Ministry for Primary Industries
Manatū Ahu Matua

Guidance Document

Chemistry and Manufacturing Information for Agricultural Chemicals

Application information for registration under the Agricultural Compounds and Veterinary Medicines Act 1997

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Title

Guidance Document: Chemistry and Manufacturing Information for Agricultural Chemicals

About this document

This document explains the chemistry and manufacturing information that should accompany an application to register or vary a registration of an agricultural chemical trade name product under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

Related Requirements

Document history

Version Date	Sections changed	Change(s) Description
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1 Purpose

This document explains the minimum information needed for MPI to consider the chemistry and manufacturing component of an application to register an agricultural chemical under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

2 Background

Before being imported, manufactured, sold or used in New Zealand, agricultural chemicals must be authorised under the ACVM Act. Authorisation is required:

- to manage risks to trade in primary produce, public health, animal welfare, and agricultural security
- to make sure that the use of agricultural compounds does not result in breaches of domestic food residue standards, and
- to ensure the provision of sufficient consumer information.

If the authorisation required for your agricultural chemical product is registration, the following is guidance to the minimum information that should accompany an application for a new product. For a variation to an existing registered product, less information may be required than for a new product.

3 Definitions

accelerated stability testing means testing of the final trade name product, in the container(s) and closure system intended for market, at exaggerated storage conditions designed to increase the rate of chemical or physical degradation of a formulation

active ingredient means the chemical(s) or microbial active ingredient(s) in a formulated product that is/are principally responsible for the effect being claimed and is/are distinct from other formulation components such as surfactants, carriers or diluents

active ingredient manufacturer means any site of manufacture that produces one or more of the active ingredients intended for use in the manufacture of the trade name product

active ingredient specification means a set of testing and assay parameters signed and dated by the manufacturer used to establish the quality and consistent manufacture of the active ingredient. Active ingredient specifications include, but are not limited to, a physical description of the active ingredient, tests for the identity of the compound, maximum and minimum limits of purity, the maximum levels of individual contaminants, and any other parameters applicable to that compound. Note: Certificates of Analysis, certificates of conformance and safety data sheets do not constitute an active ingredient specification

agricultural chemical means a subset of agricultural compound that is any substance, mixture of substances or biological compounds that are applied to plants or to land, places or water in which plants or animals are managed for the purpose of managing the animals or plants or to indirectly manage an animal

agricultural compound means 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 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 means a defined quantity of an active ingredient, formulated trade name product, or other material that is intended to have uniform character and quality within specified limits, and is produced according to a specified and validated manufacturing process during the same cycle of manufacture

CAS number means the Chemical Abstracts Service (CAS) number that serves as a specific and unique identifier for a particular chemical compound

chemistry means the chemical identity, properties, specifications, methods of analysis, purity, identity of impurities, and all other physicochemical parameters of an ingredient, combination of ingredients, or formulation

degradation product means an impurity resulting from a chemical change in the substance brought about during manufacture and/or storage of the product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient

excipient ingredient means a substance intentionally added to a formulation to manage or enhance characteristics of the formulation itself. Also known as formulants, inert or non-active ingredients

expiration date means the date placed on the container label of the trade name product designating the time prior to which a batch of product is expected to remain within the approved shelf life, if stored under defined conditions, after which it must not be used

expiry specification means the combination of physical, chemical, biological, microbiological tests and acceptance criteria that determine the suitability of the trade name product throughout its retest period, or that a trade name product should meet throughout its shelf life

finished product means the final packaged formulated trade name product available for sale at any time between market release from the manufacturing process and the time of expiry (of the shelf life)

formulation means the list of all the ingredients and concentrations that, added together, comprise the final formulated trade name product. The formulation composition describes the qualitative and quantitative formulation of the product. The formulation contains one or more active ingredient(s), and may contain excipient ingredients

impurity means any component of a formulation that is not a chemical entity defined in the formulation. Impurities include reaction products, degradation products, contaminants or chemicals added for purposes of extraction or purification

laboratory scale batch means a very small batch of product (smaller than pilot scale) produced at the research and development stage used to support formulation and package development

manufacture means the entire process of producing a trade name product from acquisition of starting materials to release for supply. The manufacture of an agricultural chemical includes all the following aspects: acquiring starting materials, preparation or extraction, dispensing, mixing, blending, in-process controls and testing, packaging, labelling, and post-production testing for market release. Manufacture also includes repacking and relabelling, if applicable

manufacturing flow diagram means the graphical representation that describes the manufacturing process from dispensing to labelling, including quality control points, that is provided in the Product Data Sheet

overage means the excess of active ingredient deliberately added to a formulation to compensate for manufacturing loss or loss during storage

packing means all operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product

packaging material means any material, including printed material, employed in the packaging of a trade name product, excluding any outer packaging used for transportation or shipment

- **primary packaging** means those packaging materials that are in direct contact with the product (e.g., bags, blisters, bottles, vials, drums, packs etc.)
- **secondary packaging** means those packaging materials that enclose the primary packaging materials (e.g. cartons, bags, etc.) It is intended to protect not only the product, but also the primary packaging
- **outers and shippers** means those packaging materials used for transportation or shipment
- **recycled packaging** means new packaging that has been produced from recycled materials
- **reused packaging** means used packaging that has been cleaned and inspected as being fit for purpose

pilot scale batch means a batch of product manufactured by a procedure fully representative of and simulating that to be applied to full production scale. This includes equipment, manufacturing site, manufacturing procedures, in-process controls and post production testing

production scale batch means a batch of product that will be produced using equipment, controls, and processes at the manufacturing site(s) proposed in the application, at a volume sufficient to allow for the routine manufacturing of the trade name product for the commercial market

real time stability testing means testing of the final trade name product, in the container(s) and closure system intended for market, at the storage conditions intended for end user storage throughout the proposed shelf life

related substance means an impurity that is structurally similar to an active ingredient, with the similar physico-chemical and other major characteristics as the active ingredient

release for supply means a step of manufacture that ensures the TNP conforms to the approved product and manufacturing specifications after manufacture or importation, and before entering the distribution chain for sale in the New Zealand market. Release for supply involves a comprehensive review of batch and related records to ensure that the approved process has been followed, and that all starting materials (including packaging), intermediate and finished product comply with the approved specifications. For products entering New Zealand it includes a verification check that the imported batch(es) comply and have not been impacted during transit

release specification means the combination of physical, chemical, biological, microbiological tests and acceptance criteria that determine the suitability of the trade name product at the time of its release

self assessable change means a change MPI allows a registrant to make to a registered TNP without prior MPI assessment or approval. These changes must be notified to MPI in accordance with this guidance

shelf life means 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 means a specific assay or testing parameter that establishes a defined acceptable limit or range for a particular characteristic of a substance, material, or formulation

stability means the ability of a substance, material, or formulation to conform to a defined set of acceptable parameters. The stability of a trade name product is denoted by adherence to the active ingredient content, impurity specifications (where applicable), and physicochemical characteristics as specified at the time of manufacture and maintained throughout the shelf life of the trade name product within the specified range established by the expiry specification

trade name product (TNP) means an agricultural compound identified and packaged under a trade name for a specified use or uses

4 Information needed

The minimum information MPI considers necessary is numbered in each section, while any further guidelines are given (without numbers) at the end of a section under '**Additional guidance**'. The guidance reflects principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. MPI recognises that there are acceptable methods, other than those described in this guideline, that are capable of achieving the principles of this document.

Applicants are responsible for providing all information required by MPI to make a decision on the application. Applications that do not contain the required information will not be assessed. If further advice is required you are advised to contract the services of an appropriate consultant prior to submitting your application.

Applicants may deviate from the requirements outlined in this guidance, but must identify and justify any such deviations with sound technical argument and supporting information.

Any of the following changes made to a registered trade name product will prompt a new registration:

a) addition, substitution or deletion of an active ingredient;
b) change in formulation type;
c) change in formulation/multiple formulations that changes the risk profile of the trade name product.

Other factors may require a new registration, but these will be assessed on a case by case basis.

4.1 Units

All units should preferably be SI units.

4.2 Dossiers

When compiling a dossier for submission to support the registration of a new product, the applicant must consider the current state of agricultural chemical development and knowledge, and include the most up to date methods and information available as applicable to the product and formulation type.

The dossier must include all information that is relevant to the evaluation of the chemistry and manufacture of the trade name product proposed for registration in the submission. Where available, all relevant data and information must be provided regardless of whether the information is favourable or unfavourable to the particulars of the application. This means that any available information that may impact the risk assessment of the product, such as stability results that do not conform to specification and/or the nominated shelf life, should be included for review.

If the product is currently or has previously been registered by an overseas authority, provide any relevant information on product defects or manufacturing issues that may impact the risk profile of the product.

