Ministry for Primary Industries
Manatū Ahu Matua

Guidance Document

Chemistry and Manufacture of Veterinary Medicines (Chemical)

Information needed to support an application to register, or vary the registration of, a veterinary medicine

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Title

Guidance Document: Chemistry and Manufacture of Veterinary Medicines (Chemical)

About this document

This document explains the chemistry and manufacturing information needed to support an application to register, or vary the registration of, a chemical veterinary medicine under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

Please refer to the guidance document Chemistry and Manufacture of Veterinary Medicines (Biologicals) for chemistry and manufacturing information needed to support an application for a biological/immunobiological veterinary medicine.

This document may be altered at any time. It is recommended that anyone intending to use this document check the MPI website (https://www.mpi.govt.nz) to confirm that it is the current version.

Related Requirement

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

Document history

Version Date	Sections changed	Change(s) Description
1 November 2003		ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines 47 ACVM 11/03
1 May 2020	All	Revised and reformatted in new template
6 October 2023	Appendix 5	Updated the table of regulatory authorities from which evidence of GMP compliance is recognised by MPI
13 February 2024	Appendix 5	Further updates to the table of regulatory authorities from which evidence of GMP compliance is recognised by MPI

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Contents

1 Purpose

This document establishes the minimum requirements for the chemistry and manufacturing information submitted in support of an application to either register a veterinary medicine or to vary the conditions on a registered veterinary medicine in New Zealand. This guidance is for chemical (non-immunobiological) products.

This document covers:

- general chemistry, manufacturing, and stability information required for the registration of new veterinary medicines;
- general chemistry, manufacturing, and stability information required for variations to existing veterinary medicines; and
- information specific to certain product types.

2 Background

The need to assess the chemistry, manufacturing and stability information for veterinary medicines in New Zealand arises from section 4 of the ACVM Act 1997, which provides for prevention or management of risks associated with the use of agricultural compounds:

- risks to trade in primary produce;
- risks to animal welfare;
- risks to agricultural security; and
- risks to public health.

The chemistry, manufacturing processes and stability of registered veterinary medicines have the potential to impact all of these risk areas. The safety to members of the public and treated animals, as well as the impacts the use of a veterinary medicine may have on agricultural security and trade, rely on the quality and consistency of the ingredients and processes used in the manufacture of these products.

3 Definitions and abbreviations

In this document, unless the context otherwise requires:

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

active ingredient means a chemical or biological component in a formulated product that is principally responsible for the effect being claimed and is distinct from other components of the formulated product such as adjuvants or additives. Also known as active pharmaceutical ingredients (APIs)

active ingredient manufacturer means any site of manufacture, including intermediate manufacturing sites, that produce one or more of the active ingredients intended for use in the manufacture of the trade name product

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

agricultural compound has the same meaning as in the Agricultural Compounds and Veterinary Medicines Act 1997

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

BP means British Pharmacopoeia

BP (vet) means British Pharmacopoeia (Vet)

bracketing means a trial schedule designed such that only the extremes of certain predetermined and justified design factors, (e.g. strength, package size, batch size) are tested.

bulk product means any product which has completed all processing stages up to, but not including, final packaging

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

CEP means a certificate of suitability to the monographs of the European Pharmacopoeia

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

climatic zone means the portion of the earth's climate according to average temperature and humidity. Climatic zones dictate the acceptable stability study conditions for pharmaceutical products as determined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). New Zealand is considered Zone II (Mediterranean/subtropical zone)

container closure system means the sum of the packaging components that together contain and product the product. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the product

continuous process verification means a process of ongoing validation in which the manufacturing process performance is continuously monitored, evaluated and documented

controlled release formulation means a veterinary medicine for which the active ingredient(s)'s release from the formulation, and/or the formulation's release from the administration device, has been modified to ensure consistent delivery of a specified amount of active ingredient(s) or formulation over time

critical excipient means a substance intentionally added to a formulation to manage or enhance characteristics of the formulation itself, but its presence has a direct impact on the efficacy, safety, or residue profile of the product. These excipients are considered critical because they have a direct impact on the active ingredient's release, absorption, elimination, or any other aspect of the product's pharmacological or therapeutic impact on the treated animal

critical process parameter (also known as critical manufacturing control point) means a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

critical quality attribute (CQA) means a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

