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Australian Pesticides and Veterinary Medicines Authority

APVMA risk assessment manual

Chemistry and manufacture

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Comments and enquiries regarding copyright:

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4988

Email: communications@apvma.gov.au.

This publication is available from the APVMA website.

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1 PURPOSE OF THIS MANUAL

This manual is intended to provide stakeholders, including industry and the general public, with a general description of the assessment approaches and practices that the APVMA applies to the evaluation of chemistry and manufacture data. The chemistry and manufacture data is evaluated as part of the APVMA determination whether the safety and efficacy criteria for the approval of active constituents and the registration of pesticide and veterinary medicine products have been met.

This manual provides more detail about the APVMA risk assessment approach and is complementary to the information provided about the APVMA approach to the safeguarding aspects of our science, risk management and regulation according to risk.

For prospective applicants, this manual should be considered in conjunction with the APVMA data guidelines for chemistry and manufacture.

Chemistry and manufacture data is evaluated and assessed to confirm the identity of the compounds contained in actives or products and to confirm the specifications for compounds or products including specifications for any impurities likely to be present. The assessment should also confirm that the manufacturing processes are under control and will produce the compounds or product formulations as described and within specifications—particularly those for any toxicologically significant impurities. For products, and for the first assessment of an active constituent an assessment of the stability of the product (active) is also conducted. The measurement techniques need to be validated to ensure they are fit for purpose to confirm that they accurately represent the compounds present and that any statistical analysis used to interpret that data is also appropriate. The chemistry data also provides physicochemical parameters useful to the human health, residues and dietary risk and environmental risk assessments of an active or a product.

This manual does not apply to immunological type active constituents in veterinary chemical products, for example vaccines.

This document applies to biological pesticides such as *Bacillus thuringiensis* and naturally derived actives or botanicals such as tea tree oil.

The assessment of Listed Chemical Products—does not require evaluation of data and consequently is outside the scope of this document.

It is expected that by using this document the user would be able to:

- determine that the chemistry and manufacture data generated to support an active constituent approval or a chemical product registration is fit for its intended purpose (ie likely to result in the granting of the approval of the active and/or registration of a chemical product application), and
- highlight to the applicant prior to the submission of an application the likely gaps in the chemistry and manufacture data that might require further data, justification or clarification or that might be expected to result in additional measures that the applicant may take to address any data gaps.

Throughout this manual it will be apparent that there are differences in the data typically required for, and the APVMA assessment processes for, pesticide active constituents and chemical products compared to veterinary

medicine active constituents and chemical products. This approach reflects the differences contained in the Agvet Code and the different approaches adopted as international best practice for pesticide active constituents and chemical products, and for veterinary medicine active constituents and chemical products.

2 LEGISLATIVE BASIS

The legislative basis for the assessment of chemistry and manufacture data associated with the approval of active constituents and the registration of pesticide chemical and veterinary medicine products is provided in the *Agricultural and Veterinary Chemicals Code Act 1994* (external site—referred to as the Agvet Code in this document)—and the *Agricultural and Veterinary Chemicals Code Regulations 1995* (external site—referred to as the Regulations in this document).

The legislation and regulations specify a number of matters that the APVMA must or may consider in its assessments these legislative matters may differ from other jurisdictions. For instance, the APVMA must consider how a product is formulated in its assessment of product safety, and must consider how an active constituent is or is proposed to be manufactured in assessing active constituent safety.

2.1 Agvet Code section 14—the safety criteria should be met

Approval and registration

1. The APVMA must approve the active constituent or label, or register the chemical product, if it is satisfied:

a) that the application meets the application requirements; and

b) for an active constituent—that the constituent meets the safety criteria; and

c) for a chemical product—that the product:

i. meets the safety criteria, the trade criteria and the efficacy criteria; or

ii. complies with the established standard for the product; and

d) for a label for a chemical product—that the label:

i. meets the labelling criteria; or

ii. complies with the established standard for the product.

2.2 Agvet Code section 5A—definition of meets the safety criteria

s5A definition of meets the safety criteria

1. An active constituent or chemical product **meets the safety criteria** if use of the constituent or product, in accordance with any instructions approved, or to be approved, by the APVMA for the constituent or product or contained in an established standard:

a) is not, or would not be, an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues; and

b) is not, or would not be, likely to have an effect that is harmful to human beings; and

c) is not, or would not be, likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

For the purposes of being satisfied as to whether an active constituent meets the safety criteria, the APVMA **must** have regard to a number of chemistry and manufacture aspects in relation to active constituent approval (subsection 5A(2)(a)) and chemical product registration (subsection 5A(3)(a)). In addition the APVMA *may* have regard to a number of further chemistry and manufacture aspects as described in subsections 5A(2)(b) and 5A(3)(b). These aspects are detailed separately for active constituents and products below.

2.3 Relevant legislation for active constituent approvals

Agvet Code section 5A(2)

For the purposes of being satisfied as to whether an active constituent meets the safety criteria, the APVMA:

a) must have regard to the following:

i. the toxicity of the constituent and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems, including human beings;

ii. the method by which the constituent is, or is proposed to be, manufactured;

iii. the extent to which the constituent will contain impurities;

iv. whether an analysis of the chemical composition of the constituent has been carried out and, if so, the results of the analysis;

v. any conditions to which its approval is, or would be, subject;

vi. any relevant particulars that are, or would be, entered in the Record for the constituent;

vii. whether the constituent conforms, or would conform, to any standard made for the constituent under section 6E to the extent that the standard relates to matters covered by subsection (1);

viii. any matters prescribed by the regulations; and

b) may have regard to such other matters as it thinks relevant.

Regulation 17C - Conditions of approval or registration—active constituents

With regard to section 5A(2)(a)(v) ‘any conditions to which its approval is, or would be, subject’ regulation 17C lists the following items as conditions to which the approval of an active constituent for a proposed or existing chemical product is subject:

Item 1

The active constituent must be manufactured in accordance with the composition and purity entered for the active constituent in the Record in accordance with paragraph 15(1)(d) of the Regulations.

Item 2

The active constituent must be manufactured by the manufacturer whose name is entered for the active constituent in the Record in accordance with paragraph 15(1)(e) of the Regulations.

Item 3

The active constituent must be manufactured at a site of manufacture entered for the active constituent in the Record in accordance with paragraph 15(1)(f) of the Regulations.

Item 4

The identifying information for the holder of the approval, and the nominated agent (if any), of the active constituent must be the identifying information for the holder and nominated agent (if any) entered for the active constituent in the Record.

Regulation 15 - Particulars of approved active constituents to be recorded

Section 5A(2)(a)(vi) states that the APVMA must have regard to any relevant particulars that are or would be entered in the Record for the constituent. These particulars are specified in regulation 15.

Additionally, as described in regulation 17C the particulars listed under reg 15(1)(d), (g) and (f) of the regulations form part of the conditions of approval of active constituents.

15 (1) For paragraph 19(c) of the Code, the following particulars are prescribed:

a) if a name is given to the active constituent by the International Union of Pure and Applied Chemistry—that name;

b) if no name is given to the active constituent by the International Union of Pure and Applied Chemistry—the name given to the active constituent in an order, publication or approval referred to in regulation 42 that specifies the standard for the active constituent for the purposes of that regulation;

c) the name of the active constituent; [interpretation: common name]

d) the composition and purity of the active constituent;

e) the name of the manufacturer of the active constituent;

f) the address of each site at which the active constituent is manufactured by the manufacturer;

g) identifying information for the holder of the approval of the active constituent;

h) the date of entry of these particulars in the Record of Approved Active Constituents; (note there is no paragraph (i) in this regulation)

j) identifying information for any nominated agent for the approval.

(2) A particular mentioned in paragraphs (1)(c) to (j) is only prescribed for an active constituent approved in accordance with section 14A of the Code if the particular is readily available to the APVMA.

Agvet Code section 15

15 Restriction on power of APVMA to register products and approve labels:

1. Subject to subsection (2), the APVMA must not:

a) register a chemical product unless:

i. the APVMA also approves each active constituent for the product; and

ii. the APVMA also approves a label for containers for the product; or

b) approve a label for containers for a chemical product unless it also registers the product.

2. Subparagraph (1)(a)(i) does not apply in relation to:

k) an active constituent that is exempted by the APVMA from the operation of that subparagraph; or

l) an active constituent for a listed chemical product.

Agvet Code section 19

Regulation 15 refers to paragraph 19(c) of the Agvet Code which states as follows:

Approval of an active constituent takes place when the APVMA enters the following in the Record:

a) the name of the person who applied for the approval as the holder of the approval;

b) the name of any nominated agent for the approval;

c) the relevant particulars, which are the distinguishing number, any instructions for the use of the constituent and any other particulars prescribed by the regulations;

d) and any conditions of the approval imposed by the APVMA.

Regulation 8AA

Section 5A(2)(a)(vii) of the Agvet Code states that the APVMA must have regard to ‘any matters prescribed by the regulations’. Regulation 8AA prescribes the following matters:

8AA Safety criteria—active constituents

For subparagraph 5A(2)(a)(vii) of the Code, the method of analysis (if any) of the chemical composition of the active constituent concerned is a prescribed matter.

2.4 Relevant legislation for product registrations

Agvet Code section 5A(3)(a) APVMA must have regard to:

5A(3) For the purposes of being satisfied as to whether a chemical product meets the safety criteria, the APVMA:

a) must have regard to the following:

i. the toxicity of the product and its residues, including metabolites and degradation products, in relation to relevant organisms and ecosystems, including human beings;

ii. the relevant poison classification of the product under the law in force in this jurisdiction;

iii. how the product is formulated;

iv. the composition and form of the constituents of the product;

v. any conditions to which its registration is, or would be, subject;

vi. any relevant particulars that are, or would be, entered in the Register for the product;

vii. whether the product conforms, or would conform, to any standard made for the product under section 6E to the extent that the standard relates to matters covered by subsection (1);

viii. any matters prescribed by the regulations; and

The relevant subsections to the chemistry and manufacturing assessment are 5A(3)(a)(iii)–(vii).

Regulation 17C(2) conditions of approval or registration—chemical products

With regard to section 5A(3)(a)(v) 'any conditions to which its registration is, or would be, subject' regulation 17C lists the following items as conditions to which the registration of a chemical product is subject:

Item 1

The chemical product must contain each of the constituents entered for the chemical product in the Register in accordance with paragraph 16(b).

Item 2

The chemical product must be manufactured:

a) in accordance with the particulars entered for the chemical product in the Register in accordance with paragraphs 16(b), (c), (d) and (da); and

b) by a manufacturer whose name is entered for the chemical product in the Register in accordance with paragraph 16(g); and

c) at a site of manufacture entered for the chemical product in the Register in accordance with paragraph 16(h).

Items 3 and 4

These relate to determination by the APVMA whether manufacturers of veterinary chemical products hold appropriate licences. These determinations are normally made by the product risk manager in conjunction with the Manufacturing Quality Licensing section.

Item 5

The formulation type of the chemical product as supplied must be the formulation type entered for the chemical product in the Register in accordance with paragraph 16(da).

Item 6

The net contents for the chemical product as supplied must be the net contents entered for the chemical product in the Register in accordance with paragraph 16(db).

Item 7

Is not relevant to the chemistry and manufacture assessment as it refers to the identifying information for the holder of the registration, and the nominated agent.

Regulation 18 conditions of registration of chemical products—containers

With regard to section 5A(3)(a)(v) 'any conditions to which its registration is, or would be, subject' regulation 18 lists the following items as conditions to which the registration of a chemical product is subject:

1. For paragraph 23(1)(a) of the Code, the registration of a chemical product is subject to the condition that the product is supplied only in a container that meets the requirements mentioned in subregulation (2).
2. The container must:

a) be impervious to, and incapable of chemical reaction with, its contents when under conditions of temperature and pressure that are likely to be encountered in normal service; and

b) have sufficient strength and impermeability to prevent leakage of its contents during handling, transport and storage under normal handling conditions; and

c) if it is intended to be opened more than once—be able to be securely and readily closed and reclosed; and

d) have sufficient excess capacity to prevent it from breaking if its contents expand during handling, transport or storage; and

e) enable all or any part of its contents to be removed or discharged in such a way that, with the exercise of no more than reasonable care, the contents cannot:

i. harm any person; or

ii. have an unintended effect that is harmful to the environment.

