled by using suitable formulations and/or dispensers.</td>
</tr>
</tbody>
</table>
ANNEX TWO:
VETERINARY MEDICINE INGREDIENT SPECIFICATIONS
FOR CITED CHEMICALS

CONTENTS

1 Magnesium-based hypomagnesaemia treatments
   • Calcined magnesite
   • Magnesium oxide (MgO)
   • Magnesium sulfate heptahydrate (MgSO$_4$.7H$_2$O)
   • Magnesium chloride hexahydrate (MgCl$_2$.6H$_2$O)

2 Oral zinc-based treatments for facial eczema
   • Zinc oxide (ZnO)
   • Zinc sulfate monohydrate (ZnSO$_4$.H$_2$O)
   • Zinc sulfate heptahydrate (ZnSO$_4$.7H$_2$O)

3 Topical zinc-based treatments for footrot control
   • Zinc sulfate heptahydrate (ZnSO$_4$.7H$_2$O) for footrot control only

4 Copper-containing oral nutritional compounds and injectable forms of copper
   • Copper sulfate pentahydrate (CuSO$_4$.5H$_2$O)
1 Magnesium-based hypomagnesaemia treatments

1.1 Calcined magnesite

The minimum standard for calcined magnesite is:

- Magnesium oxide not less than 850 g/kg
- Fluoride not more than 500 mg/kg
- Arsenic not more than 4 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 25 mg/kg
- Abrasive fillers not more than 10 g/kg

1.2 Magnesium oxide (MgO)

The minimum standard for magnesium oxide is:

- Magnesium oxide not less than 850 g/kg
- Fluoride not more than 500 mg/kg
- Arsenic not more than 4 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 25 mg/kg
- Abrasive fillers not more than 10 g/kg

1.3 Magnesium sulfate heptahydrate (MgSO₄·7H₂O)

The minimum standard for magnesium sulfate heptahydrate is:

- Magnesium sulfate heptahydrate not less than 990 g/kg
- Arsenic not more than 2 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 25 mg/kg

1.4 Magnesium chloride hexahydrate (MgCl₂·6H₂O)

The minimum standard for magnesium chloride hexahydrate is:

- Magnesium chloride hexahydrate not less than 990 g/kg
- Arsenic not more than 2 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 25 mg/kg
2 Oral zinc-based treatments for facial eczema

2.1 Zinc oxide (ZnO)

The minimum standard for zinc oxide is:

- Zinc oxide not less than 990 g/kg
- Arsenic not more than 5 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 50 mg/kg

2.2 Zinc sulfate monohydrate (ZnSO₄·H₂O)

The minimum standard for zinc sulfate monohydrate is:

- Zinc sulfate monohydrate not less than 980 g/kg
- Arsenic not more than 15 mg/kg
- Cadmium not more than 15 mg/kg
- Lead not more than 35 mg/kg

2.3 Zinc sulfate heptahydrate (ZnSO₄·7H₂O)

The minimum standard for zinc sulfate heptahydrate is:

- Zinc sulfate heptahydrate not less than 980 g/kg
- Arsenic not more than 10 mg/kg
- Cadmium not more than 10 mg/kg
- Lead not more than 25 mg/kg
3 Topical zinc-based treatments for footrot control

3.1 Zinc sulfate heptahydrate \((\text{ZnSO}_4 \cdot 7\text{H}_2\text{O})\) for footrot control only

The minimum standard for zinc sulfate heptahydrate for footrot control is:
- Zinc sulfate heptahydrate not less than 980 g/kg
- Arsenic not more than 10 mg/kg
- Cadmium not more than 100 mg/kg
- Lead not more than 100 mg/kg

4 Copper-containing oral nutritional compounds and injectable forms of copper

4.1 Copper sulfate pentahydrate \((\text{CuSO}_4 \cdot 5\text{H}_2\text{O})\)

The minimum standard for copper sulfate pentahydrate is:
- Copper sulfate pentahydrate not less than 980 g/kg
- Lead not more than 50 mg/kg
ANNEX THREE:
SHELF LIFE EXEMPTIONS FOR VETERINARY MEDICINES