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

EP or **Eur Ph** or **PhEur** means European Pharmacopoeia

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

expiration date or **expiry date** means the date placed on the container label of the trade name product designating the time prior to which a trade name product has been confirmed by data to conform to the approved shelf life specification

expiry specification: *see* **shelf life specification**

FAMI-QS means the Feed Additive and preMixture Quality System, and is an internationally-recognised third party certification programme for feed ingredients and mixtures

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

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

FSANZ means Food Standards Australia New Zealand

functional active ingredient means a substance added to a veterinary medicine specifically to provide a therapeutic or nutritional benefit to the animal being treated as an adjunct to the primary function of and claims attributed to the therapeutic active ingredient(s) in the product

GLP means good laboratory practice, a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported

GMP means good manufacturing practice. GMP is the aspect of quality assurance that ensures that trade name products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification. It defines quality measures for both production and quality control and defines general measures to ensure that processes necessary for production and testing are clearly defined, validated, reviewed, and documented, and that the personnel, premises and materials are suitable for the production of pharmaceuticals and biologicals including vaccines. GMP also has legal components, covering responsibilities for distribution, contract manufacturing and testing, and responses to product defects and complaints

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

INN means International Non-Proprietary Name

in-process control (process control) means checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or active ingredient conforms to its specification

intermediate ingredient means a material produced during steps of the processing of an ingredient that undergoes further molecular change, physical change, or purification before it becomes the ingredient incorporated in the final formulated product

intermediate product means a partly processed material that must undergo further manufacturing steps before it becomes a bulk product

ISO means International Standards Organisation

IUPAC means International Union of Pure and Applied Chemistry

JP means Japanese Pharmacopoeia

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

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

manufacturer means a person, company or entity that performs one or more steps in the production of a trade name product from starting materials to release to the market

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

matrixing means the design of a stability schedule such that a selected subset of the total number of possible samples for all parameter combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all parameter combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point

method validation or analytical procedure validation means a process by which a laboratory demonstrates that a test method is suitable for its intended purpose, and confirms that the method is valid, reliable and consistent with an appropriate level of sensitivity, specificity, accuracy, trueness, reproducibility, ruggedness and precision.

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

packing means all operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note: sterile bulk filling would not normally be regarded as part of packing as it is considered part of the manufacturing process.

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

- **primary packaging** means those packaging materials that are in direct contact with the product (e.g. ampoules, bags, blisters, bottles, syringes, single-dose containers, vials, drums, tubes, vaccine flexi-packs etc.)
- **secondary packaging** means those packaging materials that enclose the primary packaging materials (e.g. cartons, bags, etc.). Secondary packaging is intended to protect the primary packaging and product and/or contain additional packaging materials such as leaflets
- **outers and shippers** means those packaging materials used for transportation or shipment
- **recycled packaging** means new packaging that has been produced from recycled materials
- **reused packaging** means used packaging that has been cleaned and inspected as being fit for purpose

pharmacopoeia means an authoritative work containing descriptions of drugs that are used in the practice of medicine (or veterinary medicine) listing the specification parameters, their formulae and dosages, appropriate testing methods, and directions for determining purity and strength. MPI recognises the following pharmacopoeia - BP, EP (Eur Ph), USP, and JP

pharmacovigilance means the detection and investigation of the effects of the use of veterinary medicines, mainly concerning safety, efficacy, and residues in animals and safety in people exposed to the products

pilot scale batch means a batch of product manufactured by a process fully representative of and simulating that to be applied to full production scale. This includes equipment, manufacturing site, manufacturing procedures, in-process controls, post-production testing. Pilot scale is generally a minimum of 10% of the full production scale for all formulation types and pharmaceutical dosage forms

process validation means the documented evidence that the manufacturing process operated within established parameters, can perform effectively and reproducibly to produce a trade name product meeting its predetermined specification parameters and quality attributes

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

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

related substance means an impurity that is produced during the manufacturing process or through the breakdown of formulants during storage

release to market means a confirmatory step performed to ensure the TNP complies with the MPI approved registration after manufacture or importation and before entering the distribution chain for sale in the New Zealand market. This includes but is not limited to confirming conformance with the product specifications, labelling with the complete approved New Zealand product label, and conformance to approved storage conditions. For products entering New Zealand, release to market also includes a verification check that the imported batch(es) comply and have not been impacted during transit