3. Nothing in subregulation (2) is intended to affect the operation of any other law that applies in relation to containers for chemical products.

Subsections 2(a) and 2(b) are of particular relevance to the chemistry and manufacture assessment.

Regulation 16 Particulars of registered chemical products to be recorded

Section 5A(3)(a)(vi) states that the APVMA must have regard to any relevant particulars that are or would be entered in the Register for the product. These particulars are specified in regulation 16.

Additionally, as described in regulation 17C the particulars listed under reg 16(b), (c),(d), (da), (db), (e), (g) and (h) form part of the conditions for registration of chemical products.

r16 Particulars of registered chemical products to be recorded

For paragraph 20(1)(c) of the Code, the following particulars are prescribed:

a) the distinguishing name of the chemical product;

b) the constituents of the chemical product;

c) the concentration of each constituent of the chemical product;

d) if possible, the composition and purity of each active constituent of the chemical product;

da) the formulation type for the chemical product;

db) the net contents for the chemical product;

e) identifying information for the holder of the registration of the chemical product; (*note there is no subsection (f*))

g) the name of each manufacturer of the chemical product;

h) the address of each site at which the chemical product is manufactured by the manufacturer; (*note there is no subsection (i*))

j) the date of entry of these particulars in the Register of Chemical Products;

k) identifying information for any nominated agent for the registration.

The subregulations that that are relevant to the chemistry and manufacture assessment are 16(b), (c), (d), (da), (db), (g) and (h):

- the constituents of the chemical product
- the concentration of each constituent of the chemical product
- if possible, the composition and purity of each active constituent of the chemical product
- the formulation type of the chemical product
- the net contents of the chemical product
- the name and the address of each manufacturer of the chemical product.

Agvet Code section 20

Regulation 16 refers to paragraph 20(1)(c) of the Agvet Code which specifies that relevant particulars are to be entered in the Register.

s20 How registration of chemical product takes place

1. Registration of a chemical product takes place when the APVMA enters the following in the Register:

a) the name of the person who applied for the registration as the holder of the registration;

b) the name of any nominated agent for the registration;

c) the relevant particulars, which are the distinguishing number, any instructions for the use of the product and any other particulars prescribed by the regulations;

d) if the product is a listed chemical product—a notation to that effect;

e) any conditions of the registration imposed by the APVMA;

f) the date the registration ends.

Agvet Code section 23(1) — conditions of approval or registration

s23 Conditions of approval or registration

1. The approval of an active constituent, the registration of a chemical product or the approval of a label for containers for a chemical product is subject to:

a) the conditions prescribed by the regulations (whether or not the conditions are prescribed at the time the constituent, product or label is approved or registered); and

b) any conditions imposed on the approval or registration as the APVMA thinks appropriate.

Regulation 8AB safety criteria — chemical products

Section 5A(3)(a)vii) of the Agvet Code states that the APVMA must have regard to any matter prescribed by the regulations.

The matters prescribed by the regulations that are relevant to the chemistry and manufacture assessment are included in regulations 8AB(a), (d), (e) and (f).

r8AB safety criteria — chemical products

1. For subparagraph 5A(3)(a)(vii) of the Code, the following are prescribed matters for a chemical product:

a) for all chemical products—the method of analysis (if any) of the chemical composition and form of the constituents of the chemical product;

b) for a product manufactured in Australia—whether each step in the manufacture of the product complies, or will comply, with the manufacturing principles and the Australian GMP Code;

c) for a product manufactured outside Australia—whether each step in the manufacture of the product complies, or will comply, with a standard that the APVMA has determined is comparable to the manufacturing principles and the Australian GMP Code;

d) for a molluscicide in the form of a bait and of which the active constituent is metaldehyde:

i. whether the product contains sufficient green pigment or dye to colour the bait a distinctive green colour; and

ii. whether the product contains, in the bait, any bone meal or other product of animal origin;

e) for a molluscicide in the form of a bait and of which the active constituent is methiocarb:

i. whether the product contains sufficient blue pigment or dye to colour the bait a distinctive blue colour; and

ii. whether the product contains, in the bait, any bone meal or other product of animal origin;

f) for an agricultural chemical product to be applied to seeds to be stored before planting or sowing—whether the product contains sufficient pigment or dye to colour the seed to enable the seed to be readily distinguished from seed to which the product has not been applied.

Note: the GMP Code applies only to veterinary product manufacturing, not to agricultural product manufacturing.

Agvet Code section 5A(3)(b) - APVMA may have regard to:

Section 5A(b) specifies those matters that the APVMA may have regard to:

5A(3)(b) For the purposes of being satisfied as to whether a chemical product meets the safety criteria, the APVMA:

b) may have regard to one or more of the following:

i. the acceptable daily intake of each constituent contained in the product;

ii. any dietary exposure assessment prepared under subsection 82(4) of the *Food Standards Australia New Zealand Act 1991* as a result of any proposed variation notified under subsection 82(3) of that Act in relation to the product, and any comments on the assessment given to the APVMA under subsection 82(4) of that Act;

iii. whether any trials or laboratory experiments have been carried out to determine the residues of the product and, if so, the results of those trials or experiments and whether those results show that the residues of the product will not be greater than limits that the APVMA has approved or approves;

iv. the stability of the product;

v. the specifications for containers for the product;

vi. such other matters as it thinks relevant.

The subsections that are relevant to the chemistry and manufacture assessment are 5A(3)(b)(iv), (v) and (vi) regarding the stability of the product the specifications for containers of the product and any other matters that it thinks relevant.

Agvet Code section 5B — efficacy criteria:

(1) A chemical product **meets the efficacy criteria** if use of the product, in accordance with instructions approved, or to be approved, by the APVMA for the product or contained in an established standard, is, or would be, effective according to criteria determined by the APVMA by legislative instrument.

(2) For the purposes of being satisfied as to whether a chemical product meets the efficacy criteria, the APVMA must have regard to the following:

(a) whether any trials or laboratory experiments have been carried out to determine the efficacy of the product and, if so, the results of those trials or experiments;

(b) any conditions to which its registration is, or would be, subject;

(c) any relevant particulars that are, or would be, entered in the Register for the product;

(ca) whether the product conforms, or would conform, to any standard made for the product under section 6E to the extent that the standard relates to matters covered by subsection (1);

(d) any matters prescribed by the regulations.

(3) For the purposes of the operation of this Code in relation to a particular chemical product, the APVMA is required to have regard to the matters set out in subsections (1) and (2) only:

(a) to the extent prescribed by the regulations; or

(b) if there are no such regulations—to the extent that the APVMA thinks the matters are relevant.

Section 5B does not specifically list any matters routinely considered as part of the Chemistry and Manufacture assessment. However, the stability of a product (which is considered as part of the chemistry assessment, and is not excluded from Part 5B) is relevant to the efficacy of a product as well as its safety.

Agvet Code regulations schedule 6 — application fees and assessment periods

When chemical products are closely similar

1. Subject to subsection (2), an agricultural chemical product (the **proposed chemical product**) and a reference chemical product are **closely similar** if:

a) the active constituents in the proposed chemical product are the same as the approved active constituents in the reference chemical product; and

b) the concentration of the active constituents referred to in paragraph (a) are the same; and

c) either:

i. the other ingredients in the formulations of the proposed and reference chemical products are the same; or

ii. if the other ingredients in the formulations of the proposed and reference chemical products are different, those other ingredients perform similar functions (for example, as emulsifiers, surfactants, dyes or solvents); and

d) the formulation type of the proposed and reference chemical products are the same; and

e) the label of the proposed chemical product refers to the same crops, situations and pests as the approved label of the reference chemical product (that is, the proposed chemical product must have no uses additional to those of the reference chemical product); and

f) the label of the proposed chemical product includes similar instructions on how to use the product, and precautionary or safety instructions, as the approved label of the reference chemical product; and

g) either:

i. the claims on the labels of the proposed and reference chemical products are the same; or

ii. if the claims are different, the claims on the label of the proposed chemical product are fewer or reduced compared to the claims on the approved label of the reference chemical product.

2. However, the proposed agricultural chemical product and the reference chemical product are taken not to be closely similar if information about the reference chemical product is protected information.

3. Subject to subsection (4), a veterinary chemical product (the **proposed chemical product**) and a reference chemical product are **closely similar** if:

a) the active constituents in the proposed chemical product are the same as the approved active constituents in the reference chemical product; and

b) the concentration of the active constituents referred to in paragraph (a) are the same; and

c) either:

i. the non-active constituents in the formulations of the proposed and reference chemical products are the same, or are equivalent substances, at the same or equivalent concentrations; or

ii. if the non-active constituents in the formulations of the proposed and reference chemical products are neither the same nor equivalent, the differences in the formulations are minor and are not expected to have adverse implications on product quality or biological activity in terms of efficacy, safety or residues; and

d) either:

i. the proposed and reference chemical products specifications (including release and expiry limits and test methods) and physico-chemical properties (including pH, particle size, crystal form and, where applicable, dissolution profile, payout rate and payout period) are the same or equivalent; or

ii. if the specifications and physico-chemical properties of the proposed and reference chemical products are neither the same nor equivalent, the differences in the specifications and properties are minor and are not expected to have adverse implications for product quality or biological activity in terms of efficacy, safety or residues; and

Note for paragraphs (c) and (d): efficacy, safety and residues data are not required to demonstrate similarity of the proposed chemical product to the reference chemical product.

e) the dose form and formulation type of the proposed and reference chemical products are the same; and

f) the use patterns (including target animal species, dose rates, routes of administration and withholding periods) and instructions on the labels of the proposed and reference chemical products are the same; and

g) either:

i. the claims on the labels of the proposed and reference chemical products are the same; or

ii. if the claims are different, the claims on the label of the proposed chemical product are fewer or reduced compared to the claims on the approved label of the reference chemical product

4. However, the proposed veterinary chemical product and the reference chemical product are taken not to be closely similar if information about the reference chemical product is protected information.

1.3 When chemical products are similar

1. Subject to subsection (2), an agricultural chemical product (the **proposed agricultural chemical product**) and a reference chemical product are **similar** if the conditions in paragraphs 1.2(1)(a), (d), (e), (f) and (g) are complied with in relation to the products.

2. However, the proposed agricultural chemical product and the reference chemical product are taken not to be similar if information about the reference chemical product is protected information.

3. Subject to subsection (4), a veterinary chemical product (the ***proposed veterinary chemical product***) and a reference chemical product are ***similar*** if:

a) the conditions in paragraphs 1.2(3)(a), (b), (e), (f) and (g) are complied with in relation to the products; and

b) the non-active constituents in the proposed and reference chemical products have similar properties and are in similar proportions; and

c) chemistry and manufacture, efficacy or target species safety data is required to demonstrate similarity of the proposed chemical product to the reference chemical product

4. However, the proposed veterinary chemical product and the reference chemical product are taken not to be similar if information about the reference chemical product is protected information.

1.4 When chemical products are the same

1. Subject to subsection(2), a proposed chemical product and a reference chemical product are the same if they are the same in all respects except their names, their distinguishing numbers, and the name and business address of the applicant.

2. However, a proposed chemical product and a reference chemical product are taken not to be the same if information about the reference chemical product is protected information.

2.5 Relevant legislation for both active approvals and product registrations

Agvet Code section 157

The APVMA has the power to request samples to be tested while an application (for active constituent approval or product registration) is in evaluation:

s157 - samples to be given for analysis

1. For the purposes of determining an application under this Code, the APVMA may require the applicant to:

a) if the application relates to an active constituent or active constituents for a proposed or existing chemical product—give a sample of that constituent or of each of those constituents; or

b) if the application relates to a chemical product—give a sample of any constituent of the product or a sample of the product, or both;

to the APVMA or to a body named by the APVMA, for the purpose of analysis by an approved analyst.

2. The sample must:

a) be of a quantity; and

b) be taken on a day; and

c) be taken in a manner; and

d) be taken from a batch;

that the APVMA has directed.