The following compounds, pure or in any combination with each other or with inert excipients compounded for sale as a trade name product, are considered appropriate for an application of exemption from conducting stability studies:

1. Copper sulphate (any degree of hydration) for external treatment
2. Zinc sulphate (any degree of hydration) for external treatment
3. Sodium chloride-based salt licks
4. Magnesium sulphate (any degree of hydration) for external treatment
5. Magnesium chloride for external treatment
6. Alcohol ethoxylate and alcohol propylate polymers for bloat treatment or mixtures of these compounds in any proportion
### ANNEX FOUR:
**RECOMMENDED CHEMICAL AND PHYSICAL PARAMETERS FOR STABILITY STUDIES BASED ON DOSAGE FORM**

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Recommended Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosols (pressurised pharmaceutical preparations)</td>
<td>Active constituent assay&lt;br&gt;Preservative content (where appropriate)&lt;br&gt;Delivered dose or dose per actuation&lt;br&gt;Particle size distribution (suspensions)&lt;br&gt;Number of metered doses&lt;br&gt;Loss in weight&lt;br&gt;Valve corrosion</td>
</tr>
<tr>
<td>Capsules</td>
<td>Appearance&lt;br&gt;Capsule integrity (leakage for soft-gelatin capsules, brittleness for hard-gelatin capsules)&lt;br&gt;Uniformity of content/mass&lt;br&gt;Active constituent assay&lt;br&gt;Impurities (where appropriate)&lt;br&gt;Disintegration time&lt;br&gt;Dissolution profile (where appropriate)</td>
</tr>
<tr>
<td>Collars</td>
<td>Appearance&lt;br&gt;Uniformity of content/mass&lt;br&gt;Active constituent assay&lt;br&gt;Dissolution profile (release of active constituent from the inert matrix)</td>
</tr>
<tr>
<td>Dipping/jetting formulations</td>
<td>Appearance&lt;br&gt;Active constituent assay&lt;br&gt;Water dispersibility&lt;br&gt;Suspensibility&lt;br&gt;Wet sieve (suspensions)&lt;br&gt;Persistent foam</td>
</tr>
<tr>
<td>Emulsions</td>
<td>Appearance&lt;br&gt;Homogeneity (extent of separation, ease of reconstitution)&lt;br&gt;Active constituent assay&lt;br&gt;Preservative content (where appropriate)&lt;br&gt;pH&lt;br&gt;Viscosity&lt;br&gt;Effect of freezing</td>
</tr>
<tr>
<td>Granules</td>
<td>Appearance&lt;br&gt;Active constituent assay&lt;br&gt;Particle size distribution/dustiness&lt;br&gt;Moisture content&lt;br&gt;Dissolution profile (where appropriate)</td>
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<tr>
<td>Implants</td>
<td>Appearance</td>
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<tr>
<td>(sub-cutaneous, intravaginal)</td>
<td>Active constituent assay</td>
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<td>Uniformity of content/mass</td>
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<td></td>
<td>Hardness</td>
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<td></td>
<td>Friability</td>
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<td></td>
<td>Moisture content (where appropriate)</td>
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<td></td>
<td>Dissolution profile (release of the active constituent from the inert matrix)</td>
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<table>
<thead>
<tr>
<th>Injectables</th>
<th>Appearance, colour, clarity</th>
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<tr>
<td></td>
<td>Particulate matter</td>
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<tr>
<td></td>
<td>Re-suspenability (where appropriate)</td>
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<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>Impurities (where appropriate)</td>
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<td>Preservative content (where appropriate)</td>
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<td>Sterility</td>
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<td></td>
<td>Endotoxins (where appropriate)</td>
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<td></td>
<td>Pyrogens /pyrogenicity</td>
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<tr>
<td></td>
<td>pH</td>
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<td></td>
<td>Syringeability (where appropriate)</td>
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<td></td>
<td>Effects of freezing</td>
</tr>
<tr>
<td></td>
<td>Interactions with the closure (store some containers in the inverted position)</td>
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<tr>
<td><strong>Note:</strong> For formulations packaged in multi-dose containers, in-use (broached vial) testing is required.</td>
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<thead>
<tr>
<th>Mastitis products</th>
<th>Appearance</th>
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<tr>
<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>pH</td>
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<td></td>
<td>Suspenability</td>
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<tr>
<td></td>
<td>Viscosity</td>
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<tr>
<td></td>
<td>Syringeability (where appropriate)</td>
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<td></td>
<td>Effects of freezing</td>
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<thead>
<tr>
<th>Medicated shampoos</th>
<th>Appearance</th>
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<tr>
<td></td>
<td>Active constituent assay</td>
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<tr>
<td></td>
<td>Viscosity (where appropriate)</td>
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<table>
<thead>
<tr>
<th>Powders</th>
<th>Appearance</th>
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<tr>
<td></td>
<td>Active constituent assay</td>
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<tr>
<td></td>
<td>Moisture content (where appropriate)</td>
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</table>