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

repacking/relabelling means a step of manufacture in which product already enclosed in the primary packaging is labelled, relabelled, cartoned, or re-cartoned, and/or additional information (including inserts and leaflets) is added, before the TNP is sold or supplied

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

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

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

SIU or SI units means standard international units

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

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

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

USP means United States Pharmacopoeia

veterinary medicine means any substance, mixture of substances, or biological compound(s) used or intended for use in the direct management of an animal

VICH means the international body aimed at harmonising technical requirements for veterinary product registration. In English, the name means the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

4 Information needed

(1) The minimum information MPI considers necessary is presented in each section, with notes on any further guidance for a specific clause, if applicable.

(2) The guidance reflects principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. MPI recognises that there are acceptable methods, other than those described in this guideline, that are capable of achieving the principles of this document.

(3) Applicants are responsible for providing all information required by MPI to make a decision on the application. Applications that do not contain sufficient information will not be assessed.

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

(5) If further advice is required, you are advised to contract the services of an appropriate consultant prior to submitting your application.

4.1 Units

(1) All units should preferably be SI units.

4.2 Dossiers

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

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

(3) If the product is currently or has previously been registered by an overseas authority, provide any relevant information on product defects or manufacturing issues that may impact the risk profile of the product, and any pharmacovigilance information pertaining to chemistry or manufacture of the product.

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

(5) Provide full copies of all bibliographical references, including any applicable pharmacopoeial monographs.

5 Additional guidelines

(1) Chemistry and manufacture guidelines for veterinary chemical products include the following:

VICH guidelines

GL1: Validation of analytical procedures: definition and terminology

GL2: Validation of analytical procedures: methodology

GL3(R): Stability: stability testing of new veterinary drug substances (revision)

GL4: Stability testing for new dosage forms

GL5 (Stability 3): Stability testing: photostability testing of new veterinary drug substances and medicinal products

GL8: Stability testing for medicated premixes

GL10(R): Impurities in new veterinary drug substances (revision)

GL11(R): Impurities in new veterinary medicinal products (revision)

GL18: Impurities: residual solvents in new veterinary medicinal products, active substances and excipients

GL39: Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances

GL45: Quality: bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products

GL51: Statistical evaluation of stability data

Other guidelines

The FDA, EMA and Heath Canada websites may also provide useful guidance in generating chemistry and manufacture data.

U.S Food and Drug Administration (FDA) guidelines

European Medicines Agency (EMA) guidelines; eg In-use stability guideline EMEA/CVMP/424/01

Health Canada guidelines

6 Registration of a new trade name product

6.1 Product type, formulation type and description

(1) Specify the product type from the list given in Appendix 1. If more than one product type is applicable to the trade name product, list all that apply.

(2) Specify the formulation type/pharmaceutical dosage form from the list given in Appendix 2.

(3) If the product formulation is to be further altered before use (e.g. reconstituted), state how the product is altered and provide the formulation type or pharmaceutical dosage form of the end use formulation.

(4) Provide a concise summary of the pharmaceutical development of the product. This should include a concise rationale for formulation development, discussing the identity and choice of all active and excipient ingredients. The rationale should include why the ingredient was chosen, why the particular concentration of an ingredient was chosen, and the intended effect that ingredient has on the performance or function of the formulation.

(5) For controlled release formulations contained in an administration device, such as an intraruminal bolus that is contained within a casing with a delivery mechanism:

a) provide the rationale for the combination of the formulation and release mechanism (with technical drawing and/or technical description of the device);
b) supply the composition of the device components; and
c) if re-use of the device is intended, document any procedures that are carried out when the device is re-used that may impact on the risks to be managed under the ACVM Act.

6.2 Formulation of the product

6.2.1 Formulation composition

(1) The formulation of the trade name product declared in the chemistry dossier and in the product data sheet must be a complete and accurate list of the ingredients and their concentrations. As MPI regulates TNPs, there can only be one distinct formulation per TNP.

(2) The formulation composition table must include:

a) the common name of the compound
b) the CAS number, if applicable
c) a reference to the quality standard (e.g. pharmacopoeial standard or manufacturer's specifications) applicable to each ingredient in the formulation
d) the inclusion amount of each ingredient must be listed in either g/kg for solid form products or g/L for liquid form products, and
e) the function (i.e. role or purpose) of each ingredient.

i) The functions of active ingredients are to be noted as "active ingredient" or "functional active ingredient," as applicable.
ii) The function of excipients should note their role in their formulation rather than their identity as an excipient, i.e. surfactant, solvent, carrier, etc. For critical excipients, note both their function and their status as a critical excipient.