Each section of the dossier must be sequentially paginated throughout, legible, and logically organised as described in the **E-files for ACVM applications** guideline.

5 General information

(1) This guideline applies to all new product registrations (excluding B1 registrations) and all changes in formulation applied to existing registrations. The guideline covers:

a) Active Ingredient
b) Formulated Product
c) Manufacturing
d) Stability Studies
e) Analytical Methods.

(2) Provide all documentation in English.

(3) Provide justification if you do not include required information.

(4) For more guidance, use the FAO, APVMA, OECD guidance documents:

a) FAO documents
http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/manual/en/
b) APVMA documents
http://apvma.gov.au/
c) OECD document
http://www.oecd.org/chemicalsafety/pesticides-biocides/oecdguidancedocumentsforpesticideregistration.htm

Additional guidance
Deviations may be granted to reduce data that an applicant must submit.

Applicants can make deviation applications to MPI for approval prior to submitting an application.

6 Registration of a new trade name product

This section sets out the chemistry and manufacturing data that should be submitted in support of an application to register a new agricultural chemical product. These data apply to products produced by chemical synthesis. For data requirements for products produced by microbial origin see the **Guidance Document for Microbial Agricultural Chemicals**.

6.1 Active Ingredient

6.1.1 Manufacturer

An active ingredient manufacturer is any site of manufacture that produces an ingredient defined as an active ingredient and that complies with the active ingredient specification in the proposed trade name product. The following information applies to all active ingredient manufacturers.

(1) Provide sufficient information from each manufacturing site to identify:

a) the name of the organisation
b) the postal address
c) the physical address of the manufacturing site
d) site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)

(2) An intermediate supplier who is used to procure or test the ingredient prior to inclusion in the formulated product is not the manufacturer of the ingredient and must not be identified as the active ingredient manufacturer.

(3) The following ingredients are exempt from the requirements of notifying the manufacturer:

a) calcium carbonate
b) copper sulphate (any degree of hydration)
c) copper oxychloride, copper hydroxide

d) sulphur
e) food quality ingredients.

Evidence of a quality system must be provided for these actives if the manufacturer is not provided. A quality system should provide assurance that the active will meet ACVM approved specifications prior to its inclusion in the formulated product.

An internal record of the active manufacturers used and batch analysis certificates, which confirm that the active is fit for purpose, must be available for immediate inspection.

6.1.2 Identification and chemical structure

(1) Provide sufficient information to identify:

a) the chemical or IUPAC, ISO and common (INN) or proposed name
b) the chemical abstracts service (CAS) registry number (if assigned)
c) the manufacturer's code number(s) and/or synonyms
d) for active ingredients that are salts or hydrates, also provide the molecular mass of the free base/acid or anhydrous form
e) for polymeric compounds, provide weight average (M_w), number average, molecular weight (M_n) and molecular weight distribution
f) empirical molecular formula and molecular weight
g) two dimensional chemical structure.

If relevant, the structural formula should include stereochemical properties of the active ingredient. For example: geometric isomerism (*cis/trans*, *E/Z*), the number of chiral centres and the configuration of each centre. The structural formula should be given diagrammatically with all possible or known stereochemistry.

(2) Refer to section 6.1.1 for a list of active ingredients that are exempt from notification of the manufacturer, and the alternative information that needs to be provided for them.

6.1.3 Physical and chemical properties

(1) All relevant chemical and physical properties of the active ingredient should be provided. The ACVM team aligns with the APVMA on the data that should be provided. The information should include, as appropriate:

a) a general description, for example, appearance, colour, odour, physical state
b) the stereochemical properties of the molecule, for example geometric isomerism, number of chiral centres and configuration at each centre
c) if a new active ingredient contains one or more chiral centres, a specification of whether the active ingredient is a pure enantiomer, racemate or fixed combination of non-enantiomeric isomers
d) if a new active ingredient contains geometric isomers (cis/trans, E/Z), a specification of whether the active ingredient is a pure geometric isomer, or a fixed combination of geometric isomers
e) if the active ingredient is optically active, a specific optical rotation measurement with limits
f) the melting point or range (for solids)
g) the boiling point or range (for liquids)
h) if the melting and/or boiling point cannot be determined because of decomposition or sublimation, the temperature at which decomposition or sublimation occurs
i) the condensation point (for gases)
j) the refractive index (for liquids)
k) the density or specific gravity(for liquids)
l) the UV absorption maxima and molar absorptivity
m) the pH and pKa values
n) the vapour pressure
o) Henry's Law Constant

p) the solubility in water expressed as g/L or mg/L, in the neutral range, acidic range (pH 4 to 6) and in the alkaline range (pH 8 to 10)
q) the solubility in various organic solvents expressed as g/L or mg/L
r) the n-octanol/water partition coefficient (Kow)
s) the hydrolysis in aqueous solution under acid, neutral and basic conditions
t) the dissociation characteristics including dissociation constant, if appropriate
u) the flash point (where the melting point is below 40˚C)
v) the flammability including auto-flammability
w) explosive properties
x) photochemical properties
y) oxidising properties
z) the auto-ignition temperature
aa) corrosion characteristics

The purity of the test substance used to generate the physical and chemical properties should be stated.

You should also describe the methods used to generate the data provided. Where the method used is described in a scientifically recognised publication or manual—for example, those by the Organization for Economic Cooperation and Development (OECD), the Collaborative International Pesticide Analytical Council (CIPAC), or the American Society for Testing Materials (ASTM)—a reference to the relevant publication will suffice.

It is desirable that physical properties such as solubility in water and vapour pressure be determined from tests conducted at ambient temperature (20–25˚C). However, if data are available at another temperature, these may be provided. The temperature at which these tests were conducted, or other relevant test conditions, should be stated.

6.1.4 Specifications for active ingredients

(1) Provide sufficient information to identify the manufacturer's specifications – including minimum purity, isomeric ranges or ratio (where applicable) and maximum impurity content.

(2) Specifications must be consistent throughout the documentation e.g. the Declaration of Composition and Certification of Analysis should be identical.

(3) If there is difficulty in defining the active ingredient, as with some complex plant/herbal extracts, it may be challenging to adequately control the ingredient through quantitative specifications. In this case, a combination of specifications and details of the manufacturing process must be established to adequately characterise the active ingredients.

(4) MPI harmonises with the following agencies for standards for an active ingredient (in this order): NZ EPA, APVMA, FAO.

(5) Any deviation from conforming to the NZ EPA, APVMA or FAO specifications will need to be supported by technical argument. If there are no specifications from any agencies above, information or an argument needs to be supplied for the specifications chosen.

6.1.5 Active ingredient impurities

(1) You must identify and report on significant impurities under the following conditions:

a) greater than or equal to 10g/kg (1%) regardless of toxicity/ecotoxicity
b) Toxicologically significant impurities at any level must be identified, characterised and quantified

c) Any impurities where toxicity/ecotoxicity is unknown must be identified, characterised and quantified

(2) Provide sufficient information on impurities to identify:

a) Name
b) Structural formulae
c) CAS number (if available)
d) quantity (SI units)
e) maximum allowable limit.

(3) The likelihood of compounds such as dioxins, dibenzofurans, hexachlorobenzene and nitrosamines being present should be considered.

(4) Picloram – MPI has its own requirements which supersede all other agencies – the hexachorobenzene impurity must be less than 50 mg/kg (50 ppm or 0.05 g/kg or 0.005%). This standard is based on local New Zealand data for forage feed uses.

Potential sources of impurities or related substances include:

- Impurities in the starting materials
- Residual solvents, reagents or immediate precursors
- Trace elements arising from the use of catalysts or other sources
- The degradation of the active ingredient that may occur after manufacture
- The amount of water or moisture present
- The amount of solvent left after final purification

Additional guidance: Impurities of toxicological significance

A general list of toxicologically significant impurities for active ingredients is available on the APVMA standards for active ingredients page of the APVMA website.

If there is potential for the formation of toxicologically significant impurities or by-products this must be declared and quantified. You should also provide details of the conditions leading to their formation and the steps taken to control the formation of toxicologically significant impurities.

6.1.6 Manufacturing concentrate

(1) A manufacturing concentrate is a form of active ingredient that contains intentionally added inert ingredients such as stabilisers or solvents. Provide the following information:

a) final concentration of active ingredient present
b) methods used to confirm the active concentration
c) identification of diluents and/or additives uses, and their concentrations.

6.1.7 Additives

(1) Identify the purpose and specifications of additives such as stabilisers and emetics.

6.1.8 Batch analysis

(1) Provide three recent individual batch analyses of batches of the active ingredient for each site of manufacture. At least one of these batches must be commercial scale. At least one batch must be produced in the last 2 years.