<table>
<thead>
<tr>
<th>Solutions</th>
<th>Appearance (e.g. cloudiness, precipitation)</th>
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<tbody>
<tr>
<td></td>
<td>Clarity of solution</td>
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<td></td>
<td>pH</td>
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<tr>
<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>Impurity content (where appropriate)</td>
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<td></td>
<td>Preservative efficacy (where appropriate)</td>
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<td></td>
<td>Sterility (where appropriate)</td>
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<td></td>
<td>Viscosity (where appropriate)</td>
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<td></td>
<td>Specific gravity (where appropriate)</td>
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<td>Effects of freezing</td>
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<tr>
<td>Powders for injection</td>
<td>Appearance</td>
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<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>pH value for reconstituted solution</td>
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<td></td>
<td>Completeness of solution or dispersion</td>
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<tr>
<td>Suppositories</td>
<td>Appearance</td>
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<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>Softening range</td>
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<td></td>
<td>Dissolution</td>
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<tr>
<td>Suspensions</td>
<td>Appearance</td>
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<td></td>
<td>pH</td>
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<tr>
<td></td>
<td>Re-suspendibility</td>
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<tr>
<td></td>
<td>Viscosity (where appropriate)</td>
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<tr>
<td></td>
<td>Active constituent assay</td>
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<td></td>
<td>Effects of freezing</td>
</tr>
<tr>
<td></td>
<td>Particle size distribution (where appropriate)</td>
</tr>
<tr>
<td>Tablets</td>
<td>Appearance</td>
</tr>
<tr>
<td></td>
<td>Average weight</td>
</tr>
<tr>
<td></td>
<td>Active constituent assay</td>
</tr>
<tr>
<td></td>
<td>Impurities (where appropriate)</td>
</tr>
<tr>
<td></td>
<td>Moisture content</td>
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<tr>
<td></td>
<td>Tablet hardness</td>
</tr>
<tr>
<td></td>
<td>Friability (uncoated tablets)</td>
</tr>
<tr>
<td></td>
<td>Disintegration time</td>
</tr>
<tr>
<td></td>
<td>Dissolution profile (where appropriate)</td>
</tr>
<tr>
<td></td>
<td>Uniformity of content/mass</td>
</tr>
<tr>
<td>Note: For chewable tablets, testing for disintegration time and dissolution profile is not required.</td>
<td></td>
</tr>
<tr>
<td>Topical and ophthalmic preparations (powders, ointments, creams, lotions, gels and pastes)</td>
<td>Appearance, colour, clarity and odour</td>
</tr>
<tr>
<td></td>
<td>Homogeneity (extent of separation, ease of reconstitution)</td>
</tr>
<tr>
<td></td>
<td>Product consistency</td>
</tr>
<tr>
<td></td>
<td>Active constituent assay</td>
</tr>
<tr>
<td></td>
<td>Preservative content (where appropriate)</td>
</tr>
<tr>
<td></td>
<td>pH value</td>
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<tr>
<td></td>
<td>Resuspendability (lotions)</td>
</tr>
<tr>
<td></td>
<td>Effect of freezing</td>
</tr>
<tr>
<td>Note: For eye ointments, testing for sterility is required.</td>
<td></td>
</tr>
</tbody>
</table>