Developing a documented system for compounded veterinary preparations

ACVM guideline

1. Introduction

The following are guidelines for a documented system that you as a compounding veterinarian must have and must comply with when preparing a compounded veterinary preparation (CVP).

To compound means to make up, prepare, produce, or process a veterinary medicine into a preparation for treatment of animals under the care of the compounding veterinarian. This obviously includes compounding your own preparations, but it also includes:

- making modified preparations from other registered veterinary medicine products or proprietary products exempt from registration (alone or in combination)
- preparing generic chemicals for use as veterinary medicines
- altering any characteristic (concentration, formula type – tablet to liquid/paste, preparing injectable product for oral administration etc) of a trade name product
- decanting or breaking down trade name products into more convenient pack sizes with the expectation that your client will use the contents over an extended period of time.

Compounding can include all the steps from formulation of the preparation through to packaging, labelling and quality control checking before supply to your client.

Compounding does not include drawing out or separating off a quantity of product for immediate administration or supply to your client for immediate use (that is, sufficient for one treatment sequence with no protracted storage).

WHEN COMPOUNDING IS/IS NOT APPROPRIATE

The exemption for veterinary compounding is not intended to provide you with a convenient alternative to registering your preparations. CVPs cannot be advertised and cannot be sold over the counter to the public without a veterinary consultation. Furthermore, if there are appropriate preparations already on the market, such as registered veterinary medicines, then it would not be appropriate for you to compound a preparation.

However, MPI accepts that, from time to time, you may need to compound a preparation in special circumstances. This should only be done when it is essential and it should always be done in a professional manner.

2. Compliance with VCNZ Code and ACVM Regulations

The right to compound your own preparations is based on MPI's confidence that veterinarians will do it in a competent manner in compliance with the VCNZ Code of Professional Conduct (paragraphs 6, 7 and 9 of the section on veterinary medicines) and the conditions on the exemption from registration, which is entry 9 in Schedule 2 in the ACVM (Exemptions and Prohibited Substances) Regulations 2011:

> ### Compound veterinary preparations
>
> Must not be used on animals except under the direct care, or with the authorisation, of the compounding veterinarian;
>
> Preparation may be used only on animals specified by the compounding veterinarian or animal of a type specified by the compounding veterinarian.

In addition to these specific conditions on the exemption from registration, compounding veterinarians are subject to Regulations 7, 10, 11, 12 and 14 (see below and appendix).

In general, all CVPs must be fit for purpose and compounded in a way that ensures this fitness. In practical terms, this means that:

- the place where the compounding will be carried out is appropriate for the task; and

- preparation and process specifications must be set appropriately to ensure fitness for purpose; and
- the CVP must be compounded according to those specifications and checked before it is supplied to your client to ensure that it conforms to those specifications.

FIT FOR PURPOSE REQUIREMENT (REGULATION 7)

All agricultural compounds and veterinary medicines exempt from registration (including CVPs) under the ACVM Act must be fit for purpose, as described in Regulation 7. Fit for purpose means the product must not:

- spread organisms to a level or in a manner that could be harmful to humans; or
- reduce the efficacy of medicines used on humans; or
- result in residues in primary produce that exceed the limits prescribed in applicable food residue standards set in or under any enactment; or
- be toxic to animals treated with or exposed to the product to an extent that causes unnecessary or unreasonable pain or distress; or
- fail to reduce or eliminate pain or distress to animals treated with the product where the elimination of pain or distress is a stated purpose of the product; or
- transmit disease, result in physical harm, or cause unnecessary pain and distress, to animals treated with or exposed to the product; or
- transmit pests or unwanted organisms as defined in the Biosecurity Act 1993 or specified in any national or regional pest management strategy made under that Act; or
- otherwise create or be likely to create any of the risks specified in section 4(a) of the Act.

Note: the risks referred to in the last bullet point are risks to:

- public health
- trade in primary produce
- animal welfare
- agricultural security.

You must take these matters into consideration when specifying the CVP and how it is to be compounded.

DOCUMENTED SYSTEM REQUIREMENT (REGULATION 10)

The compounding process must be specified in the documented system.

Note: If you contract a third party to do the actual compounding (see below), you do not have to document the third party's manufacturing system.

A documented system for veterinary compounding is a documented quality system that describes how tasks relating to the compounding of a CVP are carried out in compliance with ACVM Regulations 10 and 12.