(2) Each batch analysis must include

a) The active ingredient clearly identified
b) the date of manufacture
c) the date of analysis
d) batch size
e) batch number
f) site of manufacture (company name and physical address)
g) results for appropriate parameters such as active content and impurities, using appropriate determinative analytical methods (including counter ions when present) – actual numerical results should be provided rather than vague statements such as 'within limits' or 'conforms'
h) content of toxicologically significant impurities (present at any level)
i) identification of the analytical method(s) used and the validation of these methods (see 6.1.10)
j) where applicable, chromatograms of the batches showing separation of impurities. Chromatograms should be clearly labelled with

i) batch numbers
ii) peak identity
iii) peak integration data
iv) a software-generated table with retention time and peak area of associated peaks

k) a copy of all raw data used to generate the final results.

(3) If none of the batches are commercial then a batch analysis is not from a commercial batch. Technical argument must be provided as to why a pilot or laboratory batch can be considered to be representative of a production batch. A commercial batch may still be required.

a) Data from pilot scale batches may be considered with appropriate technical justification as to why they are representative of production scale manufacture. The justification must include a discussion of differences (if any) in the manufacturing processes of pilot and full scale, including mixing times, temperatures, and equipment used. Providing only a statement that pilot batches are an acceptable representation of production scale will not be accepted.

(4) If the active ingredient is a manufacturing concentrate, the batch analysis must also include:

a) minimum concentration of the active ingredient in the manufacturing concentrate
b) minimum purity of active ingredient
c) maximum concentration of all impurities on a dry weight (solvent/additive free) basis
d) concentration of diluents and/or additives.

Additional guidance

To determine impurities in the active ingredient, reference standards should be prepared for each of the identified impurities, particularly those known to be toxic, and the concentration of impurities should be quantitated against their own reference standards.

It is acceptable to use the active ingredient of known purity as an external standard to estimate the levels of impurities (diluted to the appropriate concentration), provided the response factors of those impurities are sufficiently close (90 per cent or more) to that of the active ingredient. In cases where the response factor is not close, it may still be acceptable to use the active ingredient provided a

correction factor is applied. You should provide the rationale for when and how a correction factor is used.

The sum of the quantitative level of the active ingredient and impurities is often referred to as the mass balance. Mass balance is an important parameter in the batch analysis to ensure that all major impurities have been detected. The mass balance need not add up to exactly 100 per cent, because of the analytical error associated with each analytical procedure; however, it is expected to be in the range of 98–102 per cent.

6.1.9 Analytical methods

(1) You should provide full details of the test methods used for determining the active ingredient, all impurities at 1% and toxicologically significant impurities (even when present at less than 1%) in the active ingredient

(2) The following information should be included in a written analytical method:

a) A copy of the actual laboratory method. If this laboratory method is not in English, please include an English version
b) the principle of the method
c) the method summary
d) sample preparation techniques
e) equipment or reagents (for example, for chromatographic methods, details of the column include column name, manufacturer, packing material and dimensions)
f) eluent (including gradients, where applicable)
g) column temperature
h) detector and retention times of all components
i) purity of reference standard(s), source and batch number of reference standard(s)
j) where chromatographic techniques are used
    i) relevant chromatograms (blank, standard and sample) including retention times
    ii) peak-assignment and peak-integration data
    iii) original printouts from the chromatographic system which include retention times, peak areas and peak-height tables
k) worked examples of all calculations.

6.1.10 Validation data

You should provide validation data for the method(s) used to assay the active ingredients and impurities. If the method is a CIPAC or FAO method only selectivity and accuracy data are required. Address the following parameters, where appropriate:

- Selectivity or specificity
- Linearity
- Precision
- Recovery (accuracy)
- Limit of detection (LOD) and limit of quantitation (LOQ) for relevant impurities and all toxicologically significant impurities

Additional guidance

Note that LOD and LOQ are not required for the quantitation of the active ingredient, only the determination and quantitation of the impurities. ACVM harmonises with the APVMA on requirement for validation of analytical methods. Further information may be found on the APVMA website.

6.2 Formulation

6.2.1 Formulation type

(1) State the formulation type. Refer to Annex 1 for a description of formulation types. If the descriptions in Annex 1 do not appropriately describe your proposed formulation type, refer to the FAO/WHO guidelines (JMPS 2010) to provide a formulation type.

6.2.2 Formulation composition

(1) The declared formulation must be a complete and accurate list of the ingredients, their concentrations and their functions. Data presented should include:

a. the common or chemical names of the constituents and their identification or composition (trade names alone are not acceptable and should be accompanied with common or chemical names),

i. in some cases, safety data sheets (SDS) may be submitted in lieu of the manufacturer's CoA

ii. for proprietary non-active ingredients, specifications from the supplier— these may be supplied directly to the ACVM group

b. the Chemical Abstracts Service (CAS) Registry Number

c. the concentration of all active and non-active ingredients in the formulation

d. the purpose of the constituents in the formulation (for example, whether it is the active ingredient, a surfactant, an emulsifier or a filler).

(2) If possible, state a fixed quantity for each ingredient. If a range applies for the ingredient, state the maximum amount or nominal content, whichever applies, with a notation specifying how the range was determined. Explain the choice of a range instead of a fixed concentration of ingredient in the dossier with respect to the risk profile of the product.

A quantity sufficient (qs) designation may be used in place of ingredient quantity if that ingredient is added to an endpoint rather than a set nominal content; state the endpoint (e.g. qs to 1L).

(3) If an ingredient is added to the formulation as a separate precursor compound (e.g. the active ingredient is barium selenite but separate barium and selenium compounds are added), include the final compound (e.g. barium selenite) in the trade name product formulation table. The precursor compounds are to be listed in the manufacturing batch formula table (see section 6.2.2.) and the manufacturing process information (see section 6.3.3).

Based on the actual purity of the active ingredient and all non-active ingredients, you should adjust the formulation composition by calculating the concentration of constituent(s). For example, if the theoretical concentration of an active ingredient in a batch of product (that is, the label claim) is 275 grams per litre (g/L), and the purity of the technical active ingredient being used is 950 grams per kilogram (g/kg) (95 per cent weight per weight), then the factorised concentration of the technical active ingredient to be added would be:

275 g/L÷(950/1000)=289.5 g/L

Concentrations of technical active ingredients, together with the stated nominal concentration of active ingredient (and any overage), adjuvants, and inert constituents should be expressed in g/L for liquid formulations and g/kg for solid formulations. If these units are not appropriate for a particular formulation, the applicant should propose suitable units (for example, a biological unit).

Table 1: Example of a trade name product formulation table

Ingredient Name (Common or Chemical)	CAS Number	Quantity (g/L)	Function
Active Ingredient 1*	xxx-xx-xxxx	52.5	Active Ingredient
Active Ingredient 2	xxx-xx-xxxx	100	Active Ingredient
Excipient 1	xxx-xx-xxxx	2	Suspending agent
Excipient 2	xxx-xx-xxxx	15	Diluent
Excipient 3	xxx-xx-xxxx	1	Preservative
Excipient 4	xxx-xx-xxxx	2	Viscosity Modifier
Excipient 5	xxx-xx-xxxx	20	Surfactant
Excipient 6	xxx-xx-xxxx	0.05	Colourant
Water	7732-18-5	qs to 1L	Carrier
Specific gravity	1.120		
Other information about formulation (for example, overage, isomers)			
*Includes a 5% overage (2.5g/L) to manage loss on storage.			

Additional Guidance
If the product contains separate formulations such as coatings, show these as separate distinguishable formulations.

For excipients, ranges (rather than discrete) concentration values, may also be stated.

6.2.3 Physical and chemical properties of the product

(1) Where relevant, the following data on the physical and chemical properties of the product should be provided:
   a. appearance, colour, odour, physical state
   b. acidity, alkalinity or pH value
   c. bulk density (solids)
   d. density or specific gravity (liquids)
   e. viscosity and surface tension (liquids)
   f. relevant characteristics applicable to the particular formulation type (for example for wettable powder: suspensibility, wet sieve test, wettability and persistent foam)
   g. flash point
   h. flammability
   i. explosive properties
   j. oxidising properties
   k. corrosive hazard

6.2.4 Overage

(1) If an overage (small excess) of an active ingredient has been deliberately added, the actual concentration (nominal plus overage) must also be stated.

(2) Outline whether the overage is intended to cover losses during manufacture, storage, or both.

(3) Address any impacts on efficacy, safety or residues.

6.2.5 Ingredients of biological origin

(1) If any active or non-active ingredients used to formulate the product are of biological origin, and either the ingredient(s) or the finished product is being imported, a current MPI Biosecurity approval is required. If you are unsure whether an ingredient will require a Biosecurity approval (e.g. refined extracts), contact the Approvals team or the Biosecurity team directly for advice.

(2) If an approval already exists and is current, provide this with the application documents. If an approval does not already exist provide an application for Biosecurity approval, and all relevant documentation needed for the Biosecurity assessment, with the application to register.