3. The applicant must pay to the APVMA the amount that the APVMA notifies the applicant in writing to be the cost of the analysis referred to in subsection (1), including the cost of packaging and transporting the sample or samples for analysis.

3 DATA REQUIREMENTS

1. The APVMA has published data guidelines for chemistry and manufacture, being information that should be submitted to address the safety criteria for pesticide and veterinary active constituents and pesticide chemical products and veterinary medicine products. This manual does not repeat the various data type descriptions.

4 DATA EVALUATION

The following section provides details of the assessments that the APVMA conducts on the chemistry and manufacture data of pesticide and veterinary active constituents, pesticide chemical products and veterinary medicine products.

Some components of the data assessment are interlinked—the batch analysis results are considered against the limits contained in the Declaration of Composition/specification, and the analytical method validation impacts on the reliability of the batch results and stability data.

4.1 Assessment of active constituent approvals

The active constituent is defined, in relation to a proposed or existing agricultural chemical product or veterinary chemical product, as the substance that is, or is one of the substances that together are, primarily responsible for the biological or other effect identifying the product as an agricultural chemical product or a veterinary chemical product.

The purpose of the assessment of the active constituent information is to ensure that identity of the active is verified and that it is of appropriate quality to enable the safety and efficacy criteria to be satisfied when it is used in a registered product.

Instructions for use

Agvet Code s19(c)

The APVMA assesses the instructions for use for the active constituent approval holder:

- is the active constituent for use in agricultural and/or veterinary chemical products?

In assessing this information the APVMA is seeking to ensure that the relevant particular of instruction for use of the constituent is correct when entered in the Record for active approvals.

Manufacturer's name and address

Regulations 15(1)(e) and (f), and 17C(1) item 2 and item3

The APVMA may assesses the active constituent manufacturer's name and address (depending on the approval status of the active):

- are the stated manufacturer's name(s) and address(es) correct for the active constituent being assessed?
- are the stated manufacturer's name(s) and address(es) the actual physical address of the manufacturing facility as opposed to a mailing address?
- do the manufacturing site addresses cover the actual manufacture of the active constituent? Is a substantial chemical transformation taking place at the site(s) nominated? For example, the laboratory conducting the

final QC testing on the batches prior to release, or a warehouse from which the active was released for supply, would not in and of themselves be considered as the manufacturer of an active.

In assessing this information the APVMA is seeking to ensure that the name and address for the active constituent manufacturer are correct when entered in the Record.

This is listed in the data guidelines for agricultural actives (new constituents or new sources of constituents) and veterinary active constituents.

Common name

Regulation 15(1)(c)

The APVMA assesses the common name of active constituents:

- for all actives, is there a relevant entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) and does the name of the active match that in the SUSMP (in some cases the SUSMP provides a general category, rather than a specific active name, and is less relevant)?
- for pesticide active constituents only, is the stated common name consistent with the common name given in the Australian Standard for pesticide common names, or the International Organization for Standardization (ISO) Standard for pesticide common names, or in a specification published by the Joint Meeting on Pesticide Specifications of the FAO and WHO?
- for veterinary active constituents, is the stated common name consistent with the name given in a recognised pharmacopoeia[1], the WHO list of International Nonproprietary Names (INN) or the Therapeutic Goods Administration Australian Approved Name (ANN)?

Consideration may need to be given to how the active constituent is defined; whether it is a mixture of compounds that is synthesised (eg bioallethrin) or extracted from a natural source (eg pyrethrum extract), if it is a racemic mixture (eg methoprene) or it is primarily one stereoisomer but with a significant contribution of the other stereoisomer (eg S-metalochlor).

In assessing this information the APVMA is seeking to ensure that the common name for the active constituent is correct when it is entered in the Record.

Chemical name

Regulations 15(1)(a) and (b), and 42 (3)(e)

The APVMA assesses the chemical name of active constituents for both agricultural and veterinary constituents:

- is there an International Union of Pure and Applied Chemistry (IUPAC) name for the active constituent?
- is the stated IUPAC name correct?

[1]APVMA recognised pharmacopoeia are the British Pharmacopoeia, the British Pharmacopoeia (Veterinary), the European Pharmacopoeia, and the US Pharmacopoeia.

- if there is no IUPAC name, is there a name for the active constituent in any of the following (in the order shown)?
  - a standard that is specified in an order under Section 7 of the Agvet Code
  - a standard that has been made under Section 6E of the Agvet Code
  - (for veterinary only) a standard in the order: British Pharmacopoeia, or British Pharmacopoeia (Veterinary), or European Pharmacopoeia or United States Pharmacopeia
  - (for pesticides only) a standard specified in the specifications published by the Joint Meeting on Pesticide Specifications of the FAO and WHO
  - (for pesticides only) an APVMA Standard
  - is there a Chemical Abstracts Services (CAS) Name? This is considered supplementary to the IUPAC name.

In assessing this information the APVMA is seeking to ensure the chemical name of the active constituent is correct when it is entered in the Record.

Chemical abstract service registry number

The APVMA assesses the Chemical Abstract Service (CAS) registry number of active constituents for both agricultural and veterinary chemical constituents:

- is there a CAS registry number for the active constituent and is it correct?

In assessing this information the APVMA is seeking to ensure that the named active constituent is consistent with the indicated chemical structure including stereo-isomerism/configuration.

Note that some actives, eg microbial actives, plant extracts, and many mixtures may not have CAS numbers.

Molecular formula and molar mass

Regulation 15(1)(d)

The APVMA assesses the molecular formula and molar mass of active constituents for both agricultural and veterinary constituents.

In assessing this information the APVMA is seeking to ensure that the named active constituent is consistent with indicated chemical structure. This is especially relevant to new (ie not previously approved in Australia) active constituents.

Chemical structure

Regulation 15(1)(d)

The APVMA assesses the chemical structure of active constituents for both agricultural and veterinary constituents, where this is relevant.

In assessing this information the APVMA is seeking to ensure that the named active constituent is consistent with the indicated chemical structure. This is especially relevant to a new active constituent.

Structure elucidation

Regulation 15(1)(d)

The APVMA assesses the structure elucidation (such as by infrared spectrometry, mass spectrometry or nuclear magnetic resonance) of active constituents for both agricultural and veterinary constituents:

- does the spectroscopic data confirm the proposed structure of the active?

In assessing this information the APVMA is seeking to ensure that the identity and chemical structure of the active constituent are correct and accurate, so all information on the register is correct.

This information should be readily available for existing active constituents, and is generated as part of the data dossier for new active constituents. More extensive data is expected for a new active constituent.

Physicochemical properties

The APVMA assesses the following physicochemical properties of new active constituents for both agricultural and veterinary constituents:

- is the active constituent a Technical Material (TC) (usually dry basis) or a Technical Concentrate, also commonly known as a manufacturing concentrate (for stability purposes or ease of handling an active may be supplied diluted in a suitable solvent or solid diluent)?
- are the relevant physical and chemical properties (eg appearance; chirality; polymorphism; melting/boiling points; solubilities; partition coefficient; vapour pressure; hydrolysis; acid dissociation constant (pKa); safety properties, such as flash point, auto-ignition temperature, thermal decomposition, oxidising, corrosive, or explosive properties) of the active constituent provided and determined using appropriate methods?
- is the active constituent a nanomaterial (deliberately engineered to have 1 or more dimensions in the range 1-100 nm)?
- are there published analytical test methods (eg OPPTS (new name: OCSPP), OECD, JMAFF, CIPAC, pharmacopoeia) or has validation data been provided to support a different method? If published methods are varied some validation data are also sought.

In assessing this information the APVMA is seeking to ensure that relevant physical and chemical properties of the active constituent are accurately reported so that they can be relied upon in other assessments of the active constituent.

Box 1: Example of relevance of physicochemical properties

The physicochemical property results provided indicate that the n-octanol to water log partition coefficient (logKow) of the active constituent is 3.5, which indicates potential for fat solubility. The logKow acts as a screening measure for determining whether additional tests or considerations (eg additional environmental studies, or modification of animal commodity MRLs) are required to satisfy the safety, efficacy and trade criteria.

Stability

Agvet Code section 5A(2)(b)

The APVMA assesses the stability of new active constituents for both agricultural and veterinary constituents. The links provided give specific details:

- are the conditions of the stability study reported (eg storage temperature, humidity, packaging materials), and are they appropriate given the likely conditions of storage in practice?
- stability results of individual batches of the technical active. Ideally, for veterinary actives, testing is conducted on at least three batches of at least pilot scale, in accordance with VICH GL3. For agricultural active constituents, testing on at least one batch should be provided in accordance with APVMA guidelines. Valid scientific justification can be provided to justify provision of results for fewer batches, or for not providing stability data.
- was the stability of the active constituent undertaken in the proposed packaging material, or an appropriate justification provided? Suitable scientific argument that the packaging is inert and unlikely to react with the active may be provided.
- was there a significant change in the content of the active constituent on storage (typically >5 per cent)? If so is this acceptable?
- do the results before and after storage still comply with the declaration of composition (DoC) or Active Specification? If not has appropriate justification been provided?
- are there any significant increases in any of the related impurities or toxicologically significant impurities (for pesticide active constituents, is there potential for the chemical product containing the active constituent being classed as date-controlled)? Are these increases acceptable from a safety perspective?
- are any new impurities produced on storage (ie degradation products) and are these acceptable from a safety perspective?
- has the photostability of the active constituent been determined? If not is there justification?
- has the stress-related stability (acid, base, oxidation, reduction, light, heat, exposure to metals or metal salts) of the active constituent been determined? If not has appropriate justification been provided?
- if relevant, have any nanoscale properties of the active constituent been affected?
- is the stability data sufficient to conclude that the active constituent is, or will be, stable for up to a retest period of two years under normal storage conditions or such alternative conditions as specified by the applicant? If not has appropriate justification been provided?

It is the responsibility of the manufacturer to ensure that all components of a product are within retest or expiry date at the time they are used to manufacture the product and that the use of these materials produces a product which is fit for its intended purpose throughout the product's shelf-life.

In assessing this information the APVMA is seeking to ensure that the inherent stability properties of the active constituent are well understood. This information can then be taken into account for the purposes of the chemical product stability (eg the potential for adverse interactions with metals that might suggest a need to avoid metal packaging materials or adverse photostability results that might suggest a need for lightproof packaging).

For a new source of approved active, the storage stability tests are generally not required as the stability profile has been established at the initial active approval.

Method of manufacture

Agvet Code section 5A(2)(a)(ii)

The APVMA assesses the method of manufacture of a new active (either agricultural or veterinary). For new sources (new sites of manufacture) of approved actives, manufacturing process information is generally required for most agricultural and non-compendial[2] veterinary actives. For new sources of existing veterinary actives manufactured to the standard of a recognised pharmacopoeia monograph (and complying with VICH GL18 limits for residual solvents), manufacturing process is not usually required. The APVMA would request information on the manufacturing process for a new source of a compendial active, if it was determined that this was necessary to decide whether the active satisfies the safety criteria.

The following points are generally considered in a full assessment of the manufacturing process:

- do the manufacturing process description, reaction scheme and flow chart accurately depict the sequence of chemical events, all reactions and purification steps, amounts of starting materials and catalysts, reaction temperature and pressure, pH, leading to the active constituent?
- if the active constituent is a single stereoisomer or is enriched in one or more isomers how has this been achieved and is there any potential for inversion during the manufacturing process?
- what is the commercial-scale batch size, including continuous manufacture (eg kg/day) (can be a range)?
- are there any potential contaminants of the active constituent or toxicologically significant chemicals described in the manufacturing process (eg heavy metal catalysts or dimethyl sulfate)?
- are there one or more purification steps in the manufacturing process (eg recrystallisation)? Do these steps introduce potential impurities (eg solvents)?
- if relevant, are any components deliberately added to the active constituent (eg solvents to produce a manufacturing concentrate, anti-oxidants)?
- for certain veterinary active constituents only, is the active constituent sterilised? If so what method is used and is it fit for purpose?
- is there a reworking step described and does it have the potential to adversely affect the quality of the active constituent?
- is there any step in the manufacturing process that confers nano-properties on the active constituent?