Table 1: Example of formulation composition table

Ingredient Name (Common or Chemical)	CAS Number	Standard	Quantity (g/L)	Function
Active Ingredient 1[1]	xxx-xx-xxxx	USP	52.5	Active Ingredient
Active Ingredient 2	xxx-xx-xxxx	USP	100	Active Ingredient
Active Ingredient [HCl][2]	xxx-xx-xxxx	BP	1.075	Active Ingredient
Sodium Selenate[3]	13410-01-0	MS	2	Functional Active Ingredient
Copper disodium EDTA[4]	14025-15-1	MS	15	Functional Active Ingredient
Paraben	xxx-xx-xxxx	BP	1	Preservative
Xanthan Gum	11138-66-2	USP	2	Critical Excipient – Viscosity Modifier
Suspensone	xxx-xx-xxxx	EP	20	Critical Excipient – Suspending Agent
Hydrochloric acid solution 1N	7647-01-0	USP	qs to pH	pH Adjuster
Sodium hydroxide solution 1N	1310-73-5	USP	qs to pH	pH Adjuster
Blue Dye	xxx-xx-xxxx	MS	0.05	Colourant
Water	7732-18-5	MS	qs	Carrier
Specific gravity	1.120			
Other information about formulation (for example, overage, isomers)				
[1] Includes a 5% overage (2.5g/L) to manage loss on storage. [2] 1.075 g/L Active Ingredient [HCl] = 1g/L Active Ingredient [3] 2g sodium selenate provides 0.85g selenium per litre [4] 15g copper disodium EDTA provides 2.4g copper per litre				

(3) If the active ingredient is added to the formulation at less than its pure state (e.g. technical grade 90%), note the grade and potency in the "ingredient name (Common or Chemical)" cell for that ingredient.

(4) If a salt or hydrate form of an active ingredient is used, identify the salt. Note the conversion for the salt or hydrate compound quantity to its available active ingredient quantity in the "other information" box.

(5) If an ingredient is added based on potency, provide a discussion on how the quantity of ingredient is calculated based on the potency assay.

For example, if the theoretical batch quantity of an active ingredient in a batch of product is 100g, and the batch of ingredient being used has a potency of 92% w/w, then the quantity of the active would be calculated as 100g x 100/92 = 108.7g.

(6) Include ingredients used to standardise the formulation, such as pH adjustors, if these ingredients are still present in the formulation at release (i.e. if they are not entirely consumed in the manufacturing process).

(7) When an ingredient is added to the formulation as a separate precursor compound (e.g. the active ingredient is barium selenite but separate barium and selenium compounds are added), include the final compound (e.g. barium selenite) in the trade name product formulation table. The precursor compounds are to be listed in the manufacturing batch formula table (see section 6.5.2) and the manufacturing process information (see section 6.5.3(2)).

(8) When possible, state a fixed quantity for each ingredient. If a range applies for the ingredient, state the maximum amount or nominal content, whichever applies, with a notation specifying what the range is.

Explain the choice of a range instead of a fixed concentration, how that range was determined, and how the choice to use a range impacts the risk profile of the product, in the pharmaceutical development section of the dossier.

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

(10) For formulations in unit dose form, express the formulation in g/kg as the master formulation. Below this, draft a second formulation table to express the formulation on a per unit basis (e.g. mg/tablet, mg/capsule mg/vial). If these units are not appropriate for a particular formulation, suitable units, such as µg/kg or an international unit of biological activity can be used with justification as to why these units are suitable.

a) If unit dose forms have one uniform base formulation (i.e. tablet dose varies in size, but not formulation), all unit dose sizes may be registered as *one trade name product.*
b) If the formulation varies significantly between unit dose forms (e.g. each tablet size has the same ingredients but in different quantities), or contain formulation or species-specific variations (e.g. flavourings for dog tablets but not for cat tablets), each unit dose size must be registered as a *separate trade name product.*

(11) For formulations in unit dose form, specify whether the final units have a coating or capsule. If coated, include details in the trade name product formulation table. Details of the coating formulation should also be included in the batch formula (see section 6.5.2), and details of the coating process including in the manufacturing process information. For formulations presented in a capsule, provide details of the capsule composition as above.