6.2.6 Multiple formulations

(1) An alternative formulation can be registered if the proposed differences between formulations do not alter the following properties of the registered trade name product:

a) identity and concentration(s) of the active ingredient(s)
b) formulation type
c) hazard status of the product under the HSNO Act
d) physical and chemical characteristics of the formulated product to the extent that the risk profile under the ACVM Act changes.

(2) Where the manufacturing process, analytical methods, release/expiry specifications etc may be different, these must be provided and clearly marked as to which alternative formulation they are associated with.

(3) If multiple formulations are approved it must be clear in submitted documentation which manufacturer manufactures which formulation(s)

6.2.7 Excipient Ingredients (non-active ingredient)

Identification

(1) Provide sufficient information to identify:

a) chemical or IUPAC, ISO and common name
b) CAS registry number
c) The physical form in which the ingredient is used in formulation (e.g. anhydrous powder); and
d) The specific function of the excipient in the formulation

(2) If no CAS number has been assigned (or not applicable), supply full details of the excipient and include:

a) name
b) safety data sheet (SDS)

(3) If the excipient is a mixture, its full formulation information, including names, CAS numbers, and percentage of each component in the mixture must be provided.

(4) If the excipient is a proprietary mixture and details are not known to the registrant, provide formulation information for the proprietary mixture directly to MPI from the excipient's manufacturer in confidence.

(5) If the full formulation of the excipient is known, a specific excipient trade name is not required on the PDS if the exact excipient formulation details are provided in the PDS. The excipient may then be replaced by an excipient of identical composition.

Additional Guidance
If a trade name excipient that is a mixture is specified in the formulation, it cannot be exchanged for any other trade name excipient without approval by ACVM.

Impurities

(1) Identify, quantify (if appropriate), and report any impurities of toxicological/residue concern.

(2) Monitor and report toxicologically significant impurities present in the excipient ingredients in the product or formed during manufacture of the product and storage or migration of packaging material into the product.

(3) The likelihood of compounds such as dioxins, dibenzofurans, hexachlorobenzene and nitrosamines being present should be considered.

(4) Identify and quantify, if practical, any impurities present at greater than 10 g/kg in the excipients.

Critical excipients

(5) If an excipient is considered critical to the function of the final product, more information on that excipient may be required. A critical excipient would be one that has a direct impact on the efficacy, safety, or residue profile of the product by having a direct impact on the active ingredient's release, absorption, elimination, or any other aspect of the product's impact. An example of such an excipient would be a penetrant included in a herbicide product to increase the absorption of the active ingredients, the failure of which may negatively impact the product's efficacy.

6.2.8 Batch analysis

(1) Provide a minimum of one batch analysis, from a batch no more than 2 years old, for each site of manufacture.

a) The batch analysis can be from a laboratory, pilot or commercial production batch. Data from laboratory or pilot scale batches may be considered with appropriate technical justification as to why they are representative of production scale manufacture. The justification must include a discussion of differences (if any) in the manufacturing processes of pilot and full scale, including mixing times, temperatures, and equipment used. Providing only a statement that pilot batches are an acceptable representation of production scale will not be accepted.

(2) The time zero analysis from the stability study can be used as the batch analysis.

(3) Each batch analysis must include:

a) the date of manufacture
b) batch number
c) batch size
d) site of manufacture (company name and physical address)
e) results for all parameters included as release specifications, using the specified methods, and
f) identification of the analytical method(s) used.

(4) If batch analyses for production batches have not been supplied, MPI may require additional information post-registration under conditions of registration 86 and/or 101

(5) Report all results, including those that do not conform to an established specifications

6.2.9 Product specifications

Specification rationale

(1) Provide a rationale explaining how the specification proposed for the formulated product will manage the risks associated with the product's manufacture, storage, and use. This includes both the parameters being chosen and the value or range proposed as acceptable for those parameters.

(2) The rationale may refer to information obtained during product development, international guidelines (e.g. FAO), test data for active ingredients and formulated products used in toxicology, residues (if applicable) and analytical and manufacturing variability

(3) Discuss the criticality of each chosen parameter in the specification

(4) Base the value(s) chosen as the acceptable limits for each parameter on a risk assessment relative to the efficacy, safety, residue, and stability risk profile of the product and product type.

Release specifications

(1) These are the specifications which each batch of the product must meet before it is released for sale. They must include:

a) active ingredient content (including relevant impurities formed during manufacture)
b) relevant chemical and physical characteristics
c) toxicologically significant impurities.
d) methods used to test each parameter.

(2) Refer to Appendix 1 for parameters for each formulation type.

(3) The active ingredient content must be at least within the following tolerances:

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

*The tolerances stated refer to percentages of the declared (label) content. They are not cumulative e.g. the expiry tolerance of + 5% is considered against the active content stated on the label (100%) and not against the release specification (100% + 5%).

Note: In each range the upper limit is included (Sourced from JMPS, 2010)

(4) It is expected all parameters from Appendix 1 are included. If parameters are omitted, relevant scientific argument must be provided.

(5) If the formulation type is not listed in Appendix 1 or in the FAO/WHO guidelines (JMPS 2010) use the one that bears the closest resemblance to the formulation type required. In such cases consideration should be given to whether it may be appropriate to add additional parameters.

(6) Justification is required where the proposed specifications for an active ingredient are outside the above tolerances.

(7) For a formulation containing multiple active ingredients, specifications must be provided for each active ingredient.

(8) Packaging stability is not used as a release specification.

Expiry specifications

(1) These are the specifications which the product must remain within during the approved shelf life. They must include:

a) active ingredient content (including degradation products over storage)
b) relevant chemical and physical characteristics
c) methods used to test each parameter
d) Toxicologically significant impurities.

(2) Refer to Appendix 1 for parameters for each formulation type.

(3) The active ingredient content must be at least within the following tolerances:

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

*The tolerances stated refer to percentages of the declared (label) content. They are not cumulative e.g. the expiry tolerance of + 5% is considered against the active content stated on the label (100%) and not against the release specification (100% + 5%).

(4) It is expected all parameters from Annex 1 are included. If parameters are omitted, relevant scientific argument must be provided.

(5) If the formulation type is not listed in Annex 1 or in the FAO/WHO guidelines (JMPS 2010), use the one that bears the closest resemblance to the formulation type required. In such cases consideration should be given to whether it may be appropriate to add additional parameters.

(6) Justification is required where the proposed specifications for an active ingredient are outside the above tolerances.

(7) For a formulation containing multiple active ingredients, specifications must be provided for each active ingredient.

(8) Expiry specifications will usually be justifiably wider than release specifications, particularly where the formulation has a degree of instability. The reason for this is that if the product is released at the low end of the specification, and the release and expiry specifications are the same, there is a likelihood the expiry specifications will be breached during the product's shelf life.

Packaging specifications

(1) Provide sufficient information about the packaging to be marketed to detail:

a) size
b) shape
c) colour (where applicable for light sensitive products)
d) construction material
e) lining/layers

(2) If the formulated product has inherent chemical characteristics, and the packaging is designed to manage the associated risks, e.g. high acidity, comments on the packaging must be made. These could cover:

a) porosity
b) permeability
c) impact strength
d) closure type
e) stability (photolytic and hydrolytic stability of biodegradable packaging).

(3) Provide a description of the container closure system, including the composition of the construction materials of each primary packaging component and its specification. Identify and briefly discuss any specialised closure systems, such as tamper-resistant lids and multi-layer closure systems required to manage product-specific risks.

(4) New component packaging materials must be used unless approval for use of second hand materials is granted by MPI.

Additional Guidance
A pack size range can be requested. A pack size range may be approved if it is considered that there is no additional risk associated with pack sizes within the assessed range after consideration of the product, its specifications, and packaging-specific details such as construction materials.

Additional pack sizes within the approved range and specifications can be chosen and marketed without submitting stability data for assessment. An amended Product Data Sheet and label(s) identifying the new pack sizes and any new relevant label information will be required at the next variation or registration renewal to bring the product details current. If different from the container volume, specify the product fill volume.

6.2.10 Toxicologically significant impurities

(1) Where the concentration of toxicologically significant impurities is known to increase as the active ingredient degrades upon storage, the level of these impurities should be analysed at the commencement and completion of the relevant product storage stability study. The concentrations found after product storage should be in a proportionally appropriate concentration to meet the APVMA standard for the active ingredient. Examples of such products are those that are date-controlled (mancozeb, zineb, diazinon, dimethoate). However, where toxicologically significant impurities are the result of 'carry-through' from raw materials and/or as a by-product of the manufacturing process for the active ingredient and do not increase on storage, then no analysis of these impurities is needed in the relevant product stability study.

(2) An expiry date is required for products the active ingredients of which are associated with increases of impurities of toxicological concern during storage.