In assessing this information the APVMA is seeking to ensure that the manufacturer is in control of the manufacturing process, and is able to manufacture the active to a consistent and acceptable quality.

If known toxicologically significant compounds are used as reagents, solvents or catalysts in the manufacturing process (such as cyanide salts, dimethyl sulfate or heavy metal catalysts), then details of the measures

[2]Actives not having a monograph in an APVMA recognised pharmacopoeia.

undertaken during the manufacturing process to minimise the levels in the final product are likely to be required, in addition to testing for the compound as an impurity in the batch analyses.

The DoC or specifications should always be included in the data for approval of the Active constituent so that the amount, type and batch-to-batch consistency of any impurities present can be evaluated as part of determining the quality of the active constituent.

Box 2: Consideration of manufacturing process

The manufacturing process is assessed to ensure that the steps described are likely to result in manufacture of the active to meet the Declaration of Composition (DoC)—minimum level of the active constituent, isomeric composition (if applicable), and maximum levels of impurities. This feeds into determination of satisfaction with respect to the safety criteria for actives, and in turn, the safety and efficacy criteria for products using the active. As part of this the assessor must consider the properties and toxicity of both the raw materials and any intermediate chemicals formed during the synthesis pathways proposed by the applicant and whether the process adequately controls the levels of any resulting impurities.

For example dioxins are unwanted toxic impurities that may be formed during high temperature or high pH processes to manufacture certain chlorinated pesticides. The chemistry assessor examines the proposed synthesis pathways and conditions to determine whether there is a risk of dioxin formation and whether there are adequate controls or purification steps to reduce the risk of dioxins being present in the final active constituent.

Quality controls

When considering the manufacturing process for an active, the APVMA assesses the quality controls of manufacture of active constituents for both agricultural and veterinary constituents:

- are specifications for the raw materials available? Is there potential for introduction of toxicologically significant impurities into the technical active via any of the raw materials?

Note: these specifications of the raw materials refers to the acceptance criteria for precursor chemicals used in the synthetic process for the manufacture of the active constituent. The purity of the precursors directly impact the purity and composition of the active constituent.

- are there appropriate quality controls on any isolated intermediates?
- are there critical steps in the manufacturing process that require specific control and are measures in place to provide this specific control (eg keeping the temperature or pH within a certain range)?

In assessing this information the APVMA is seeking to ensure that the quality controls used in the manufacture for the active constituent are suitably fit for the purpose of consistently producing the active constituent of an acceptable quality.

Animal-sourced materials

The APVMA assesses the potential for veterinary active constituents to contain material that might cause transmissible spongiform encephalopathy (TSE) such as bovine spongiform encephalopathy (BSE):

- if relevant, have details of the biological source, country of origin, manufacturer and specifications been provided? If not has appropriate justification been provided?

- are any of the raw materials sourced from animals that might contain (including as contamination) a specific risk material such as brain and spinal cord? Typically an appropriate declaration stating the TSE status of the raw material is provided.

In assessing this information the APVMA is seeking to ensure that the TSE contamination risk of the active constituent is minimised.

Note: if a declaration is not provided indicating the TSE status of any animal origin material, the application may not satisfy the safety criteria of the Agvet Code.

Genetically Modified Organisms (GMO)

The APVMA considers:

- is the active constituent a GMO?
- is the active constituent derived from a GMO?
- is the active constituent produced using a GMO?
- are any of the raw materials derived from GMO material?

The Agricultural and Veterinary Chemicals (Administration) Act 1992 requires APVMA to consult with the Gene Technology Regulator when deciding whether to approve an active constituent, register an Agvet chemical product, approve a label, vary or reconsider any approvals or registrations, or issue a permit for a GM product. APVMA must ensure that any advice given by the Gene Technology Regulator is taken into account when we make a decision on the approval, registration or reconsideration of such products.

Therefore, if your application contains any active constituent or product derived from or produced by a GMO, you must inform the APVMA. This includes any organism that has been modified by gene technology and any organism that has inherited particular traits from an organism in which the traits in the parent organism were the result of genetic modification.

Impurities

Agvet Code section 5A(2)(a)(iii)

The APVMA assesses the impurities of active constituents for both agricultural and veterinary constituents:

GENERAL

- are the impurities in absolute amounts eg g/kg or per cent w/w relative to the active constituent?
- are any of the impurities also active constituents (eg simazine in atrazine)?
- are any of the impurities isomers of the active constituent?
- have the likely sources (eg unreacted starting materials or intermediates, side reaction products) of the impurities been discussed and are these plausible?

These considerations are connected to the assessment of the manufacturing process.

SIGNIFICANT IMPURITIES (RELATED IMPURITIES)

- are all impurities that are expected and/or shown to be present at or greater than the following levels identified and quantified?
    - pesticide active constituents: 1 g/kg (0.1 per cent w/w)
    - veterinary active constituents: see Note 2

Note 1: Mass Spectrometry (MS) and the associated fragmentation pattern of specific impurities may be used to determine the structures of specific impurities present, along with an understanding of the manufacturing process for the active.

The Level of Detection (LoD) and level of Quantification (LoQ) of the method used will also impact on the understanding of the levels of impurities present.

Note 2*:* VICH GL10(R) Section 7 *QUALIFICATION OF IMPURITIES* describes the appropriate levels of impurities that are to be reported. As this document is descriptive and includes reference to a number of appendixes, the text has not been reproduced in this document. Additional information can be gained from VICH GL39. The APVMA evaluator will refer to these VICH guidelines and other internationally recognised guidance documents when assessing your application.

TOXICOLOGICALLY SIGNIFICANT IMPURITIES (RELEVANT IMPURITIES)

- are there any impurities of toxicological and/or ecotoxicological concern that are present in the active constituent at any level, including less than 1 g/kg? See the APVMA website for a list of compounds and classes of compounds regarded as toxicologically significant, or refer to the relevant APVMA standard or pharmacopeia monograph.
- are any compounds of known toxicological concern (eg dimethyl sulfate) used as reagents, solvents or catalysts during the manufacturing process?
- are the toxicologically and/or ecotoxicologically significant impurities known or new? If new what maximum limit in the active constituent does the toxicological assessment of the active constituent allow?

In assessing this information the APVMA is seeking to ensure that the extent (and nature) of the impurities resulting from the manufacture of the active constituent are well understood.

Box 3: Example of significant impurities

Certain organophosphate pesticides (eg diazinon, malathion) may contain impurities that are significantly more toxic than the active, or have different toxicological end points from the active.

For a new active, any toxicologically significant impurities will be included in the APVMA standard with appropriate maximum limits. Subsequently approved new sources of that active must meet the APVMA standard, including maximum levels for any toxicologically significant impurities.

Box 4: Note about the composition and purity of the active constituent

Purity: the content of active substance expressed as a percentage or in grams per kilogram or grams per litre. Purity may be expressed on the technical active as supplied, or subject to a modification (eg on a dry weight basis).

Composition: the identities and amounts of related impurities present in the active constituent. These impurities may be starting materials that were not fully consumed in the manufacturing process, products of side chemical reactions that took place during the manufacturing process, or impurities present in the starting materials.

When a new active constituent or a new site of manufacture of an existing active is approved, the DoC or specification is assessed based on the batch analysis data provided. The DoC or specification is also compared to any relevant standard (eg the APVMA standard and/or an FAO/WHO Joint Meeting on Pesticide Specifications standard for an agricultural active, or a pharmacopoeia monograph for a veterinary active. Once the new site of manufacture of an active has been approved the composition (DoC) or specification for that active is entered onto the record.

Note 1: an active constituent must comply at all times with the relevant standard and with the compositional details as assessed and approved for that active source.

Declaration of Composition (DoC) or specification

Agvet Code section 5A(2)(a)(iii) and (via), section 6E and regulation 17C(1)(Item 1)

The APVMA assesses the Declaration of Composition (DoC) (pesticides) or Specifications (veterinary) for active constituents:

AGRICULTURAL/PESTICIDE ACTIVE CONSTITUENTS:

- is there an FAO/WHO specification for the active constituent? Is the proposed specification consistent with the FAO/WHO specification?
- is the minimum purity specified?
- where relevant, is the isomeric composition (eg S/R isomer ratio) specified?
- if the active constituent is a manufacturing concentrate is the purity on a dry weight basis specified and does it meet the APVMA standard, or has appropriate justification been provided?
- have the maximum contents of all Related/Significant impurities present in the Batch Analysis at 1 g/kg (0.1 per cent w/w) or greater been specified?
- does the active constituent comply with or address the relevant points in the general requirements in this section?

VETERINARY ACTIVE CONSTITUENTS:

- is there a specification (monograph) for the active constituent in an APVMA recognised pharmacopoeia? Is the proposed specification consistent with the pharmacopoeia specification and if not has appropriate justification been provided (eg a pharmacopoeia standard active is not required for the use pattern of the proposed product(s) using the active)?
- is the minimum purity specified?
- where relevant, is the isomeric composition (eg S/R isomer ratio) specified?
- if the active constituent is a manufacturing concentrate is the purity on a dry weight basis specified?
- are maximum levels specified for all significant related impurities reported in the batch analyses/certificates of analysis?

- are the residual solvents, if any, present at levels consistent with VICH GL18(R) or has a justification been provided?
- are other impurities (eg water, sulphated ash, heavy metals), if any, present? Where relevant, are these consistent with VICH guidelines or has appropriate justification been provided?
- if required, are other parameters (eg appearance, pH, particle size, microbiological quality) specified with appropriate limits?
- does the active constituent comply with or address the relevant points in the general requirements in this section?

GENERAL REQUIREMENTS FOR ACTIVE CONSTITUENT SPECIFICATIONS:

- are any administrative type details (eg manufacturer's name and factory address, active common name, signature and date of approved person) missing?
- have the appropriate chemical names (company codes if relevant), CAS registry numbers (if applicable/available), or monograph method references been specified?

In assessing this information the APVMA is seeking to ensure that where appropriate that the composition and purity, including the extent to which the active constituent will contain impurities, of the active constituent is appropriate and aligns with any relevant national or international standard. Ultimately, this information is assessed to ensure the active satisfies the safety (and efficacy) criteria.

Batch analysis

Agvet Code section 5A(2)(a)(iv)

The APVMA assesses the batch analysis of active constituents for both agricultural and veterinary constituents. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or scientific argument has been provided by the applicant.

- agricultural/pesticide active constituents: have results for at least five recently manufactured and analysed (date of analysis <five years before the date of application) commercial-scale batches of the active constituent been provided? This is to ensure that the batch analysis results are relevant to the composition and purity of active constituent that will be supplied. Appropriate justification will be considered if some or all of the batch analyses are more than five years old.
- if data on commercial-scale batches are not available, have batch analysis for pilot-scale batches manufactured using the same process as intended for commercial-scale batches been provided?
- is the calculated mass balance in the range 98–102 per cent w/w?
- does the active constituent comply with or address the relevant points in the general requirements in this section?

VETERINARY ACTIVE CONSTITUENTS:

- have results for at least three recent commercial-scale batches of the active constituent been provided?

- is there a pharmacopeia standard for the active, if so, does the active comply with all test parameters, or has appropriate justification been provided?
- where there is a pharmacopeia standard the content is usually expressed as a range, eg 98–102 per cent. Has this been met?
- does the active constituent comply with or address the relevant points in the general requirements in this section?

GENERAL REQUIREMENTS (AGRICULTURAL/PESTICIDE AND VETERINARY ACTIVE CONSTITUENTS):

- is the batch analysis from the proposed manufacturing site(s)?
- are details of the batch number, date of manufacture and date of analysis included?

Note: the Agvet Code Act requires that you retain batch documentation including those details listed in the dot point above for the statutory time period.

- is the batch size consistent with the scale of the proposed manufacturing process?
- does the active content comply with the proposed Declaration of Composition (DoC) or specification?
- where relevant, does the isomeric composition comply?
- are all Related/Significant impurity limits complied with?
- are all Toxicologically Significant/Relevant impurity limits complied with?
- if a Declaration of Composition/specification limit is not complied with has a valid scientific justification and/or additional data been provided?