6.2.2 Stability–related overages

(1) If an overage of active ingredient is deliberately added to compensate for active degradation and/or potency loss on storage, state the actual total concentration (nominal content plus overage) in the formulation table. Explain the reason for the overage with respect to stability, and any impact on efficacy, safety, or residues.

(2) State the nominal content and the overage content, along with the reason for the overage, in the formulation notes section of the product data sheet.

(3) Address overages added to compensate for loss during the manufacturing process in the manufacturing information – see section 6.5.4.

6.2.3 Ingredients of biological origin

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

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

6.3 Active ingredients

6.3.1 Identification of active ingredients

(1) Provide the following identifying details for each active ingredient in the formulation:

a) molecular formula, molecular mass and structural formula;
b) for active ingredients existing as salts or hydrates, also provide the molecular mass of the free base/acid or anhydrous form; and

c) for polymeric compounds, provide the molar mass distribution in the form of the mass average molar mass (Mm) and number average molar mass (Mn).

If relevant, the structural formula should include the stereochemical properties of the active ingredient, such as the relative configuration (e.g. *cis/trans, d/l*) and absolute configuration (eg *E/Z, R/S*). If possible, the structural formula should be given diagrammatically with all known stereochemistry.

(2) If relevant, the structural formula should include the stereochemical properties of the active ingredient, such as the relative configuration (e.g. *cis/trans, d/l*) and absolute configuration (e.g. *E/Z, R/S*). If possible, the structural formula should be given diagrammatically with all known stereochemistry.

6.3.2 Active ingredient specification

(1) Nominate an appropriate standard with which an active ingredient complies, i.e. pharmacopoeial or manufacturer's specification (MS).

(2) Provide an active ingredient specification from each active ingredient manufacturer that lists all physical and chemical qualitative and quantitative parameters including acceptance limits and validated test methods. These parameters should be set within an appropriate limit, range, or distribution to ensure the desired quality of the active ingredient and thereby the formulated product.

(3) If the efficacy, safety or residue profile of the final product is dependent on a particular characteristic of the active, such as isomer proportion or polymorphism, state this and explain the limits set.

(4) If the active ingredient is difficult to quantify, a combination of specification parameters and details of the manufacturing process will need to be provided to adequately characterise the active ingredients.

(5) The tests and limits expected in the specification for an active ingredient should include (but are not limited to):

a) appearance/description;
b) test for identity;
c) maximum and minimum limits of purity;
d) maximum limits for impurities (e.g. synthetic impurities and degradation products, residual solvents, heavy metals);
e) additional tests relevant to the risk profile of the active ingredient as they pertain to the product in which it will be included (e.g. solubility, micronisation, pH, sterility); and
f) all relevant physical and chemical properties of the active ingredient.

(6) The information should include the following parameters as applicable to the product and its risk profile:

a) Physical characteristics:

i) a general description (for example, appearance, colour, odour and physical state)
ii) melting point/range for solids
iii) boiling point/range (atmospheric pressure) for liquids
iv) condensation point (for gases)
v) density/ specific gravity (for liquids)
vi) particle size distribution (sieve tests, with median and range reported)
vii) viscosity (liquids only)

b) Chemical characteristics:

i) isomeric content (enantiomeric, rotational, diastereometric and/or geometric)
ii) solubility (in water and organic solvents)
iii) hydrolytic properties
iv) photolytic properties
v) polymorphism
vi) pKa and/or (aqueous) pH values
vii) hygroscopicity
viii) n-octanol/water partition coefficient (P_{ow} or log P_{ow})

ix) chelating and/or encrypting properties.

6.3.2.1 Active ingredients conforming to a pharmacopoeial monograph

(1) Confirmatory evidence of test method validation is not required for active ingredients conforming to BP, EP (Eur Ph), USP, or JP. A copy of the monograph to which the active ingredient conforms is expected as part of the dossier.

a) A CEP can be accepted with a copy of the corresponding EP monograph.