6.3 Manufacturing

6.3.1 Manufacturer of the trade name product

(1) Provide sufficient information from each site of manufacture to detail:

a) the name of the organisation
b) the postal address
c) the physical address
d) site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)

Information should be provided for all manufacturing facilities involving in any step of the manufacture of the product. This includes toll or contract manufacturers and subcontractors involved in packaging and labelling, and testing, up to and including release for supply.

6.3.2 Responsible manufacturer

(1) Provide sufficient information from each responsible manufacturer to detail:

a) the name of the organisation
b) the postal address
c) the physical address
d) A telephone number and/or email address (to enable MPI to quickly contact the manufacturer if necessary)

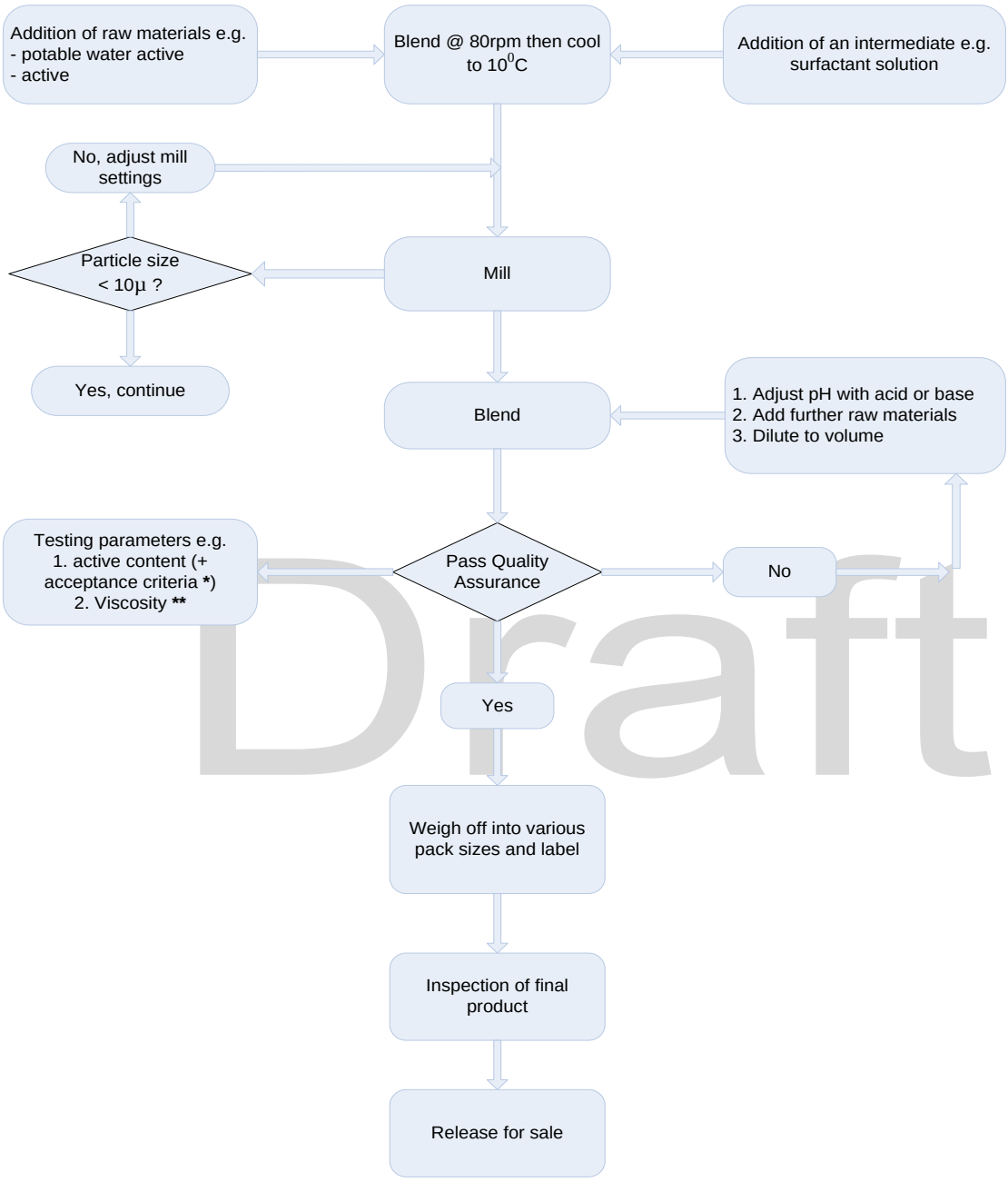
Additional Guidance
The responsible manufacturer is the entity who ensures the formulated agricultural chemical is in compliance with ACVM registration and releases the product for sale.

6.3.3 Manufacturing process

(1) Provide a description of all stages involved in the manufacturer of the trade name product, in the form of a simple flow diagram with explanations. The flow chart should have sufficient information to detail:

a) the entire manufacturing process, from raw materials through to the packaged and labelled product
b) the sequence of manufacturing steps
c) typical batch size
d) the process controls used during production to ensure the release specifications are met
e) where raw materials enter the manufacturing process
f) critical control points
g) in-process and final product quality control testing with references to the analytical method used
h) filling, packing and labelling description, and
i) final release for sale description.

Example of Manufacturing Flow Chart



***** Active concentration determined by HPLC method1 (reference section 7)
****** Viscosity is determined by Brookefield cup method

(2) All essential steps and processes should be detailed such as when the product or ingredients are exposed to heat or processes likely to lead to toxic impurities.

(3) The critical control points should be relevant and controlled by objective measurement.

(4) All quality control tests need to be supported by ranges, limits or acceptance criteria.

(5) If the manufacturing process is complex, a full description can be provided instead of a flow diagram.

(6) A description of the process to deal with a product that does not comply to release specifications should be provided.

(7) If a large batch size range is proposed, please provide a technical justification for the manufacturing equipment used in the process by all manufacturers being able to perform consistently over the wide range of batch sizes proposed.

6.3.4 Cleaning of manufacturing equipment

(1) You should provide a description of the method and specifications for cleaning of equipment between different batches that contain different active ingredients, non-active ingredients or formulations.

6.4 Stability Testing

Unlike veterinary products, most agricultural chemical products do not have a shelf life or fixed expiry date under the ACVM Act. For the bulk of agricultural chemical products, data should confirm that the formulated product will remain within specification for at least two years, when stored in its unopened original container, away from direct sunlight, at or above 20 ˚C ('normal storage conditions').

(1) Provide evidence of how certain specified characteristics of the product vary with time under the influence of a variety of environmental factors such as temperature, humidity and light, which enables recommended storage conditions and shelf lives to be established.

(2) Nominate a proposed shelf life. The length of time must be supported by stability data. The maximum acceptable proposed shelf life will be the point at which product released at the low end of the acceptable release parameter range will still conform to the low end of the corresponding expiry specification.

(3) State storage conditions (including temperature range and other specific conditions) on the label and product literature.

(4) Identify and quantify any toxic degradation products.

(5) Discuss any observed variations from the expiry specifications and the likely impact of these on the proposed shelf life.

(6) Discuss any unusual results and any significant changes within a given parameter, even if the product is released within the proposed release specification and remains within the expiry specification over the duration of the trial.

(7) If the formulated product is altered before use (e.g. diluted/dissolved), any changes occurring over the shelf life of the product should be confirmed as not adversely affecting that process (Such as water-soluble bags).

6.4.1 Stability study

(1) Provide a full stability study report.

(2) Stability studies must be conducted on the trade name product in the commercial packaging, in a representative pack size of those to be sold.

(3) Smaller packaging of the same construction and material than that proposed to be sold may be used. Applicants may also wish to market their products in a smaller container at a later date, therefore undertaking the stability study in a smaller container of the same material and construction would demonstrate the product pack is fit for purpose for not only the current marketed product size but for future, smaller pack sizes.

(4) Provide sufficient information on the stability study to detail:

a) batch identifier
b) date of manufacture
c) batch size
d) site of manufacture (company and physical address).

(5) All recommended parameters for the formulation type must be tested before and after storage. If not, then a justification for not testing all recommended parameters must be provided. Full details of the methods used for each of the parameters must be provided.

(6) The batch tested can be a production batch or representative of a production batch in terms of process (e.g. laboratory or pilot scale which simulates equipment, procedures and controls). Technical argument should be provided if a production batch is not used. Stability data generated on batch sizes of less than five kilograms or five litres are normally not acceptable as they are not adequately representative

(7) If multiple formulations and/or packaging types are proposed, data must be generated for each. The formulation(s) must be the same as that proposed for registration in New Zealand.

(8) Stability testing carried out in superior packaging (e.g. HDPE) can never be used to support stability in an inferior packaging (e.g. LDPE).