In assessing this information the APVMA is seeking to ensure that the nominated manufacturer can consistently manufacture the active constituent in compliance with both the DoC/specification and any standard that may exist for this active constituent. This feeds in to the determination of whether the active constituent satisfies the safety criteria (section 5A of the Agvet Code), and in turn, whether a product using the active will satisfy the safety and efficacy criterial (sections 5A and 5B).

Table 1: Example of a summary of the batch analysis data for an active constituent.

Compound	Specification	Batch No. 1	Batch No. 2	Batch No. 3	Batch No. 4	Batch No. 5
Active	Min. 970 g/kg	**940.2 g/kg**	977.1 g/kg	970.6 g/kg	979.7 g/kg	973.7 g/kg
Impurity A	Max. 10 g/kg	9.9 g/kg	7.6 g/kg	**16.2 g/kg**	9.6 g/kg	5.6 g/kg
Impurity B	Max. 3 g/kg	2.3 g/kg	2.8 g/kg	1.9 g/kg	2.4 g/kg	2.7 g/kg
Impurity C	Max. 2 g/kg	**2.8 g/kg**	1.7 g/kg	0.9 g/kg	1.3 g/kg	1.7 g/kg
Toxicologically significant impurity D	Max 10 mg/kg (10 ppm)	8.1 ppm	5.2 ppm	6.4 ppm	3.2 ppm	N.D.*
Totals		**955.2 g/kg**[1]	989.2 g/kg	989.6 g/kg	993.0 g/kg	983.7 g/kg

*Noncompliant results marked in **bold***

[1]SUM 95.52 per cent (outside the generally accepted mass accountability limits of 980-1020 g/kg (98-102%).

Ave: 968.26 g/kg

**: N.D. = not detected (LoD: 0.1 ppm)*

Analytical methods and validation

Regulation 8AA

The APVMA assesses the analytical methods and validation of active constituents. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or scientific argument has been provided by the applicant:

- is the analytical method for the assay of the active constituent purity a published 'regulatory method' (eg CIPAC, AOAC, pharmacopoeia)?
- if the analytical method for the assay of the active constituent purity is not a published 'regulatory method' have complete details of the method and relevant validation been provided?
- for chromatographic methods (eg HPLC, GLC) or non-chromatographic methods (eg qNMR, AAS) does the validation data demonstrate adequate validation of selectivity, linearity, range, and precision (and accuracy if matrix effects may be a factor, eg for a manufacturing concentrate) for the active, plus accuracy and Limit of Detection (LoD) and Limit of Quantification (LoQ) for toxicologically significant impurities, as per the APVMA guidelines?
- for impurities structurally related to the active and not specified as toxicologically significant, it is recognised that in many cases, reference standards will not be available. Quantification for these impurities is sometimes achieved by area normalisation with respect to the active constituent (see box 5 below).
- how is the active constituent purity quantified (eg external or internal calibration) and is it fit for purpose?
- if relevant, have representative blank, standard and sample chromatograms and/or spectra for the active constituent been provided demonstrating an absence of interfering peaks/signals?
- is the analytical method for the assay of the active constituent purity also used for the determination of the content of the impurities (including toxicologically significant) and is it capable of detecting and quantifying the impurities? If not has one or more separate analytical methods been provided that is capable of detecting and quantifying the impurities?
- how are the impurities (including toxicologically significant) quantified (eg external standard with or without a correction factor, area normalisation)?
- does the validation data for the toxicologically significant impurities demonstrate adequate validation of selectivity, linearity, precision, accuracy, Limit of Detection (LoD) and Limit of Quantification (LoQ)?
- if relevant, have the analytical methods for the analysis of the nano-properties of the active constituent been detailed and validated?
- if relevant, have the analytical method transfer study details and validation been provided?

In assessing this information the APVMA is seeking to ensure that the analytical method is fit for purpose so that the analysis results used by the drug product manufacturer can be considered reliable.

Box 5: Example of determination of related impurities without a specific standard

Purity: the content of active substance expressed as a percentage or in grams per kilogram or grams per litre. Purity may be expressed on the technical active as supplied, or subject to a modification (eg on a dry weight basis).

Composition: the identities and amounts of related impurities present in the active constituent. These impurities may be starting materials that were not fully consumed in the manufacturing process, products of side chemical reactions that took place during the manufacturing process, or impurities present in the starting materials.

When a new active constituent or a new site of manufacture of an existing active is approved, the DoC or specification is assessed based on the batch analysis data provided. The DoC or specification is also compared to any relevant standard (eg the APVMA standard and/or an FAO/WHO Joint Meeting on Pesticide Specifications standard for an agricultural active, or a pharmacopoeia monograph for a veterinary active. Once the new site of manufacture of an active has been approved the composition (DoC) or specification for that active is entered onto the record.

Note 1: an active constituent must comply at all times with the relevant standard and with the compositional details as assessed and approved for that active source.

Packaging

The APVMA assesses the packaging of active constituents:

- is the size and the detailed material composition of the container that is in contact with the active constituent specified? Is any other secondary-type packaging material used?

Analytical reference standards

Agvet Code section 157

The APVMA generally requires that the following analytical reference standards for new agricultural or veterinary active constituents be submitted to the National Analytical Reference Laboratory (part of the National Measurement Institute):

- 1 gram of an analytical reference standard of the pure active constituent, or where the active is a mixture of isomers that can be separated, 1 gram of a reference standard of each isomer
- 100 grams of the technical active constituent (ie the active as manufactured for use in products; the percentage purity must be specified)
- 10 milligrams of an analytical reference standard for each toxicologically significant manufacturing impurity present in the active (if any)
- 100 milligrams of an analytical reference standard for each metabolite of the active included in the residues definition for compliance (enforcement) with the Maximum Residues Limits.

The APVMA has built up a considerable repository of reference materials that are stored by the NMI. These standards are commonly used by the National Residues Survey (NRS) for analyses of food sample for pesticide or veterinary medicine residues, particularly where reference standards may not be commercially available. Maintenance of this library of reference materials supports the efficient functioning of the National Registration

Scheme for agricultural and veterinary chemicals[3], and ultimately, supports exports of Australian agricultural produce through ensuring compliance with Australian and overseas MRLs.

The amounts of material are a guide, and smaller quantities may be acceptable in some cases.

Provision of reference standards is not necessary in some cases and a valid argument can be provided, eg:

- microbiological active constituents;
- where the is no use (either currently or likely in the future) in food producing crops or animals;
- where no MRLs are proposed or required (eg Table 5 entries[4])
- where an active is not generally analysed using a standard of the active, or where it is analysed using a standard that is widely available commercially.

APVMA active constituent standards

The standard for an agricultural chemical typically specifies the minimum purity of the active constituent, the isomeric composition where relevant, and the maximum level of the relevant impurities, including those of toxicological significance. The toxicological profile of the active constituent is directly linked to its purity and the associated impurities. Where possible, the APVMA seeks to align its standards with the pesticide specifications published by the Joint Meeting on Pesticides Specifications, an expert ad hoc body administered jointly by FAO and WHO[5].

For **veterinary** pharmaceuticals if there is a pharmacopoeial standard published in any of the following:

- British Pharmacopoeia (BP); or
- British Pharmacopoeia (Veterinary); or
- European Pharmacopeia (EP); or
- United States Pharmacopeia (USP)

the APVMA will refer to those standards. The APVMA may consider establishing a standard for a veterinary active constituent that does not have a relevant pharmacopoeia standard.

[3]https://apvma.gov.au/node/3187

[4]Table 5 includes substances and situations where MRLs are not necessary as residues do not or should not occur in foods or animal feeds; or where the residues are identical to or indistinguishable from natural food components; or otherwise are of no toxicological significance.

[5]http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/en/

Non-prescribed conditions

Agvet Code section 23(1)(b)

The APVMA can impose conditions as it thinks appropriate on the approval of the active constituent under section 23(1)(b) of the Agvet Code Act.

In assessing this information the APVMA is seeking to ensure that it can be satisfied with respect to the safety criteria, which may require certain non-prescribed conditions to be placed on the approval. Possible conditions could include requiring starting materials to be sourced from particular manufacturers, or to be manufactured to a particular specification.

4.2 Assessment of chemical products

AGRICULTURAL CHEMICAL PRODUCT

An agricultural chemical product is defined as the substance or mixture of substances that is represented, imported, manufactured, supplied or used as a means of directly or indirectly; destroying, stupefying, repelling, inhibiting the feeding of, or preventing infestation by or attacks of, any pest in relation to a plant, a place or a thing, or destroying a plant, or modifying the physiology of a plant or pest so as to alter its natural development, productivity, quality or reproductive capacity, or modifying an effect of another chemical product, or attracting a pest for the purpose of destroying it.

VETERINARY CHEMICAL PRODUCT

A veterinary product is defined as the substance or mixture of substances that is represented as being suitable for, or is manufactured, supplied or used for, administration or application to an animal by any means, or consumption by an animal as a way of directly or indirectly; preventing, diagnosing, curing or alleviating a disease or condition in the animal or an infestation of the animal by a pest, or curing or alleviating an injury suffered by the animal, or modifying the physiology of the animal so as to alter its natural development, productivity, quality or reproductive capacity, or so as to make it more manageable or modifying the effect of another veterinary chemical product.

PURPOSE OF THE ASSESSMENT

The purpose of the assessment of the chemistry aspects of an agricultural or veterinary chemical product is to confirm that the product is manufactured to an appropriate and consistent quality and composition, and that it will satisfy the safety and efficacy criteria of the Agvet Code.

Formulator name(s) and plant address(es)

Regulations 16(g) and (h) and 17C(2) Item 2(b)

The APVMA assesses and records the chemical product formulator's (manufacturer) name(s) and plant address(es).

In assessing this information the APVMA is seeking to ensure that the name(s) and plant address(es) for the chemical product manufacturer(s) are correctly entered into the Register. The manufacturer's name and manufacturing site addresses are relevant particulars for a product.

Box 6: Note regarding plant addresses

The APVMA may seek clarification from overseas regulators to authenticate the status of specific manufacturers.

Formulation type

Regulations 16(da) and 17C(2) Item 5

The APVMA assesses the formulation type of chemical products:

- is the formulation type appropriate for the pesticide chemical product?
- is the formulation type and/or dose form appropriate for the veterinary medicine product?

In assessing this information the APVMA is seeking to ensure that the formulation type (and/or dose form) of the chemical product is correct when entered in the Register. The formulation type of a product may determine the first aid and safety directions or the directions for use required for the product, and is an important piece of information in assessing products relying on reference products.

Note: formulation type means:

1. for an agricultural chemical product—the formulation code and description that:
    - are set out in guidelines made under section 6A of the (Agvet) Code as in force from time to time, and
    - apply to the product, and
2. for a veterinary chemical product—the form of the product.

Examples: a capsule, emulsifiable concentrate, injectable solution, implant, intramammary treatment, oral drench or tablet.

Active constituent

Regulations 16(d) and 17C(2) Item 1

The APVMA assesses the active constituents of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or scientific argument has been provided by the applicant:

- is/are the active constituent(s) to be contained in the chemical product an approved active constituent, or has an application for approval been made?

- are the active constituents to be contained in the chemical product exempted from the requirement for approval[6]?
- is there a suitable quality standard for the active constituent in the chemical product?
- is a certificate(s) of analysis provided or referenced for the active constituent?
- is the quality of the active constituent acceptable, noting the proposed use pattern and form of the product?

In assessing this information the APVMA is seeking to ensure that the composition and purity of the active constituents used in the chemical product are consistent with any relevant quality standards and the approved active constituent details, and that the active is of suitable quality to enable the safety and efficacy criteria to be satisfied in respect of the product.

Box 7: Example of consideration of the active constituents in a product

When an active constituent is approved, the DoC or specifications is assessed in conjunction with the batch analysis data provided. The DoC or CoA is also compared to the relevant standard t. Once the new site of manufacture of an active has been approved the composition and purity for that active is entered onto the record, as a relevant particular for that active.

When evaluating an associated product that uses an approved active, a CoA is also provided for the active constituent.