It may include items such as work instructions, procedures, tasks, preparation and process specifications. It always includes quality control before supply at which point the CVP can be determined to be fit for purpose and to conform to its specifications. The documented system is no more detailed than is necessary for you to have confidence in the resulting CVP and to provide evidence that you have taken due care to comply with the Code of Professional Conduct and the ACVM Regulations.

The documented system does not have to be approved by MPI and MPI does not require the system to be documented in a particular form. However, it must be recorded or otherwise maintained in a way that makes the content of it readily accessible and retrievable at any time. If there are suspicions or allegations of a breach in the conditions of exemption, MPI will investigate and request to examine the documented system and the records kept on how the product is compounded in accordance with the system.

3. What must be included in a documented system

Regulation 10 of the ACVM Regulations 2011 specifies that a documented system for compounding CVPs **must** include:

Content	Explanation
Description of the preparation that is supplied to users	It is expected that the CVP will not have a specific trade name. However, there must be enough of a description of the CVP to identify it.
Formulation or recipe of the compound	This is, in effect, the master formulation for the CVP. It includes the identity (and minimum characteristics) and concentrations of all active and non-active ingredients.
Description of the compounding process	This would usually take the form of a process flow chart that identifies the critical control points that must be monitored and the parameters that must be monitored and

	recorded. It covers the quality control checks before the CVP is supplied that confirm the product conforms to the CVP specifications. All steps relevant to the activities being carried out should be included, from CVP development and setting preparation and compounding specifications, receiving raw materials into stock, through to releasing finished CVP. If an activity such as formulation of a particular proprietary ingredient has already been carried out, then that part of the process does not have to be detailed, but the quality check on that ingredient input does have to be included.
Description or illustration of packaging and labelling requirements (if any) for the preparation	Packaging must be appropriate for the kind of CVP and the label must have at least the information required under Regulation 12 (see below).
A nominated person (that is, the compounding veterinarian) to monitor compliance with the requirements of the documented system	This refers to the designated person(s) responsible for the compilation and maintenance of the documented system, and responsible for ensuring that relevant people comply with the system and record the performance at the specified critical control points in the compounding process. This is the person who would assist an MPI investigator to review the application of the documented system. This means you as the compounding veterinarian. If you contract a third party to compound a CVP on your behalf, you are still the person responsible.
Any other matter relevant to the manufacture of the product that is specified by the Director-General	While this is stated in Regulation10, at this time there have been no additional requirements for CVPs specified by the Director-General.

4. Guidelines for developing your documented system

Personnel

If any of your staff is involved in the compounding process, you must ensure that they are competent and reliable. Staff responsibilities must be defined, including responsibilities for critical control steps (such as releasing raw materials for use in compounding or releasing the finished CVP).

Premises and equipment

The system should include an appropriate description of the plant or premise. This may include such things as a line diagram of the buildings and/or equipment, and indication of their use. In a small compounding operation it may be as simple as designating the place in your veterinary clinic where the activity will take place, and the facilities or equipment involved.

Compounding process

The compounding process must be described adequately, including step-by-step descriptions of the stages. This should include any contractors involved. Rather than a description of the steps carried out by the contracted party, your documented system should include a description of how activities of the contractor are linked to yours and how the contractor's input is confirmed as satisfactory in regard to its impact on the final CVP specifications.

CVP development

You may need to consider the following and record them as part of your documented system so that you can demonstrate that the CVP has been designed to be suitable for its intended use. Document:

- a clear profile of what the CVP is intended to achieve (its purpose and intended outcome); class of animal/species/age etc product intended for;
- duration of intended use, if applicable;
- steps taken to ensure that the CVP will not cause toxicity, malnutrition, physical harm or pain and distress in the target animal from other causes;
- specification and selection of the materials used as ingredients that are appropriate for the compounding process so that the final CVP will be fit for purpose.

Compounding stages

All steps of compounding should be included. The following should be considered and recorded as part of the documented system, as necessary, to provide evidence of how the CVP conforms to its specifications.

Plant, premise and personnel

- Compounding areas must not present a risk to the CVP.
- Surfaces should be impermeable and permit cleaning.
- Staff bathrooms must be away from manufacturing area.
- The premise should preclude the entry of vermin and insects.

- There must be scheduled cleaning.
- CVP must not be compounded in an area, or using the same equipment, where pesticides and other hazardous chemicals are stored.
- Equipment must be designed so it doesn't present a risk to the CVP (risks including
- Equipment shedding paint, plastic or metal into a product).
- Equipment must be cleaned regularly.
- Cleaning chemicals must not present a risk to the CVP.
- Staff must not present a risk to the CVP. In some cases staff may need to wear protective clothing to protect the product.
- Staff must not eat or smoke in compounding area.
- Staff must notify the management if they are diagnosed with an infectious disease and must not be involved in manufacture where this poses a risk to the CVP (for example, Salmonellosis or Campylobacteriosis).
- Staff must be trained to ensure minimum compounding requirements are met and personal hygiene requirements are sufficient.