(9) The condition of the containers should be examined at the beginning and end of the study to determine any obvious signs of package failure or deterioration. You must note and discuss any adverse effect of formulations on the containers in the stability report

(10) If the product is to be marketed only in containers which makes stability testing impractical, smaller containers of the same materials and construction may be used to extrapolate to larger contains. A technical argument should be provided to support this. For example: When a 1 litre pack is used to represent a 200 litre commercial pack of a suspension concentrate where suspensibility may be in an issue in the larger pack.

(11) The following compounds, pure or in any combination with each other or excipients, may be exempt from the requirements of conducting stability studies:

a) copper sulphate (any degree of hydration)
b) sulphur
c) carbonate, sulphate and phosphate salts of calcium, magnesium or zinc (any degree of hydration)
d) mineral oils
e) chitosan
f) iron phosphate
g) iron EDTA
h) Canola oil/methyl canolate.

6.4.2 Stability study conditions

(1) Stability studies may be conducted as either accelerated and/or real time studies, except for those actives listed below which require real time studies:

a) organisms (including nematodes, bacteria, viruses, algae or protoaza)
b) Mancozeb, including testing for ethylene thiourea
c) Acephate, including testing for O,O,S-trimethylphosphorothioate
d) Diazinon, including testing for O,O,O',O'-tetraehtyl thiopyrophosphate (O,S-TEPP) and O,O,O',O'-tetraethyl dithiopyrophosphate (S,S-TEPP)
e) Dimethoate, including testing for O,O,S-trimethyl phosphorodithioate
f) vapour releasing product
g) zineb

(2) Real time studies may be required for novel compounds. For example where impurities of toxicological concern may develop over time. Accelerated studies may be accepted if a scientific argument is provided why real time studies are not required.

6.4.3 Accelerated studies

An accelerated storage stability test is designed to increase the rate of chemical and physical change of a product. The currently preferred method for accelerated storage stability testing is the Collaborative International Pesticides Analytical Council (CIPAC) MT 46.3: accelerated storage procedure.

(1) 14 days duration at 54°C or 8 weeks at 40°C, considered to support a 2 year shelf life if expiry specifications are not exceeded.

(2) Include initial (time = 0 days) and final readings for each batch.

(3) Some formulations may not be stable under these conditions. Alternative time/temperature regimes may be proposed, along with a reasoned, scientific argument.

(4) If the active content differs by >5% of the initial reading, or there is a change of concern in any parameter, a suitable interim shelf life may be granted while a real time study is undertaken.

6.4.4 Real Time studies

Stability tests at elevated temperatures are designed to increase the rate of chemical degradation or the physical change of a product. Data from an accelerated study can give a useful indication of a product's stability, but note that products may pass this test and yet still be unstable on long-term storage. Therefore, it is recommended that applicants provide stability data generated at ambient temperatures over a period of two years. For example, if the proposed product has the ability to cake over time or is subject to contamination from bacterial or fungal growth, accelerated stability would not be suitable to demonstrate the stability of the product; in this case, real-time stability testing would be appropriate.

(1) Ambient temperature or at or above 20°C. Note: If the product is stored at special conditions during use (e.g. frozen or under refrigeration), these conditions must be used.

(2) Include initial (time = 0 days) and final readings for each batch.

Additional Guidance
It is recommended that the frequency of testing is every 3 months over the first year, every 6 months over the second year, then annually thereafter. If testing is not carried out at regular intervals and final results are unsatisfactory, a significantly reduced shelf life will be assigned if there are no interim results for assessment.

6.4.5 Cold testing

(1) Liquid formulations (for example, emulsifiable concentrates, oil-in-water emulsions, micro-emulsions, soluble concentrates and suspension concentrates) may be adversely affected by storage at low temperatures. Cold-stability testing should be carried out at 0 ±2 °C or lower for seven days (CIPAC method 39.3).

Note: Cold-stability testing is not necessary if the product label contains a warning against exposure to low temperatures.

6.4.6 Toxicologically significant impurities

(1) Refer to section 6.2.10.

6.5 Analytical methods

You should provide a full description of the analytical methods used for testing the product. This includes methods for the active ingredient, formulated product and stability study. The methods of analysis should be appropriate for the type of active ingredient and the formulation matrix of the product. You should provide the following information to demonstrate the suitability of the analytical methods used to generate data for product registration:

(1) full details of the analytical methods used for determining the active ingredient and, where appropriate, relevant toxicologically significant impurities in formulated agricultural chemical products during stability testing. Full details do not need to be provided if they are published by FAO or CIPAC.

(2) a description and purity of the reference standards

(3) where chromatographic techniques are used, representative chromatograms of the

a) blank
b) reference standard
c) product sample

(4) chromatograms labelled with

a) batch number
b) peak identity
c) peak integration data
d) X and Y axis labels

(5) worked examples of the calculations.

6.5.1 Validation data

You should provide validation data for the methods used for the determination of active ingredient concentration in both the active and the formulated product and, where appropriate, relevant impurities. If the method is a CIPAC or FAO method only selectivity and accuracy data are required.

A method validation must be provided from each site where the method is used. The following parameters should be addressed:

(1) selectivity or specificity
(2) linearity
(3) range
(4) precision
(5) recovery (accuracy)
(6) limit of detection (LOD) and limit of quantitation (LOQ) for relevant impurities and all toxicologically significant impurities

A subset of the above information may be accepted when justified by scientific argument.

Additional Guidance
The ACVM group harmonises with the APVMA position on method validation. Method validation guidance may be found on their website. The above guidance in 6.5.1. also applies to methods used in stability studies.

6.6 Changes that prompt a new registration

Any of the following changes to a trade name product or its formulation will prompt a new registration:

- Addition, substitution or deletion of an active ingredient
- Change in formulation type
- An application for a change in formulation/multiple formulations that significantly change the risk profile of the product.

Other factors may require a new registration. These will be assessed on a case-by-case basis.

6.7 Alternative formulations under one registration

On the basis of their risk, an alternative formulation for a trade name product can be registered when the proposed changes do not alter the following properties of the registered trade name product:

- Concentration(s) of the active ingredient(s)
- Trade name of the product
- Hazard status of the product
- Formulation type
- Physical and chemical characteristics of the formulated product to the extent that the risk profile under the ACVM Act changes, requiring reassessment.

7 Variations to a registered trade name product

(1) The registrant must assess the effects of every change to a registered trade name product.
(2) Applications to vary the details of a registered trade name product are required whenever there is a change to the approved product information.
(3) Applications must be submitted and approved prior to the implementation of the associated change, and prior to release of the changed product for sale in New Zealand. It is not acceptable to retrospectively apply for a variation to the registration unless prior permission has been granted by MPI in exceptional cases (e.g. corrective actions to manage an issue identified during post-registration management).
(4) Most changes will require data and/or technical rationale to be provided. An acceptable technical rationale for deviation from data requirements will include discussion of the proposed change relative to the information or parameter currently approved, and potential impacts on quality, stability, efficacy, safety or residue profile of the product. If there is little or no impact, explain why you have determined this to be so.
(5) If the change is administrative in nature but affects the technical details of the product (e.g. changes to label wording that may impact the interpretive meaning of the label relative to providing sufficient consumer information), a technical discussion or justification may be required to support the change

7.1 Changes to approved formulation details

(1) Submit a variation application for changes in the qualitative and/or quantitative formulation, including active ingredients and excipients.

*Note: Adding or removing an active ingredient(s) is **not** a variation to an existing product. If such a change is proposed for a previously approved formulation, the new formulation is considered a new trade name product, and you must submit an application to register that product.*

(2) Provide:

Amended Product Data Sheet
Technical rationale for the change
Current formulation table and proposed formulation table, with differences highlighted
Updated manufacturing process flow chart and description if the manufacturing process has changed. Provide discussion on any areas affected by the process change: i.e. physical and chemical properties, stability, residues, crop safety and efficacy
Outline the new QC procedures/test methods/method validation if the quality control procedures have changed. Provide discussion on any areas affected by the QC changes: i.e. physical and chemical properties, stability, residues, crop safety and efficacy.
Release specification, with any changes from that currently approved highlighted
Expiry specification, with any changes from that currently approved highlighted
Discussion on any areas affected by the formulation change: i.e. physical and chemical properties, stability, residues, target crop safety and efficacy

Stability data to support formulation changes that impact on the stability of the product
If the above data are not provided, a scientific argument must be provided justifying why they have not been included.

