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ACVM REGISTRATION STANDARD AND GUIDELINE FOR THE CHEMISTRY OF VERTEBRATE TOXIC AGENTS

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Endorsement:
Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR THE CHEMISTRY OF VERTEBRATE TOXIC AGENTS

1 INTRODUCTION

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

The standard is compulsory for applications to register a trade name vertebrate toxic agent, 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 vertebrate toxic agent, or to vary the conditions on a registered vertebrate toxic agent.
The standard provides specifications for:

- formulation and ingredient requirements
- manufacturing requirements (of final product)
- specifications (of final product)
- 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 vertebrate toxic agent.

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
- fulfiling 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 vertebrate toxic agent, 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 or vertebrate toxic agent 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

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.

EuPh
European Pharmacopoeia

Excipient
All other intentionally added components of a vertebrate toxic agent excepting those active ingredients upon which the biological activity is dependent as defined above. Also known as formulants, 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 vertebrate toxic agent, '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 vertebrate toxic agent for the purposes of sale.

Manufacturer
Any person who manufactures a vertebrate toxic agent.

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 vertebrate toxic agent) 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 vertebrate toxic agent 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.

Vertebrate toxic agent
Any substance, mixture of substances or biological compound used, or intended for use, to kill or reduce the viability of vertebrate animals. It does not include attractant or repellent substances that are not toxic.

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

1.3 Units

All units should preferably be SI units.

1.4 References

- *ACVM Registration Information Requirements for Vertebrate Toxic Agents in New Zealand*
- *ACVM Standard for Good Manufacturing Practice*
- *ACVM Guideline for Good Manufacturing Practice*
- *ACVM Guidelines for Information Waivers*

2 FORMULATION AND INGREDIENT REQUIREMENTS

2.1 Formulation type

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

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.

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

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

2.3.2.1 The active ingredient specification must include:

- **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 manufacturing site, this must be provided for each site separately;**
- **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).**

NB: Should the active ingredient have pharmacopocial standard, then details of this standard can be substituted in lieu of the above.

2.3.2.2 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.

2.3.2.3 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 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 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.

2.4 Excipient (non-active ingredient) requirements

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

- **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 The applicant must address the issue of impurities present in the non-active ingredient(s):

- **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.

(a) Active ingredient content
The active content should be at least within the following tolerances[#].

Declared content g/kg or g/L at 20°C	**Tolerance**
Up to 25	**± 15% of the declared content for homogeneous formulations (EC, SC, SL, etc.), or ± 25% for heterogeneous formulations (GR, WG, etc.)**
Above 25 Up to 100	**± 10% of the declared content**
Above 100 Up to 250	**± 6% of the declared content**
Above 250 Up to 500	**± 5% of the declared content**
Above 500	**± 25 g/kg or g/L**

As accepted by the FAO group of experts.

Where the proposed release or expiry (see section 4.2) specifications for an active substance are outside the above tolerances then this must be fully justified. Where the formulation contains more than one active ingredient, specifications must be provided for all active ingredients present.

(b) Impurity content
Where the impurity is one specified (see section 2.3.2.2) or derives from the active ingredient or an excipient and significantly increases the toxicity of the trade name product. Examples of this are organophosphorus compounds, which may oxidise or hydrolyse to the more toxic oxygen analogue, sulphinyl or sulphone form or to a more toxic organophosphorus ester.

(c) Chemical and physical characteristics
Appropriate chemical and physical characteristics of the product such as colour, state, density, sedimentation and appearance. See Annex 3 for recommended parameters.

4.2 Expiry specifications

These specifications are the limits within which the product must be maintained during its shelf life. These will be generally either the same as the release specifications or a justifiable wider specification. The appropriate specifications would usually include the parameters outlined above and any appropriate limits for degradation products.

The expiry (shelf life) specifications for the trade name product at the end of its claimed shelf life must be provided and justified.

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

'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 vertebrate toxic agent 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 vertebrate toxic agents 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 formulation type are given in Annex 3. 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 applicable only to vertebrate toxic agents that are subject to practical sub-ambient storage conditions. This applies to any vertebrate toxic agent 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

5.5.1 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 vertebrate toxic agents 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

OECD: Guidelines for Testing of Chemicals 1981.

APPENDIX

SAMPLE DECLARATION FOR EXEMPTION FROM STABILITY STUDIES FOR FORMULATIONS CONTAINING VERTEBRATE TOXIC AGENTS

< company letterhead>

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

I *<name of signer>* declare for the product *<product name>*, being a vertebrate toxic agent 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 Vertebrate Toxic Agents* 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