Materials

- Raw material should be sourced from known suppliers who must be able to supply raw materials to the specification required by the veterinarian.
- Raw materials should be checked for conformation to specification before use.
- Depending on the raw materials, they may require testing to verify conformance or to check for contamination. For example:
  - microorganisms (bacteria, mould, grains contaminated with aflatoxin or mycotoxin etc)
  - chemicals that may cause detectable residues in finished product (herbicides and other pesticides, trace metals)
  - substances capable of causing harm to the target species
  - putrefaction, deterioration or fermentation that would make the product unsuitable (for example, when food by-products such as bread, fruit, and dairy products are used in feed)
  - adulterants (such as melamine where protein content is a specification of the raw material)
  - physical contaminants (pieces of metal and broken plastic or glass etc).

- Packaging materials must be fit for purpose (for example, for animal foods the packaging should be food grade). The packaging must sufficiently protect the CVP from contamination, moisture etc to ensure it remains fit for purpose and unspoilt throughout its shelf life.
- Raw materials, work in progress and finished CVPs must be stored appropriately, so as to prevent contamination or spoiling (for example, some products may require refrigeration, and products should be kept away from hazardous chemicals).
- All materials should be labelled appropriately. Where transport of the finished product is under the control of the compounding veterinarian, transport conditions should meet storage requirements.

5. Labelling requirements

The label of a product is the source of important information to the client. It explains what the product is, what it is to be used for and how it is to be used. It establishes the intended purpose and provides a means to guide the actions of the consumer. While labels in general have to be appropriate to guide the intended use, they must have at least the information specified in Regulation 12.

Note: Under the ACVM Act, all the information provided with the product is part of the label, including the label stuck to the immediate container, any outer packaging or leaflets/inserts/pamphlets.

When you administer the CVP, a label may not be needed. This is because you are not depending on the label to ensure the product is used appropriately and safely. On the other hand, if you supply the CVP with the expectation/direction that your client will administer the preparation, the CVP must be supplied with a label so that your client will know how to use the CVP safely and appropriately.

The minimum labelling information specified on Regulation 12 of the ACVM Regulations includes:

Information	Explanation
The name (if any) under which it is sold/supplied	It is assumed that almost all CVPs will not have a specific trade name and will probably be identified by a description of the CVP.
A description of the product or preparation sufficient to enable the user to determine the nature and purpose of the product	This can be a very brief statement of the intended use of the CVP. This may be the same as above.

The name and contact details of the manufacturer or, in the case of a CVP, the veterinarian who made the preparation	The label must inform the client (or consumer) about the veterinarian who is responsible for the CVP and how the veterinarian can be contacted.
Active ingredients	The whole formulation does not have to be stated on the label. Only the ingredients that are expected to produce the intended outcome (that is, active ingredients) have to be listed.
Directions for use	The label must have enough information to ensure that the user knows how to administer the CVP correctly. Where applicable, it should state a withholding period.
Use by date or expiry date, if applicable	The label must provide enough information to know how long it can be expected that the CVP will still be fit for purpose. While many products can deteriorate, some products are so stable that they could remain fit for purpose for a very long time or indefinitely. In such cases setting an expiry date may not be necessary and, consequently, an expiry date does not have to be stated on the label.
Details of precautions, if any, that should be taken	The label must warn the consumer of likely or significant (from the compounding veterinarian's perspective) negative effects they should be aware of.
Batch number (or equivalent)	To facilitate investigations of non-compliant CVPs, there must be some identifier like a batch number on the label that would link that batch of product to a date and place of manufacture. However, CVPs are always directly linked to a veterinary consultation, and the veterinarian can provide the necessary link in any way he or she considers appropriate (such as record keeping of date and place of supply).
Any other information needed to meet the relevant exemption from registration	This refers to any specific labelling requirement in Schedule 2, column 2 of the ACVM Regulations for that kind of product. There are none for CVPs.

We recommend that you also consider the labelling requirements of other legislation but this is not specifically required as a condition of exemption from registration under the ACVM Regulations 2011.