7.2 Changes to approved active ingredient manufacturer(s)

7.2.1 Adding or replacing an active ingredient manufacturer / active ingredient testing site

(1) Submit a variation application to add an additional active ingredient manufacturer /testing site, or to replace a currently approved active ingredient manufacturer /testing site with another.
(2) Provide:

Amended Product Data Sheet
Details of the proposed manufacturing site(s):' - Name of organisation - Postal address - Physical address - Site telephone number and/or email address
Batch analysis data from one recent commercial-scale batch of active ingredient from the proposed manufacturer as evidence that the active ingredient from the proposed manufacturer will conform to the approved active ingredient specification. Recent means analysed in the last two years. The data should include test results from all parameters listed in the approved specification. The results should include: - Batch size, batch number, date of manufacture, date of analysis - Manufacturing site (and testing site, if different to manufacturing site) - Parameters tested, acceptance criteria and test results
Analytical test methods, and validation of test methods (see 6.5)
Technical rationale and/or data to confirm equivalence of the proposed source of the active ingredient to currently approved sources, where stability, physical and chemical properties, stability, residues, target crop safety and efficacy are affected

7.2.2 Removing an active ingredient manufacturer / active ingredient testing site (if only one site is approved)

(1) Submit a variation application to remove the sole active ingredient manufacturer and/or QC testing site. MPI will assess this change, and likely apply condition 101 to registration approval.

[Condition 101: The registrant must provide additional information specified by the Ministry for Primary Industries at or before the expiry of the current product registration period].
(2) Provide:

Covering letter/email stating reason for removal of the site
Amended Product Data Sheet

7.2.3 Removal in active ingredient manufacturer / active ingredient testing site (if 2 or more sites are approved)

(1) Self-assessable change. Advise the change and provide amended documents (i.e. PDS) with the next variation or registration renewal application.

Declaration of self-assessable change made in covering letter/email
Amended Product Data Sheet

7.3 Changes to approved active ingredient(s)

7.3.1 Changes to active ingredient(s) specification(s)

(1) Submit a variation application for changes to the active ingredient(s) specification(s). This includes changes to the parameters, acceptance criteria and analytical test methods.
(2) Provide:

Amended Product Data Sheet
Technical rationale for the change
Current active ingredient specification table and proposed specification table, with differences highlighted
Batch analysis data on minimum of one batch of active ingredient. The data should include: - batch size, number, date of manufacture and date of analysis - site of manufacture (if not tested by the actual site, then evidence of origin from the site is required) - results of all analytical determinations. For quantitative tests (e.g. active ingredient concentration, individual and total impurities) provide the actual numerical results. Vague statements such as "within limits" or "conforms" is not considered acceptable.
Details of any new analytical test methods and validation
Discussion on any areas affected by the proposed change: i.e. quality, stability, residues, target crop safety and efficacy of the TNP
Toxicology and/or safety data may be required where the proposed change alters the parameter(s) for an impurity of toxicological significance. This includes changes to the impurity profile that stem from either changes in manufacture or storage of the active ingredient

7.3.2 Change in name of active ingredient(s)

The active ingredient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

(1) Submit a C9 variation
(2) Provide:

Relevant application forms
Amended Product Data Sheet and label
Evidence of name change

7.4 Changes to approved formulated product manufacturers

Approval must be granted before the change is implemented for any new manufacturer that manufactures any technical concentrate used in the production of a trade name product, formulates the trade name product itself, conducts testing or quality control activities (laboratories), and repacks, relabels, or otherwise alters the product packaging.

7.4.1 Additional manufacturers of the formulated product

(1) Submit a variation application to add an additional manufacturing site, or to replace a currently approved manufacturing site with another
(2) If multiple formulations are approved it must be clear in submitted documentation which manufacturer manufactures which formulation
(3) Provide:

Amended Product Data Sheet
Details of the proposed manufacturing site(s): - Name of organisation - Post address - Physical address - Site telephone number and/or email address
Step(s) of the manufacturing process conducted at each site, as described in 6.3. If one manufacturer manages the entire process from procurement of raw materials to filling of the market packaging, it is appropriate to state “all steps”
Data to demonstrate the proposed manufacturing site(s) will manufacture the product equivalent to that currently approved.
Batch analysis data a minimum of one batch of TNP from the proposed manufacturer. (Refer to 6.2.8). The results should include: - Date of manufacture - Date of testing - Batch size - Site of manufacture - Evidence that the batches conformed to approved release specification, using specified and validated methods
If any portion of the manufacturing process at the new site differs from that currently approved for the product, outline and appropriately with an explanation of the differences and reason for the change
If it is determined that the risk profile of the product, including stability, may be significantly altered by the differences in manufacturing at the new or additional site, stability data and/or data directly addressing one of the other risk areas may be required

7.5 Changes to manufacturing process and quality control

7.5.1 Change to manufacturing process and/or quality control

(1) Submit a variation application if it is proposed to change the details of the currently approved manufacturing process or any quality control procedures. This includes changes to any point of the manufacturing process itself, in-process critical control points and/or analytical methods, equipment used, increase or decrease in batch size or range and any details in the process and control procedures that may impact the risk profile or quality of the product.
(2) Provide justification that the proposed changes will not affect: chemistry, efficacy, residues and plant safety;

Amended Product Data Sheet
Technical rationale explaining the reason for the change(s) and the expected impact(s) the change(s) will have on the quality and stability profile of the product. Relate these impacts to any potential impacts on the efficacy, safety and residue risk profile of the product
Manufacturing data, such as a batch analysis, to support the proposed change
If more than one manufacturing process has been nominated for the manufacture of the trade name product, demonstrate that changes that impact one of the processes will not negatively impact the batch-to-batch and site-to-site consistency of the manufacture of the product across all approved sites

7.6 Changes to finished product specification or test methods

(1) Submit a variation application if it is proposed to change any parameter or test method currently approved in the finished product release and/or expiry specifications.

Amended Product Data Sheet and label
Reason for the proposed change
Current release / expiry specification table and proposed release / expiry specification table, with differences highlighted
For changes to analytical test methods for the active ingredient, provide method validation for the proposed method. Refer to 6.1.10.
Discussion on any areas affected by the proposed change: i.e. quality, stability, residues, target crop safety and efficacy of the TNP
If the proposed changes are significantly different to the currently approved specifications and/or test methods, stability and/or other data may be required to demonstrate that the new specifications can be met consistently from batch to batch

7.7 Changes to product packaging

7.7.1 Change in composition of primary packaging and/or container closures

(1) Submit a variation application for any proposed change to the product packaging including primary packaging materials, closures, packaging specifications, pack sizes, and any changes to secondary packaging.

(2) Provide:

Amended Product Data Sheet and label
Packaging specification data on the new packaging and/or container closure (e.g. comparative data on permeability for O_2, CO_2, and moisture)
Technical rationale explaining the reason for the change(s) and the expected impact(s) the change(s) will have on the quality and stability profile of the product (e.g. such as photosensitivity, temperature sensitivity, and any other relevant parameters). Relate these impacts to any potential impacts on the efficacy, safety and residue risk profile of the product
Stability data to demonstrate that the product will remain equivalently stable throughout the approved shelf life, if the changes in the primary packaging materials and/or closures are significantly different to that approved for the product

7.7.2 Change in pack size

(1) Provide:

Amended Product Data Sheet
Packaging specification data on the new pack size(s)
Data and justification appropriate for the product type and its practical use in the market relative to the risk profile of the product. For example: - If the proposed pack size is larger than the current approved pack sizes and the formulation type a suspension concentrate the possibility of sedimentation/separation needs to be addressed either with stability data or justification - If the proposed pack size is smaller than the currently approved pack sizes then stability needs to be addressed either with data or justification (state if the original stability trials were performed on the proposed or smaller pack size

7.7.3 Addition of a new marketed pack size within the currently approved size range

Self-assessable change. Advise the change and provide amended documents (i.e. PDS) with the next variation or registration renewal application. The package must be of the same packaging material and closure type.

Example: If a new pack size is proposed within an already approved pack range (e.g. product is approved for pack sizes of same packaging materials between 10L and 20L, and the proposed pack size is 15L).

(6) Provide:

Details of the change made, and declaration that the change has been self-assessed to have no significant impact on the risk profile of the product, in a covering letter or email.
Amended Product Data Sheet

7.7.4 Change in secondary packaging

(1) Provide:

Amended Product Data Sheet and label
Details of the change including packaging specification information as applicable.
Where the secondary packaging **serves to protect or preserve product quality** provide a technical rationale explaining the reason for the change(s) and the expected impact(s) the change(s) will have on the quality and stability profile of the product (e.g. such as photosensitivity, temperature sensitivity, and any other relevant parameters). Relate these impacts to any potential impacts on the efficacy, safety and residue risk profile of the product. Provide stability data and information to support the change if appropriate. Where the secondary packaging **does not have a direct impact on product preservation or quality**, the change will be reviewed as a self assessable change. Provide a summary of the change proposed with a declaration that the change will have no significant impact on the risk profile of the product at the next registration renewal.