Aerosol:	A container-held formulation that is dispersed generally as a propellant as fine droplets/particles upon the actuation of a valve.
Bait concentrate:	A solid or liquid intended for dilution before use as a bait.
Bait (ready to use):	A formulation designed to attract and be eaten by the target pest (includes grain baits).
Dustable powder:	A free flowing powder, suitable for dusting.
Emulsifiable concentrate:	Liquid homogeneous formulation with emulsifiers in an organic solvent that forms a dispersion when added to water as a diluent.
Emulsifiable suspension:	A stable emulsion for application to the seed either directly or after dilution.
Gas:	A gas packed in a pressure bottle or pressure tank.
Gas generating product:	A product that generates gas by chemical reaction.
Gel:	A homogeneous, gelatinous formulation to be applied as an emulsion after dilution in water.
Granule:	Solid formulation comprising particles of defined size (>80µm diameter) for application without further dilution, usually to soil.
Grease:	Very viscous formulation based on oil, solvent or fat.
Liquids (ready to use):	Self defining
Paste:	Water-based, film forming composition.
Soluble concentrate:	A liquid, homogeneous formulation to be applied as a true solution of the active ingredient after dilution in water.
Suspension concentrate:	A stable suspension of active ingredient(s) in a fluid, which may contain other dissolved active ingredient(s), intended for dilution with water before use.
Tablet:	Solid formulation in the form of small, flat plates for dissolution in water.
Technical concentrate:	A technical material either in solution or diluted with solid adjuvants for use only in the preparation of formulations.
Technical material:	A material resulting from a manufacturing process comprising the active ingredient together with associated impurities. This may contain small amounts of necessary additives.
Vapour releasing product:	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.
Wettable powder:	A powder formulation to be applied as a suspension after dispersion in water.

ANNEX TWO:

SHELF LIFE EXEMPTIONS FOR VERTEBRATE TOXIC AGENTS

Currently there are no exemptions for vertebrate toxic agents.

ANNEX THREE:
RECOMMENDED CHEMICAL AND PHYSICAL PARAMETERS FOR STABILITY STUDIES BASED ON FORMULATION TYPE

Any variations from the tests must be explained and justified.
In some cases it may be applicable to test for additional parameters.
If the formulation type is not listed below, use the one that bears the closest resemblance to the formulation type required, bearing in mind it might be appropriate to add additional parameters.
Collaborative International Pesticide Analytical Council (CIPAC) methods are published in the *CIPAC Handbook*s, details of the CIPAC handbooks may be obtained from Black Bear Press, Kings Hedges Road, Cambridge, U.K.

AEROSOL

Recommended Test Parameters	Relevant CIPAC Method/Comments
Active content	Appropriate validated method
Packaging stability	Observation of packaging stability (no corrosion and no nozzle blockage)

BAITS: INCLUDING BAIT CONCENTRATE, BAIT (READY TO USE)

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	Observation of physical appearance are required e.g. sedimentation
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Retention of palatability	Only required if significant physical changes were observed on storage
Packaging stability	Observation of packaging stability and integrity

DUSTABLE POWDER

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Dry sieve test	MT 59.1
Particle size distribution	OECD 110
Packaging stability	Observation of packaging stability; there should be no caking in the pack on storage

EMULSIFIABLE CONCENTRATE

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Emulsion characteristics	MT 36.1, MT 36.2 or MT 173
Packaging stability	Observation of packaging stability

GEL

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	Evidence the physical state has been maintained and there has been no phase separation
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Kinematic viscosity	MT 22, OECD 114
Miscibility	Only required if to be dispersed in water
Emulsion characteristics	MT 36.1, MT 36.2 or MT 173; only required if to be emulsified in water
Wet sieve test	MT 59.3; Only required if to be dispersed in water
Suspensibility	MT 160; Only required if to be suspended in water
Packaging stability	Observation of packaging stability

GRANULES

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Particle size distribution	MT 58.*2* or 58.3
Dust content	MT 171
Friability and attrition characteristics	MT 178
Release rate of active constituent	Suitable validated method/ Only applicable to controlled release granules
Packaging stability	Observation of packaging stability; there should be no loss of granule integrity or caking on storage

LIQUID (READY TO USE)

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Packaging stability	Observation of packaging stability

SOLUBLE CONCENTRATE

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Packaging stability	Observation of packaging stability

SUSPENSION CONCENTRATE

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Pourability	MT 148
Suspensibility	MT 161
Spontaneity of dispersion	MT 160
Wet sieve test	MT 59.3
Packaging stability	Observation of packaging stability to include a statement on claying, sedimentation and re-dispersiblity.

TABLETS

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Tablet Integrity	The data should demonstrate the mechanical robustness of the tablets
Degree of dissolution and solution stability *	MT 179
Suspensibility #	MT 168
Wet sieve test	MT 167
Disintegration time	
Packaging stability	Observation of packaging stability

* Where the table is water-soluble then degree of dissolution and solution stability should also be tested.
# Where the tablet is water-dispersible, then suspensibility should also be tested.

WETTABLE POWDER

Recommended Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 31 or MT 75
Wet sieve test*	MT 59.3
Suspensibility*	MT 15.1 and MT 177
Wettability*	MT 53.3
Dissolution of water-soluble bags	MT 176/ Only for the product packaged in a sealed water soluble bag
Packaging stability	Observation of packaging stability; include a statement on caking on storage

*Where the product is packaged in a water-soluble bag, then the wet sieve test, suspensibility and wettability test must be carried using a solution of the product and water-soluble bag in the actual ratio of application.