(2) Active ingredients conforming to a third country pharmacopoeia (e.g. CP) will be considered provided a copy of the monograph, accompanied by translation when appropriate, and evidence confirming validation of the test methods contained in the monograph, is provided. Purity testing, and the suitability of the monograph to control those potential impurities, should be demonstrated as per the procedures listed in BP, EP (Eur Ph), USP, or JP and be submitted with a comparative technical discussion when purity testing and/or impurity assay methods differ.

(3) The nominated pharmacopoeial standard will apply to the ingredient in its entirety. If multiple monographs are to apply to a single manufacturer, the final specification should be managed like a manufacturer's specification.

(4) MPI allows more than one MPI-recognised pharmacopoeial specification to be proposed for a single ingredient, such as when an active ingredient is sourced from multiple manufacturers and each is using different MPI-recognised pharmacopoeial standards. Each manufacturer must conform to a single monograph as per (3) above.

(5) MPI expects that the active ingredient will comply with the latest monograph. If the latest monograph is not or will not be used, specify and justify the monograph used.

6.3.2.2 Active ingredients conforming to a non-pharmacopoeial specification

(1) If a manufacturer's specification (MS) is used, provide a discussion of the critical parameters and limits assigned, and how those particular parameters and values will be sufficient to manage the risks associated with the active ingredient's use in the final formulated product. This is particularly important if a manufacturer chooses to set a MS when a pharmacopoeial specification exists for that active ingredient.

(2) Parameters and limits accepted for the MS should reflect those listed in section 6.3.2 (5) as applicable.

(3) The MS should be accompanied by evidence confirming validation of the test methods used.

6.3.3 Active ingredients impurities

(1) Impurities include both those impurities that result from the manufacture of the active ingredient, and those that develop during storage of the active ingredient.

(2) For all impurities, explain both the relationship of the impurity to the ingredient from which it originated, and how it was produced (e.g. changes on storage of the ingredient, changes that occurred during processing).

(3) The identity information provided about an impurity must include:

a) name(s)
b) CAS number (if available)
c) quantity (S.I. units),
d) maximum allowable limits.

(4) The additional information expected for impurities will depend on their concentration and toxicological significance:

a) report any impurities present at a concentration of 1 g/kg (0.1% or more);
b) report and identify any impurities present at a concentration of 2 g/kg (0.2%) or more; and
c) report, identify, and quantify any impurities present at a concentration of 5 g/kg (0.5%) or more.

(5) Identify, quantify, and report impurities of toxicological significance present at any level, including those present at less than 1 g/kg (0.1%). Impurities of particular toxicological residue concern include, but are not limited to, dioxins, heavy metals, persistent organ-carbon compounds, primary aromatic amines, polychlorinated biphenyl (PCB) compounds, and nitrosamines.

(6) Identify, quantify, and report any specified compounds subject to international treaty or bilateral or multilateral agreement (e.g. certain hormones and growth promotants) present at any level, including those present at less than 1g/kg (0.1%).

6.3.4 Active ingredient batch analyses

(1) Provide batch analysis results for at least three recent production scale batches of the active ingredient from each nominated manufacturer, to demonstrate the active ingredient is manufactured consistently to meet the proposed pharmacopoeial monograph or manufacturer's specification. The selection of batches to demonstrate routine compliance with the pharmacopoeial monograph or manufacturer's specification should be the same as that described in VICH GL3(R).

(2) Batch analysis data must include:

a) batch number, date of manufacture and date of analysis;
b) site of manufacture (if not tested by the actual site, then evidence of origin from the site is required); and
c) results of all analytical determinations.

(3) For quantitative tests (e.g. active ingredient concentration, individual and total impurities) provide the actual numerical results. Vague statements such as "within limits" or "conforms" are not considered acceptable.

(4) Any additives such as stabilisers added to the active ingredient must be identified.

6.3.5 Active ingredient test methods and validation

(1) Active ingredients conforming to BP, EP (Eur Ph), USP, or JP will be accepted without confirmatory evidence of test method validation.

(2) For active ingredients that do not conform to BP, EP, USP or JP in their entirety, provide full details of the analytical methods used for all active ingredients. Include the following information in a written analytical method:

a) principle of the method;
b) method summary;
c) sample preparation techniques;
d) equipment/reagents, e.g. for chromatographic method details of the column, eluent (including gradients, if applicable), temperature, detector, and retention times;
e) purity of reference standards;
f) if chromatographic techniques are used, provide relevant chromatograms including peak assignment and peak integration data;
g) worked examples of the calculations, if applicable; and
h) specificity, sensitivity, precision and accuracy of the method.