This DoC or CoA may also be compared to the details on the register to ensure the manufacturer is manufacturing the active to the standard (composition and purity) recorded on the register for that site of manufacture.

If the DoC or CoA indicates non-conformance with the relevant standard or with information on the register then this is a trigger for relevant information to be passed to the Compliance Section for investigation as the manufacturer of the active may be in breach of the Agvet Code Act.

Note: an active constituent must comply at all times with the relevant standard and also comply with the compositional details as entered onto the register.

For veterinary chemical products in particular, not all approved sources of active may be of appropriate quality for the particular product. Many active constituents are supplied to different grades for different purposes, and an active constituent that is of appropriate quality for use in a feed premix may not for example be of sufficient quality for use in a formulation for injection. Provision of a certificate of analysis ensures that the active used is of suitable quality for the product in question, and will ensure that the product meets the safety criteria.

Formulation composition

Regulation 16(b) and (c)

The APVMA assesses the formulation (composition) of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or scientific argument has been provided by the applicant:

- are the common and/or chemical names of the constituents correct for the constituents specified?
- if relevant, have complete compositional details for any Trademark named (proprietary) constituents been provided?

[6]https://apvma.gov.au/node/4176

- where available, are the Chemical Abstracts Service (CAS) registry numbers specified for the constituents?
- are the quality standards of the constituents, including the composition and purity of each active constituent, specified?
- are the concentrations for each of the constituent correct and consistent with the formulation process details and the label claim(s)?
- has the concentration specified for the active constituent accounted for the nominal purity of the active as stated on the accompanied CoA?
- are the purposes of the constituents correct?
- does the sum of the constituent concentrations match the total mass/mass or mass/volume amounts for the chemical product?
- is the density or specific gravity of the product correct?
- are all constituents listed present in the chemical product as marketed? Constituents that are not present in the final packaged product because they are removed during a step in the formulation process (eg water added to granulate a product which is then removed in a subsequent drying step) should not be included in the formulation composition. The formulation process description (see below) should include details of the constituents that are used in the formulation process of the product but are not present in the final packaged product.

In assessing this information the APVMA is seeking to ensure that the information relating to the constituents of the chemical product are correct when entered in the Register. The constituents of a chemical product, the concentration of each constituent of the chemical product, and where possible/relevant, the composition and purity of each active constituent of the product are all relevant particulars for the product. Together, these particulars are the formulation of the product.

Regulations 8AB(1)(d)(i) and (ii), 8AB(1)(e)(i) and (ii), and 8AB(1)(f)

- for a molluscicide in the form of a bait with either metaldehyde or methiocarb as the active constituent does the product contains any bone meal or other product of animal origin and is it a distinctive green or blue colour, respectively?
- for a product applied to seeds to be stored does the product contain sufficient pigment or dye so as to colour the seed and thus enable it to be readily distinguishable from non-treated seed?

In assessing this information the APVMA is seeking to ensure that legislative requirements for certain specific formulation types (snail baits and seed treatments) are complied with.

Box 8: Example of formulation composition problems

Example 1: An immediate release tablet product is proposed without any constituent that would perform a disintegrant role (eg sodium starch glycolate). This inappropriate formulation composition would be identified as part of the APVMA assessment and the applicant would be required to confirm the accuracy of the formulation submitted or provide a corrected formulation prior to registration.

Example 2: A product is proposed to be registered with the following formulation composition for a granule type product that uses water to form a slurry of the ingredient prior to the drying step that produces the granule:

- Active 500 g/kg

- Filler 400 g/kg
- Binder 100 g/kg
- Water 100 g/kg

In this situation the stated total mass of the constituent is 1,100 g/kg. The applicant has failed to take into account that the water is removed during the drying stage and hence is not present in the formulation composition of the product.

Formulation comparisons

Regulations schedule 6

Where a product is proposed to be registered under Items 5, 6, 7 or 8 the APVMA must consider whether it meets the definitions provided in Schedule 6 to the Regulations of 'similar to', 'closely similar to' or 'the same as' the reference product. As these items require a limited data set (in the case of item 5 and 6) or no data (in the case of item 7 or 8), the APVMA needs to base some or all of its satisfaction with respect to the safety, efficacy and trade criteria on the risks associated with the new product being sufficiently similar to those associated with a product already registered.

The risk manager for the product will seek advice from the Chemistry and Manufacture section regarding whether the proposed and reference products can be determined to be similar or closely similar (and whether a determination of close similarity can be made in the absence of a chemistry package, as for an item 7).

The APVMA is only able to provide limited information regarding the outcome of such determinations, as the APVMA is precluded from disclosing information regarding the reference product, which is confidential to the holder of the reference product. The APVMA's approach to managing confidential commercial information (CCI) is provided on the APVMA website[7].

Analogous questions may arise with item 12 or 14 applications, where an applicant wishes to vary a product registration to change a formulation, or include an additional formulation. The APVMA needs to be satisfied that the new or additional formulation will also meet the safety criteria, and be functionally equivalent to the existing formulation.

Item 5 (agricultural chemical products)

From a Chemistry perspective, for an agricultural chemical product to be similar to that of the reference product, it must have:

- the same active constituent(s); and
- the same formulation type.

[7]https://apvma.gov.au/node/11966

Confirming whether or not two agricultural chemical products are similar is a straightforward task; in fact for two registered products this determination can be made using publicly available information, as the active constituent(s) and formulation type of a registered product are available in PubCRIS.

Item 5 (veterinary chemical products)

From a Chemistry perspective, for a veterinary chemical product to be similar to that of the reference product, it must have:

- the same active constituent(s) at the same concentrations;
- the same dosage form and formulation type; and
- excipients (non-active constituents) with similar properties and present in similar proportions.

The requirements for veterinary chemical products to be determined similar are more stringent than for agricultural chemical products. In addition to the requirement for the active and the formulation type to be the same, the active concentration must be the same, and the excipients must have similar properties and be present in similar proportions. For a liquid formulation, if the reference product contained a solvent, dye, and preservative, the proposed product would need to contain ingredients performing these functions, they would need to have similar properties and be present in similar proportions (replacement of water as the diluent with vegetable oil would not be acceptable, as these do not have similar chemical properties).

Item 6 and 7 (agricultural chemical products)

From a Chemistry perspective, for an agricultural chemical product to be closely similar to that of the reference product, it must have:

- the same active constituent(s), at the same concentration(s);
- excipients (non-active constituents) that are the same, or if different, will perform similar functions; and
- the same formulation type.

For an item 6, a Chemistry and Manufacture data package must be provided; for an item 7, a Chemistry and Manufacture data package is not required. For an item 7 agricultural chemical product application to be accepted therefore, the APVMA must be able to determine that the excipients will perform similar functions to those in the reference product, without Chemistry data being provided for the agricultural chemical product.

Examples of where a determination of close similarity might be able to be made when Chemistry data is available (item 6), but might not be able to be made in the absence of Chemistry data (item 7) include:

- there is a significant difference in the identities and/or concentrations of the surfactants (eg, emulsifiers in an EC, wetters/dispersers in a WG, WP or SC), such that, in the absence of chemistry data, the APVMA cannot be satisfied that the ingredients would perform similar functions to those of the reference product. Chemistry data provided with an item 6 could show for example, whether or not the product was capable of forming a stable emulsion, or suspension; while for an item 7 such data would not be provided

- there is a significant differences in the identities and/or concentrations of the suspending or viscosity modification agents in a suspension concentrate. Again, chemistry data could show for example, whether or not the product was capable of forming a stable suspension
- there is a significant difference in the concentration (or an absence of) an antifoam which is present in the reference product. Chemistry data could show whether or not the product produced unacceptable levels of foam on dilution and agitation (excessive foam production can be a WHS risk to mixers/loaders of pesticides).

Item 6 and 7 (veterinary chemical products)

From a Chemistry perspective, for a veterinary chemical product to be closely similar to that of the reference product, it must have:

- the same active constituent(s) at the same concentrations;
- the same dosage form and formulation type;
- either the same or equivalent excipients (non-active constituents) at the same or equivalent concentration, or if the excipients and/or their concentrations are not the same or equivalent, the differences in the chemical products are minor and not expected to have adverse implications for product quality, safety, efficacy or residues (safety, efficacy and residue data are not required) and
- either the product specifications (including release and expiry limits and test methods) and physico-chemical properties (including pH, particle size, crystal form, and where applicable dissolution profile, payout rate and payout period) are the same or equivalent, or, if different, the differences are minor and not expected to have an adverse effect on product quality, safety, efficacy or residues.

For an item 6, a Chemistry and Manufacture data package must be provided; for an item 7, a Chemistry and Manufacture data package is not required. For an item 7 veterinary chemical product application to be accepted therefore, the APVMA must be able to determine that any differences in the excipients and the specifications will not have an adverse effect on product quality, safety, efficacy or residues, without Chemistry data being provided for the chemical product.

Different formulation types have differing levels of sensitivity to differences in the excipients. For example, the efficacy, animal safety and residue behaviour of pour-on formulations is significantly more sensitive even to minor changes in the excipients than is the case for an orally administered drench. Therefore, greater differences in the excipients of a reference and proposed drench formulation are likely to be accepted as being ‘closely similar’ than for a pour-on. Similarly, oil-based injectable formulations are more sensitive than aqueous injectable formulations.

For the specifications, differences that result in the new product having more stringent limits are not likely to be an issue. For example, if the proposed product has a pH specification range that is narrower than for the reference product, and within the range of the reference product specifications, this would not adversely impact on a determination of close similarity. Generally, adding extra specifications provides greater assurance of the quality and would not impact on a closely similar determination (eg, addition of microbial quality specifications for a proposed oral liquid formulation when these were not present in the specifications for the reference product). Omission of a specification for a key parameter, such as preservative content, where a preservative is critical to ensure the microbial quality of the formulation, would not be acceptable, and would result in the products being determined not to be closely similar.

Item 8

Item 8 products must be the same in all respects as the reference product, with the exception of the product name, distinguishing number, and the name and business address of the applicant. From a Chemistry and Manufacture perspective, this means the chemical products must be identical, use the same packaging material and pack sizes, and be manufactured in the same factory to the same specifications using the same ingredients.

Non-active constituents (excipients) specifications and compositions

Agvet Code section 5A(3)(a)(iv)

The APVMA assesses the excipients (including those not present in the final product such as processing solvents or inert atmospheres) of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or argument has been provided by the applicant:

- are suitable quality standards specified for the non-active constituents in the chemical product?
- are any non-active constituents sourced or derived from:
  - animal material;
  - a genetically modified organism (GMO);
  - nanomaterials?
- are specifications, certificates of analysis and/or safety data sheets (SDS) (provided or referenced for the non-active constituents?
- is the quality of the non-active constituents acceptable?

In assessing this information the APVMA is seeking to ensure that the compositions and purities of the non-active constituents used in the chemical product are consistent with suitable quality standards.

Manufacturing process

Agvet Code section 5A(3)(a)(iii)

The APVMA assesses the following aspects of how the chemical product is formulated. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or argument has been provided by the applicant:

- is the commercial-scale of the chemical product manufacturing process specified?
- have complete details (eg raw material amounts (accounting for purity and any manufacturing loss or stability overages) and order of addition, heating processes, mixing speed and time, filtering steps, filling steps) of the manufacturing process been provided?
- are the manufacturing steps used consistent and complete for the formulation type?
- is an overage of the active constituent used to account for manufacturing or stability losses?

- is there any potential for reactions to occur during the manufacturing process of the chemical product, including between the active constituents and the non-active constituents and any solvents used? For example, the APVMA has recently become aware of transesterification of some ester active constituents with alcohols present in the formulation (eg solvents for surfactants in the formulation)
- for veterinary chemical products only, has the chemical product manufacturing process been validated and is it adequate?
- what, if any, quality control measures are in place and are they considered adequate?
- has a description of any production equipment cleaning processes been provided?

In assessing this information the APVMA is seeking to ensure that the method of manufacture for the chemical product is fit for purpose and will consistently produce the chemical product to the proposed specifications.