6. Quality control

There must be appropriate quality checks of the finished CVP before each batch is released for sale. This should include a review of the batch records to ensure each step of compounding has been carried out correctly and recorded. There should be a quality control check of the physical condition of the product and packaging, including label accuracy (batch number, expiry, use instructions, storage information etc).

Quality control checks may need to include laboratory testing to verify specification, or to check for microbial contamination, presence of toxins or residues. There must be a record of all of these quality control steps.

There must be a process by which inquiries, complaints and notices of adverse events are dealt with and investigated if necessary. The process must include:

- how relevant officials are notified of significant findings if necessary; and
- advice on the remedial action taken or to be taken; and
- the timeframe.

7. ‘Third party’ contractors

You may contract a third party, such as a compounding pharmacist, to carry out the actual compounding. However, the responsibility remains with you. You must be confident that the third party can carry out the process competently and reliably. You will be held liable for the outcome, so care should be taken in the quality control step to ensure the CVP conforms to the preparation specifications.

You must also follow-up all complaints, adverse events, or suspicions or allegations that the CVP does not conform to specifications.

APPENDIX: Relevant ACVM Regulations

Regulation 7: Fitness for purpose: importation, manufacture, or sale of exempt compound

An exempt agricultural compound that is imported, manufactured, or sold must be such that, when used as recommended, it will not—

a. spread organisms to a level or in a manner that could be harmful to humans; or

b. reduce the efficacy of medicines used on humans; or

c. result in residues in primary produce that exceed the limits prescribed in applicable food residue standards set in or under any enactment; or

d. be toxic to animals treated with or exposed to the product to an extent that causes unnecessary or unreasonable pain or distress; or

e. fail to reduce or eliminate pain or distress to animals treated with the product where the elimination of pain or distress is a stated purpose of the product; or

f. transmit disease, result in physical harm, or cause unnecessary pain and distress, to animals treated with or exposed to the product; or

g. transmit pests or unwanted organisms as defined in the Biosecurity Act 1993 or specified in any national or regional pest management strategy made under that Act; or

h. otherwise create or be likely to create any of the risks specified in section 4(a) of the Act.

Regulation 10: Compounded veterinary preparation to be prepared in accordance with documented system

A compounded veterinary preparation must be prepared in accordance with a documented system for that preparation that contains the following:

a. the description of the preparation that is supplied to users; and

b. the formulation or recipe of the compound; and

c. a description of the compounding process that is sufficient to ensure that the preparation, when used as recommended, complies with the conditions of exemption applicable to the preparation under these regulations; and

d. a description or illustration of packaging and labelling requirements (if any) for the preparation; and

e. a nominated person or persons to monitor compliance with the requirements of the documented system(which must be, or include, the compounding veterinarian);and

f. any other matter relevant to the preparation that is specified by the Director-General.

Regulation 11: Regulation 9 and 10 not to apply if operating plan required

Nothing in Regulation 9 or 10 applies in respect of an agricultural compound that is exempt from registration under section 21 or section 27 of the Act on the condition (specified in these regulations) that an applicable operating plan is approved and complied with.

Regulation 12: Information requirements

1. This regulation applies to:

a. an exempt compound product, when supplied to the user; and

b. a compound veterinary preparation, when supplied with a label to a user.

2. The product or preparation must be supplied with the following information:

a. the name (if any) under which it is sold or supplied; and

b. a description of the product or preparation sufficient to enable the user to determine the nature and purpose of it; and

c. the name and contact details of the manufacturer or importer or, in the case of a compounded veterinary preparation, the compounding veterinarian; and

d. the active ingredients; and

e. directions for use; and

f. use by or expiry dates, if applicable; and

g. details of precautions (if any) to be taken to prevent or manage the risks described in section 19 of the Act when using the product or preparation; and

h. in the case of an exempt compound product only, the batch number or other information sufficient to allow the date and place of manufacture or preparation to be ascertained; and

i. any other information specified in Schedule 2 in relation to the exempt compound, or exempt compounds, concerned.

Regulation 14: Recording of documented system and of actions taken in accordance with documented systems

1. A documented system must be recorded or otherwise maintained in a manner that enables evidence of the content of it at any given time to be readily accessible and retrievable.

2. A person who manufactures an exempt compound product must keep records in relation to that product of the application of the specified processes, and taking of required steps, identified in the documented system in accordance with Regulation 9(1).

3. When a compounded veterinary preparation is prepared, the compounding veterinarian must keep records in relation to that preparation of:

a. the matters specified in regulation 10(a) to (d) and (f); and

b. the date on which, and place at which, the preparation was made.

For more information, contact us (approvals@mpi.govt.nz).