(3) Provide evidence of validation for the analytical methods used to assay the active ingredient and impurities. Address the following parameters, if appropriate:

a) specificity
b) linearity
c) precision
d) recovery (accuracy)
e) limit of quantification.

For further information regarding the validation of analytical methods, refer to VICH GL1: Validation of analytical procedures: definitions and terminology and VICH GL2: Validation of analytical procedures:

methodology.

(4) For sterile active ingredients, provide the analytical method and evidence of site-specific sterility test method validation.

6.3.6 Functional active ingredients

Functional active ingredients are those ingredients that provide a therapeutic or nutritional benefit to the animal being treated, but are not responsible for the main therapeutic indications of the product. For example, a mineralised anthelmintic contains therapeutic active ingredients responsible for the anti-parasitic action of and claims for the product, and functional active ingredients in the form of minerals that provide nutritional supplementation to the animal. Similarly, a teat sanitiser product will contain therapeutic active ingredients in the form of the antimicrobial agents responsible for the mastitis prevention action and claims, and functional active ingredients in the form of emollients that provide a skin conditioning effect for the treated cow.

(1) Identify functional active ingredients as such in the formulation table, batch formula table, and the supporting dossiers.

(2) The identification, quality, specification, and impurities of the functional active ingredient are expected to be managed overall as per a therapeutic active ingredient, though the specification parameters and other details may be adjusted to reflect their risk profile. For example, it may be appropriate to include only a release specification parameter to control the amount of mineral functional active ingredient added to a formulation and omit a corresponding shelf life parameter when it can be demonstrated that the ingredient will remain stable throughout the product's shelf life.

(3) Provide batch analyses for functional active ingredients as per section 6.3.4.

(4) If a product claim or claims to treat, manage, or alleviate disease are attributed to an ingredient that would otherwise be considered a functional active ingredient, the ingredient must be managed as per a therapeutic active ingredient and all of sections 6.3.1 to 6.3.5 will apply.

(5) If an ingredient that would be considered a functional active ingredient is the sole active in a formulated product, the ingredient should be controlled like a therapeutic active ingredient with respect to raw ingredient quality, manufacturers, and product manufacturing processes, but the information provided may not need the same level of detail as a therapeutic active ingredient.

6.3.7 Active ingredient manufacturers

An **active ingredient manufacturer** is any site of manufacture that is involved in the production of an active ingredient. The following information applies to all active ingredient manufacturers, including those producing functional active ingredients.

(1) Provide the following details for every site of manufacture of the active ingredients:

a) name of organisation;
b) physical address;
c) site telephone number and/or email address (to enable MPI to quickly contact the site if necessary); and
d) function as applicable (e.g. manufacturer, sterilisation, etc.).

(2) For non-sterile active ingredient manufacturers and non-sterile intermediate active ingredient manufacturers, provide all information listed in (1).

(3) For sterile active ingredient manufacturers, provide all information listed in (1) above and all of the following:

a) confirmation of whether the manufacturer is undertaking the sterillisation of the ingredient themselves, or contracting a secondary site to fulfil this function;
b) details of the sterilisation process(es) and method validation;
c) details of the quality control laboratory performing sterility testing on the active ingredient; and

d) a certificate from MPI or a recognised authority confirming conformance to GMP. Active ingredients that are not further sterilised as part of the formulated product manufacturing process must be sterilised in a GMP facility.

(4) If active ingredients are sterilised at a secondary facility, provide details for this facility in the PDS as an active ingredient manufacturer.

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

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

6.3.7.1 Intermediate active ingredient manufacturers

Active ingredients may undergo further processing before they are used in the final formulated product. This further processing can include filtration, granulation, micronisation, or other processes that alter their molecular, physical, or chemical properties, or their purity.

Active ingredients that undergo these processes after they are procured for formulated product manufacture on the direction of the registrant or formulated product manufacturer are considered **intermediate active ingredients**. Active ingredients that undergo these processes before they are procured for formulated product manufacture are not considered intermediate active ingredients.