Box 9: Example of assessment of the manufacturing process

The data package specifies the manufacturing process steps for the manufacture of a suspension concentrate product. Assessment of the process details reveal that no attempt (eg milling or sieving) is made to standardise the particle size ranges of the dry ingredients. Consequently, when the product is manufactured the particle size range might be expected to vary depending on the particle size of one or more of the raw materials used in the manufacture of the product. This variability would not necessarily be displayed in the batch and/or storage stability results because those batch samples likely used a limited (if not just one) range of raw material batches. The applicant would be expected to address this by providing further data concerning the raw material particle sizes (eg additional specification limits to control particle size) or by adding steps to the manufacturing process such as milling or sieving, including appropriate quality control tests (eg particle size analysis).

Physicochemical properties (agricultural chemical products)

The APVMA evaluates the physical and chemical properties of the product:

- have relevant physical and chemical properties of the chemical product been provided, particularly if the product contains a new active, a new combination of actives, or contains existing actives, but with a new formulation type?

In assessing this information the APVMA is seeking to ensure that the physico-chemical properties of the chemical product do not indicate potential hazards (eg high flammability), or that if hazards are indicated, appropriate safety measures and warnings are included on the product label.

Product specifications

Agvet Code section 5A(3)(a)(iii) and (via), and regulations r8AB(1)(d)(i) and (ii) and r42

The APVMA assesses the product specifications of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA considers whether an appropriate justification or argument has been provided:

AGRICULTURAL/PESTICIDE CHEMICAL PRODUCTS:

- for pesticide chemical products is the allowable variation range for the content of the active constituent consistent with the allowable variations for the labelled concentration of the active constituent?
- for a molluscicide with either metaldehyde or methiocarb as the active constituent, is the product a distinctive green or blue colour, respectively?
- for a product applied to seeds to be stored before planting does the product contain sufficient pigment or dye to readily distinguish treated seed from non-treated seed?
- for a product that requires an emetic, is there sufficient emetic in the product?
- does the chemical product comply with or address the relevant points in the general requirements in this section?

VETERINARY CHEMICAL PRODUCTS:

- is there a relevant pharmacopeia monograph for the product and if so does the proposed product comply with the monograph?
- in general, is the allowable variation range for the content of the active constituent consistent within the limits of ±5 per cent at release and ±10 per cent at expiry. The allowable variation range can also take into account any pharmacopeia monograph. If required, is an overage included to compensate for losses of the active during storage?
- does the chemical product comply with or address the relevant points in the general requirements in this section?

GENERAL REQUIREMENTS (AGRICULTURAL/PESTICIDE AND VETERINARY CHEMICAL PRODUCTS):

- is there a section 6E Standard (Agvet Code) for the chemical product and if so does the proposed product comply?
- are all the physico-chemical test parameters recommended for the formulation type/dosage form of the product included for both agricultural and veterinary products?
- are the test method references specified?
- are any nano-properties relevant for the chemical product specified?

In assessing this information the APVMA is seeking to ensure that the product is manufactured to a standard appropriate to satisfy the safety and efficacy criteria.

Batch analysis

Agvet Code section 5A(3)(a)(iii)

The APVMA assesses the batch analysis of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA then considers whether an appropriate justification or argument has been provided by the applicant.

AGRICULTURAL/PESTICIDE CHEMICAL PRODUCTS:

- for pesticide products only, has at least one batch (of at least 5 kg or 5 L) of the proposed product been analysed (this can be the initial results of the stability study for the chemical product)?
- does the chemical product comply with or address the relevant points in the general requirements in this section?

VETERINARY CHEMICAL PRODUCTS:

- for veterinary medicine products only, have at least three pilot-scale or production-scale batches of the proposed product been analysed (can be the initial results of the stability study for the chemical product)?

Note: see VICH GL3(R) (QUALITY) *Stability: Stability Testing of New Veterinary Drug Substances (Revision).*

- for veterinary medicine products, are the batches from the nominated product manufacturer(s) and are all product manufacturers represented?

Note: if you have nominated more than one site of manufacture, batch data is generally required from each manufacturer to demonstrate that the specific manufacturer has the capability to make the product, or a valid scientific argument may be provided.

- does the chemical product comply with or address the relevant points in the general requirements in this section?

GENERAL REQUIREMENTS (AGRICULTURAL/PESTICIDE CHEMICAL PRODUCTS):

- have the dates of manufacture and analysis of the batches been provided?
- does the active constituent content comply with the product specifications (ie with the specified limits for all test parameter)?

Note: subjective statements such as ‘within limits’ or ‘conforms’ are not valid results for quantitative analyses (eg the active content as determined by a chromatographic method). The use of the term ‘within limits’ or ‘conforms’ is acceptable for qualitative or semi-quantitative tests such as thin layer chromatography or appearance tests involving comparison with a colour standard.

- if a product specification is not complied with, has a valid scientific justification and/or additional data been provided?
- if toxicologically significant impurities are known (or are expected) to increase during storage of the product have these been monitored and do the levels comply with the specification limits?

Note: the APVMA may call upon corporate knowledge and experience with similar compounds to inform the assessment of potential toxicologically significant impurities. For example, it is known that tetraethyl pyrophosphates (TEPPs) in diazinon products may be formed under certain conditions.

In assessing this information the APVMA is seeking to ensure that the nominated manufacturer(s) can consistently manufacture the chemical product in compliance with the product specifications and the product will satisfy meet the safety and efficacy criteria.

Stability

Agvet Code section 5A(3)(b)(iv)

NON-DATE CONTROLLED CHEMICAL PRODUCTS

Pesticide chemical products, except those that are listed in the Agvet Code Regulations as date-controlled (see below), are expected to remain stable (that is continue to meet the limits contained in the product specifications) for at least two years under normal storage conditions (typically at approximately 25 °C, in a cool dry place out of direct sunlight). Pesticide chemical products remain fit for use as long as any changes do not result in any adverse effects on the use of the product, the biological performance, the safety of operators, consumers of treated produce, or the environment.

The APVMA assesses the storage stability of non-date controlled chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA then considers whether an appropriate justification or argument has been provided by the applicant:

- has the storage stability study been undertaken using one of the study conditions (eg 54 °C, 45 °C or 40 °C) and durations (eg two, six or eight weeks) recommended in the APVMA stability data guidelines for agricultural products?
- how many batches of the product have been used in the study?
- is the batch more than 5 L or 5 kg in size and was the scale indicated (eg laboratory, pilot, production)? A batch size of 5 L or 5 kg is generally the smallest amount that can demonstrate consistency of manufacture of the product
- does the formulation composition used in the stability study match that of the proposed chemical product?
- were initial and final results provided for all product stability specification test parameters recommended for the formulation type of the product?
- was the stability testing of the product conducted in the primary packaging, (the container material, size and product quantity), or a suitable alternative?
- if the product is to be packaged in water soluble packaging (WSP) such as water soluble bags, was the product stored in the WSP for the stability trial, and were tests involving dilution with water conducted in the presence of the WSP. This is particularly important for properties which may be affected by the presence of the WSP (eg wet sieve analysis, suspensibility, pH, persistent foam)
- if there are multiple pack sizes, can the stability of the product be extrapolated to the other pack sizes?
- does the active constituent content comply with the product specifications?
- was there a significant decline (greater than five per cent loss should be justified) in the concentration of the active constituent?
- if relevant, is the inclusion of an overage for the active constituent justified by the extent of decline in the active constituent concentration?

- do all physicochemical properties (eg pH, suspensibility, pourability) comply with their specified limits and/or with generally accepted limits specified in the stability guideline for agricultural chemical products[8]?
- are there any significant changes in any product parameter and has an appropriate explanation been provided? Any significant unexplained change in any test result may be indicative of an underlying issue with either the product or the manufacturing process
- if a product specification test parameter is not complied with has a valid scientific justification and/or additional data been provided?
- was the primary packaging material of the product stable on storage? If the primary packaging material was affected by the product, is this change significant and is it acceptable from a safety perspective?
- if relevant to the formulation type (such as liquid formulations), has the low temperature stability of the chemical product been demonstrated using an accepted method, eg CIPAC MT39?
- if relevant, have the nano-properties of the chemical product been investigated in the study and are they acceptable?
- is the stability data sufficient to conclude that the pesticide chemical product is, or will be, stable for up to two years at normal storage conditions (at or above 25 °C) or such alternative conditions as specified by the applicant?

A shorter shelf life may be appropriate where the data do not support acceptable product stability of at least two years (see date-controlled pesticide chemical products).

In assessing this information the APVMA is seeking to ensure that after storage the chemical product will remain fit for use with no adverse effects on safety (to people, crops, animals or the environment) or efficacy.

Box 10: Discussion of accelerated stability testing and pack sizes

The stability of the product was determined by storing a sample for two weeks at 54 °C in the smallest of the proposed pack container sizes. The initial and final results for the active constituent content were 200.0 g/L and 195 g/L, respectively (2.5 per cent decrease), thus indicating good stability of the active constituent.

Date-controlled chemical products

Regulations 4(a) and (b), schedule 1 to the regulations

All *veterinary* chemical products are defined in the regulations as date-controlled chemical products.

Certain *agricultural* chemical products are also subject to specific control of their storage conditions and durations (ie expiry date) by regulation. These date-controlled pesticide chemical products are those containing organisms (including, in particular, nematodes, bacteria, viruses, fungi, algae or protozoa); *Bacillus thuringiensis*; or the chemicals mancozeb; zineb; diazinon and dimethoate as active constituents. Schedule 1 of the Agvet Code Regulations 1995 lists the date-controlled agricultural chemical products.

[8]https://apvma.gov.au/node/1042

The APVMA assesses the storage stability of date-controlled chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA then considers whether an appropriate justification or argument has been provided by the applicant.

DATE-CONTROLLED AGRICULTURAL CHEMICAL PRODUCTS

- is the formulation composition used in the study that of the proposed product?
- is the batch more than 5 L or 5 kg in size?
- was the stability testing for the product conducted in the primary packaging, including the container material, size and product quantity?
- a suitable alternative approach may be provided along with argument describing why a different approach was used
- if there are multiple pack sizes can the stability of the product be extrapolated to the other pack sizes?
- was the study undertaken under the recommended real-time storage conditions?
- if appropriate, has real time stability data for the purpose of establishing a shelf life been provided?
- are the test intervals as per APVMA guidelines?
- were initial, intermediate and final results provided for all product specification parameters recommended for the formulation type of the product?
- does the active constituent content comply with the product specification test parameter limit?
- was there a significant decline in the concentration of the active constituent? If so why?

Note: a loss of greater than 5 per cent for agricultural products should be justified.

- if relevant, is the inclusion of an overage for the active constituent justified by the extent of decline in the active constituent concentration?
- are there any significant changes in any other product specification test parameters that might be a cause for concern?
- if a product specification test parameter is not complied with has a valid scientific justification and/or additional data been provided?
- if relevant, does the content of any toxicologically significant impurities increase? Does it meet the specified limits and are these acceptable from a safety perspective? The APVMA may call upon corporate knowledge and experience with similar compounds to determine the expected presence of toxicologically significant impurities
- was the primary packaging material of the product stable on storage? If the primary packaging material was affected by the product, is this change significant and is it acceptable from a safety perspective?
- if relevant to the formulation type, has the low temperature stability of the chemical product been demonstrated using suitable method?
- if relevant, have the nano-properties of the chemical product been investigated in the study and are they acceptable?

- based on the storage stability, what shelf life (expiry date) and storage conditions should be assigned to the date-controlled chemical product?

VETERINARY CHEMICAL PRODUCTS

- is the formulation composition used for the stability study the same as that of the proposed product?
- was the stability testing of the product conducted in the primary packaging, including the container material, size and product quantity?

Note: a suitable alternative approach may be provided along with justification.

- have at least three batches of the proposed product been used in the study? Are these batches of at least pilot scale?
- if relevant, has the study been conducted with upright and/or inverted storage of the product containers to investigate potential interactions with the closure? If not, or if issues are evident, should a 'store upright' warning be considered for the product?
- has the study been conducted using any bracketing and/or matrixing techniques for the container sizes and/or test parameters[9]? If so are they appropriate?
- was the study undertaken under one of the recommended study conditions and duration (eg 24 months at 30 °C/65 per cent RH)?
- are the test intervals consistent with APVMA guidelines?
- are there any significant changes in the active content or any other product parameters that might be a cause for concern?
- if relevant, is the inclusion of an overage for the active constituent justified by the extent of decline in the active constituent concentration?