Appendix 1: Chemical and Physical Parameters Based on Formulation Type

Additional guidance: Packaging stability is not used as a release specification

AEROSOL DISPENSERS (AE)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour, odour)	No CIPAC method
Active content	Appropriate validated method
Internal pressure	No CIPAC method
Discharge rate	No CIPAC method
pH	No CIPAC method
Clogging of aerosol dispenser valves	No CIPAC method
Packaging stability	Observation of packaging stability (no corrosion and no nozzle blockage)

AQUEOUS CAPSULE SUSPENSION (CS)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Pourability	MT 148.1
Suspensibility	MT 184
Spontaneity of dispersion	MT 160
Wet sieve test	MT 185
Persistent foam	MT 47.3
Particle size distribution (if required)	MT 187
Packaging stability	Observation of packaging stability and integrity
Freeze/thaw stability	Testing of stability parameters (acidity/alkalinity/pH range, pourability, suspensibility, spontaneity of dispersion, wet sieve test) required after freeze/thaw cycle

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

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	Observation of physical appearance are required, eg sedimentation
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Retention of palatability	Only required if significant physical changes were observed on storage

Packaging stability	Observation of packaging stability and integrity

DUSTABLE POWDER (DP)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Dry sieve test	MT 170
Packaging stability	Observation of packaging stability; there should be no caking in the pack on storage

EMULSIFIABLE CONCENTRATE (EC) and EMULSION (WATER IN OIL) (EO)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Emulsion characteristics	MT 36.1, MT 36.2, MT 36.3, MT 173 or MT 183
Persistent foam	MT 47.3
Packaging stability	Observation of packaging stability

EMULSION, OIL IN WATER (EW)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Emulsion characteristics	MT 36.1, MT 36.2, MT 36.3, MT 173 or MT 183
Pourability	MT 148.1
Persistent foam	MT 47.3
Packaging stability	Observation of packaging stability

SUSPO-EMULSION (SE)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Dispersion stability	MT 180
Pourability	MT 148.1
Wet sieve test	MT 185

Persistent foam	MT 47.3
Packaging stability	Observation of packaging stability to include a statement on claying, sedimentation and re-dispersibility

GELS (GD)

Expected 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 75.3 or MT 191
Miscibility	Only required if to be dispersed in water
Emulsion characteristics	MT 36.3 (0.1-5% dilution) or MT 183 (1% dilution) or MT 180 ; only required if to be emulsified in water
Wet sieve test	MT 185; Only required if to be dispersed in water
Suspensibility	MT 184; Only required if to be suspended in water
Packaging stability	Observation of packaging stability

GRANULES (GR)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Pour and tap density	MT 186
Nominal size range	MT 170
Dustiness	MT 171.1
Attrition resistance	MT 178
Release rate of active ingredient (if required)	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)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Packaging stability	Observation of packaging stability

OIL MISCIBLE LIQUID (OL)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Miscibility with hydrocarbon oil	MT 23
Packaging stability	Observation of packaging stability

POWDER FOR DRY SEED TREATMENT (DS)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Adhesion to seeds	MT 194
Dry sieve test	MT 170
Packaging stability	Observation of packaging stability

SMOKE GENERATOR (FU)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Burning time	
Evidence of combustibility	The quantity of material remaining after combustion should be determined
Packaging stability	Observation of pack integrity

SOLUBLE CONCENTRATE (SL)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Solution stability	MT 41.1
Persistent foam	MT 47.3
Packaging stability	Observation of packaging stability

SUSPENSION CONCENTRATE (SC)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75.3 or MT 191
Pourability	MT 148.1
Suspensibility	MT 184
Spontaneity of dispersion	MT 160
Wet sieve test	MT 185
Persistent foam	MT 47.3
Particle size distribution (if required)	MT 187
Packaging stability	Observation of packaging stability

TABLETS (TB)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Tablet Integrity	The data should demonstrate the mechanical robustness of the tablets

Expected Test Parameters	Relevant CIPAC Method/Comments
Tablet hardness	No CIPAC method
Degree of attrition	MT 193
Degree of dissolution and solution stability *	MT 179
Suspensibility #	MT 184
Wet sieve test	MT 185
Disintegration time	
Packaging stability	Observation of packaging stability

* If the table is water-soluble, then degree of dissolution and solution stability should also be tested.

If the tablet is water-dispersible, then suspensibility should also be tested.

ULTRA LOW VOLUME LIQUID (UL)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Viscosity	MT 22
Packaging stability	Observation of packaging stability

WATER-DISPERSIBLE GRANULES (WG)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Wet sieve test*	MT 185
Dispersibility	MT 174
Suspensibility*	MT 184
Wettability*	MT 53.3
Persistent foam*	MT 47.3
Dustiness	MT 171.1
Flowability	MT 172.1
Dissolution of water-soluble bags	MT 176/ Only for the product packaged in a sealed water-soluble bag
Attrition resistance	MT 178.2
Packaging stability	Observation of packaging stability

*If the product is packaged in a water-soluble bag, you should do the wet sieve test, suspensibility, wettability test and persistent foam test using a solution of the product and water-soluble bag in the same ratio as in the recommended application.

WATER-DISPERSIBLE POWDER FOR SLURRY SEED TREATMENT (WS)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Wet sieve test	MT 185
Wettability	MT 53.3
Persistent foam	MT 47.3
Adhesion to seeds	MT 194
Packaging stability	Observation of packaging stability

WATER-SOLUBLE GRANULES (SG)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Dustiness	MT 171.1
Degree of dissolution and solution stability*	MT 179.1
Persistent foam*	MT 47.3
Attrition resistance	MT 178.2
Flowability	MT 172.1
Dissolution of water-soluble bags	MT 176/ Only for the product packaged in a sealed water-soluble bag
Packaging stability	Observation of packaging stability

*If the product is packaged in a water-soluble bag, then the wettability, degree of dissolution and solution stability test must be carried using a solution of the product and water-soluble bag in the same ratio as in the recommended application.

WATER-SOLUBLE POWDER (SP)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Persistent foam*	MT 47.3
Wettability*	MT 53.3
Degree of dissolution and solution stability	MT 179.1
Dissolution of water-soluble bags	MT 176/ Only for the product packaged in a sealed water-soluble bag
Packaging stability	Observation of packaging stability

*If the product is packaged in a water-soluble bag, then the wettability, degree of dissolution and solution stability test must be carried using a solution of the product and water-soluble bag in the same ratio as in the recommended application.

WETTABLE POWDER (WP)

Expected Test Parameters	Relevant CIPAC Method/Comments
Appearance (physical state, colour)	
Active content	Appropriate validated method
Acidity/alkalinity or pH	MT 75 or MT 191
Wet sieve test*	MT 185
Suspensibility*	MT 184
Wettability*	MT 53.3
Persistent foam*	MT 47.3
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 no caking on storage

*If the product is packaged in a water-soluble bag, you should do the wet sieve test, suspensibility, wettability test and persistent foam test using a solution of the product and water-soluble bag in the same ratio as in the recommended application

Appendix 2: Stability Study Exemptions for Agricultural Chemical Compounds

The following compounds, pure or in any combination with each other or excipients, may be appropriate for an application of exemption from conducting stability studies:

- Copper sulphate (any degree of hydration)
- Copper oxychloride
- Sulphur
- Carbonate, sulphate and phosphate salts of calcium, magnesium or zinc (any degree of hydration)
- Mineral oils
- Chitosan
- Iron phosphate
- Iron EDTA
- Canola oil / methyl canolate

Appendix 3: Active Ingredients that Require Real Time Stability Studies of the Trade Name Product

- Organisms (including, in particular, nematodes, bacteria, viruses, algae or protozoa)
- Mancozeb, including testing for ethylene thiourea

- Acephate, including testing for O,O,S-trimethylphosphorothioate
- Diazinon, including testing for 0,0,0',0'-tetraethyl thiopyrophosphate (0,S-TEPP) and 0,0,0',0'-tetraethyl dithiopyrophosphate (S,S-TEPP)
- Dimethoate, including testing for 0,0,S-trimethyl phosphorodithioate
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Appendix 4: Active Ingredients Exempt from Notification of the Manufacturer

- Calcium carbonate
- Copper sulphate (any degree of hydration)
- Copper oxychloride, copper hydroxide
- Sulphur
- Food quality ingredients. These food quality ingredients must comply with a recognised standard such as the Food Standards Code FSANZ). If these additives comply with a recognised standard, reference the standard.

Evidence of a quality system needs to be provided for these actives if the manufacturer is not notified. A quality system should provide assurance that the active will meet ACVM approved specifications prior to its inclusion in the formulated product. If the exemption applies, then the applicant must demonstrate to the satisfaction of the ACVM group that they are managing the risk for the active ingredient.

An internal record of the active manufacturers used and batch analysis certificates which confirm that the active is fit for purpose must be available for immediate inspection.