Note: subjective statements such as 'within limits' or 'conforms' are not valid results for quantitative analyses (eg the active content as determined by a chromatographic method). The use of the term 'within limits' or 'conforms' is acceptable for qualitative or semi-quantitative tests such as thin layer chromatography or appearance tests involving comparison with a colour standard.

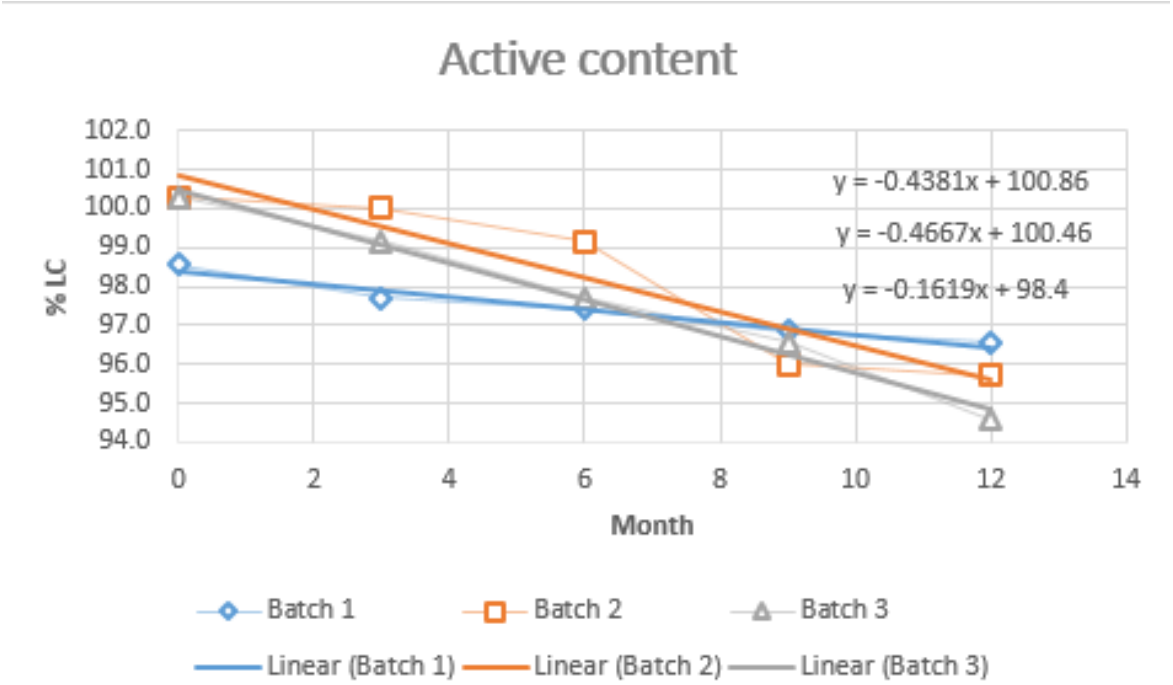
- if a product specification limit is not complied with has a valid scientific justification and/or additional data been provided?
- if relevant, does the content of any toxicologically significant impurities increase? Does it meet the specified limits and are these acceptable from a safety perspective?
- if relevant, has the sterility or other microbial parameters (eg total aerobic microbial count, total yeast and moulds) been demonstrated (at least initially and at the end of the study)?
- was the primary packaging material of the product stable on storage? If the primary packaging material was affected by the product, is this change significant and is it acceptable from a safety perspective?

[9]Refer to VICH GL45, https://apvma.gov.au/node/1059.

- if relevant to the formulation type, has the low temperature stability of the chemical product been demonstrated using a suitable method?
- has an appropriate statistical analysis of the real-time and accelerated stability data for the purpose of establishing a shelf life for the product been provided (eg VICH GL51 (see below for further details)?

The APVMA uses a linear regression model where the data shows evidence of a decline of the active or preservative content or an increase in degradation products. The APVMA follows the methodology of VICH GL 51 with one difference. APVMA (in line with the TGA) requires that any batch released with the active or preservative content at the lower release limit (eg 95 per cent of label claim) or a degradation product at the higher release limit) should still meet the expiry specifications limits at the end of the shelf life.

Example of stability data for a shelf life of 12 months



- if relevant, has the preservative efficacy been demonstrated for the minimum specified concentration of the preservative(s)?
- if relevant, have the nano-properties of the chemical product been investigated in the study and are they acceptable?
- based on the storage stability what shelf life (expiry date) and storage conditions should be assigned to the veterinary chemical product?

In assessing this information the APVMA is seeking to ensure that on storage the chemical product remains fit for use for the entire shelf life (ie up to the label expiry date) with no adverse effects on safety (to people, animals or the environment) or efficacy.

In-use stability of veterinary products

Where applicable, the APVMA assesses the in-use storage stability of veterinary chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA then considers whether an appropriate justification or argument has been provided:

- is an in-use shelf proposed, or is a default in-use label statement (eg 'discard unused portion of the product within 24 hours of first broaching', appropriate for injectable products without in-use stability data) included on the label in lieu of demonstrating a longer in-use shelf life for the proposed product?
- has a closure system broach pattern broadly consistent with the use pattern specified on the product label been used?
- how many batches have been tested for in-use stability (at least one and preferably two), and what age were the batches (eg freshly manufactured, or already aged (stored) for a specified period under the proposed storage conditions?
- if relevant, has the content of the preservatives decreased significantly (eg >five per cent)? If so why and is there sufficient preservative to maintain the efficacy of the preservative system?
- has the sterility of the product been demonstrated (can be inferred via a properly conducted seal integrity test or a no change in the preservative content or preservative efficacy)?
- have all of the other product specification parameters (including the content of the active constituents) been met?
- are there any significant changes in any of the product specification parameters? If so what is the significance?
- if relevant, was the container closure exposed to the product by inverted or side-on storage of the container? If not should a 'store upright' label warning be considered?

In assessing this information the APVMA is seeking to ensure that the product continues to comply with the product specifications (particularly with respect to microbial contamination) following the initial and any subsequent broaching of the seal for the period specified on the label and justified by the in-use stability data.

Analytical methods

Regulation 8AB(1)(a)

The APVMA assesses the analytical methods of chemical products. Where a particular piece of information has not been provided or a criterion has not been met the APVMA then considers whether an appropriate justification or argument has been provided by the applicant:

- is the analytical method for the assay of the active constituent content in the chemical product a published 'regulatory method' (eg CIPAC, AOAC, pharmacopoeia)? If so then have selectivity and accuracy validation been demonstrated?

Note: regulatory methods have been developed and extensively validated to ensure that they are fit for the intended purpose, however the analytical laboratory and staff undertaking those methods of analysis need to also

demonstrate that they are capable of using those methods appropriately and that the method selected is appropriate for the particular product. This is why providing data on selectivity and accuracy should be provided to demonstrate that the laboratory and staff are capable of using those regulatory methods appropriately.

- if the analytical method for the assay of the active constituent content in the chemical product is not a published 'regulatory method' or is a modified version of a 'regulatory method' have complete details of the method and validation been provided?

Note: as stated in the note above, regulatory methods have been validated to demonstrate that they are fit for their intended purpose. There are key aspects of the method that if changed will alter the characteristics of the method and in turn render the original method validation invalid.

It is for this reason that minor changes only are acceptable, for example a maximum of 5 per cent variation in the mobile phase to ensure that the analyte elutes within the appropriate time window.

- for chromatographic methods (eg HPLC, GLC) does the validation data demonstrate adequate validation of selectivity, linearity, range, precision and accuracy of the active constituent in the chemical product as per the APVMA guidelines for agricultural or veterinary (VICH GL 1 and 2) products?
- is the analytical method for the assay of the active constituent content in the chemical product also used for the determination of the contents of the impurities (including toxicologically significant impurities) and is it capable of detecting and quantifying the impurities? If not, has one or more separate analytical method(s) been provided that is capable of detecting and quantifying the impurities?
- if relevant, for chromatographic methods (eg HPLC, GLC) or non-chromatographic methods (eg qNMR, AAS) does the validation data demonstrate adequate validation of selectivity, linearity, range, precision, accuracy, limit of detection and limit of quantification of the degradation products and any toxicologically significant impurities in the chemical product as per the APVMA guidelines for agricultural or veterinary (VICH GL 1 and 2) products?
- has a worked example of the analyte concentration calculations been provided?
- has the purity of the analytical reference standard been provided?
- if relevant, have the physico-chemical tests (eg sterility, pH, particle size, suspensibility) been conducted using recognised (eg pharmacopoeia, CIPAC) analytical methods? If not are method details provide and are the methods fit for purpose?

In assessing this information the APVMA is seeking to ensure that the batch analysis and storage stability results can be considered reliable.

Packaging

Agvet Code section 5A(3)(b)(v), and Regulations 17C(2) item 6, and 18(2)(a), (b), (c), (d),(e)(i) and (e)(ii)

The APVMA assesses the containers and packaging of chemical products:

- are the net contents of the chemical product as stated?
- has the storage stability of the product been demonstrated in the proposed packaging material?

- has the storage stability of the smallest proposed pack size for the product been demonstrated?
- are there any physico-chemical changes to the packaging material? If so what significance do they have?
- have any product stability related issues that require special instructions relating to the packaging (eg need for the container to be replaced after use back into its outer carton due to photostability concerns) been addressed?

In assessing this information the APVMA is seeking to ensure that the net contents of the product are correct when entered in the Register and that the packaging, including the primary container, closure and any critical secondary packaging is fit for purpose.

Label

Regulation 17(1)(c),(d) and (f)

For the chemistry and manufacture risk assessment, the APVMA assesses the following aspects of the labels of chemical products:

- are the active constituent names correct?
- are the active constituent concentrations correct?
- if relevant, are any non-active constituents that are classified as poisons in the current Poisons Standard included and are they correctly named with the correct concentration?
- for agricultural products, have standard or other appropriate storage instructions been included (see the Ag Labelling Code, Section 19: Storage and Disposal Statements)?
- if relevant, is the in-use storage statement supported by data?
- for veterinary products, has a storage temperature been specified and is it supported by the stability data?
- are the any required instructions (eg ‘Protect from light’, ‘Do not expose to low temperature conditions’) related to storage (either proposed by the applicant, or arising from the evaluation of the product) included on the product label?
- are there any statements on the product label that are not supported by appropriate chemistry and manufacture data?

In assessing this information the APVMA is seeking to ensure recorded registered particulars and the label particulars are correct and consistent.

APVMA chemical product standards

The APVMA may make standards for chemical products. These are normally the result of an assessment of a new active constituent but can also be the result of a chemical review.

Product standards may include:

- the allowed minimum content of the active content

- the allowed ratio of stereoisomers
- the allowed maximum content of the any toxicologically significant impurities.

Non-prescribed conditions

Agvet Code sections 5A(3)(a)(v) and 23(1)(b)

Subsection 5A(3)(a)(v) of the Agvet Code states that the APVMA must have regards to any conditions to which the product registration is, or would be, subject. The standard condition for products are stated in Regulations 17 and 18. The APVMA can also impose additional conditions considered appropriate on the registration of the chemical product under section 23(1)(b) of the Agvet Code Act.

The APVMA assesses non-prescribed conditions for a chemical product including:

- the chemical composition and their levels
- physicochemical properties
- the safety information.

In assessing this information the APVMA is seeking to ensure that the conditions of registration of the chemical product are fit for purpose.

5 STATISTICS

Throughout the assessment process the APVMA confirms any statistical analyses are appropriate and correctly applied in line with international guidance, such as the VICH guideline GL51: Statistical evaluation of stability data or in the appendix to the OECD Guidance Document for single laboratory validation of quantitative analytical methods—Guidance used in support of pre-and-post-registration data requirements for plant protection and biocidal products.

(Series on Testing and Assessment No. 204).