(1) It is expected that registrants will ensure that the specifications applied to the active ingredient and any other testing performed will manage the quality and consistency of the active ingredient to ensure its suitability for inclusion into the formulated product after the additional processing is complete.

a) For example, if micronised fenbendazole is obtained by the formulated product manufacturer to make an anthelmintic product, and the fenbendazole had already been micronised when purchased, the fenbendazole manufacturer is identified as an active ingredient manufacturer. If the ingredient was already micronised when purchased, the fenbendazole manufacturer is the only active ingredient manufacturer listed even if they had it micronised at a separate facility prior to sale. The expectation is that the active ingredient manufacturer will be responsible for ensuring quality control related to the micronisation process prior to sale.

b) If, however, the formulated product manufacturer purchases fenbendazole and then has the ingredient micronised at a separate facility, the manufacturer originally supplying fenbendazole is the active ingredient manufacturer and the micronising site is the intermediate active ingredient manufacturer. Both the active ingredient manufacturer and the intermediate active ingredient manufacturer are to be listed in the PDS. The expectation in this case is that the formulated product manufacturer will be responsible for ensuring quality control related to the micronisation process prior to use.

(2) If an intermediate active ingredient is used in a formulated product, details of the intermediate manufacturer(s) and the processing step(s) for which they are responsible are to be listed in the active ingredient manufacturers section of the PDS. Provide details of their processes in the dossier.

6.4 Excipient ingredients

6.4.1 Excipient identity

(1) Clearly identify each excipient, including:

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

d) the chemical and physical characteristics of the excipient as per 6.3.2 (6), as applicable;
e) the specific function of the excipient in the formulation; and
f) the standard with which the excipient complies.

(2) For any excipient that has no assigned CAS number or a CAS number is not applicable, supply full details of the excipient. The details must include:

a) name;
b) the material safety data sheet (MSDS);
c) the physical form in which the ingredient is used in the formulation; and
d) the specific function of the excipient in the formulation.

(3) If the excipient is a mixture, provide its full formulation information including the name, CAS number, and amount of each component in the mixture.

(4) Nominate and provide a copy of the appropriate standard with which each excipient ingredient complies. If a pharmacopoeial monograph is nominated, it must be from a pharmacopoeia recognised by MPI – i.e. BP, EP (Eur Ph), USP, or JP. The nominated pharmacopoeial standard will apply to the ingredient in its entirety, and MPI expects that the excipient ingredient must/will comply with the current version of the monograph. If the current version of the monograph is not, or will not be used, specify and justify the version used.

(5) If the excipient does not meet a pharmacopoeial or other recognised standard (e.g. Food Grade, FCC) and the manufacturer has nominated their own specification (MS), provide the following:

a) details of the manufacturer's specification for the compound; and
b) a discussion of how the chosen parameters will manage any associated risk.

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

6.4.2 Excipient ingredient impurities

Excipient ingredient impurities include both those impurities that result from the manufacture of the excipient, and those that develop during storage.

(1) When an impurity requires reporting, identification, and/or quantification, explain both the relationship of the impurity to the ingredient from which it originated, and how it was produced (e.g. changes on storage of the ingredient, changes that occurred during processing).

(2) The identity information provided about an impurity must include:

a) name(s);
b) CAS number (if available);
c) quantity (S.I. units); and
d) maximum allowable limits.

(3) The additional information expected for impurities will depend on their concentration and toxicological significance:

a) report any impurities present at a concentration of 1 g/kg (0.1% or more;
b) report and identify any impurities present at a concentration of 2 g/kg (0.2%) or more; and
c) report, identify, and quantify any impurities present at a concentration of 5 g/kg (0.5%) or more.

(4) Identify, quantify, and report impurities of toxicological significance present at any level, including those present at less than 1 g/kg (0.1%). Impurities of particular toxicological residue concern are as per the description in section 6.3.3.

(5) Identify, quantify, and report any specified compounds subject to international treaty or bilateral or multilateral agreement present at any level, including those present at less than 1g/kg (0.1%).

6.4.3 Critical excipients

Although it is acknowledged that all excipients are integral to their formulations, **critical excipients** are those ingredients that are included in the formulation to manage the formulation itself, but have a direct impact on the efficacy, safety, or residue profile of the product when administered to the animal. A change to the identity or concentration of a critical excipient will therefore have a more significant impact on the risk profile of the product than a change to a standard excipient.

Examples of critical excipients include preservatives in sterile formulations, penetrants in pour-on and topical formulations, and viscosity modifiers in topical formulations that need to remain within a certain range for distribution and adherence. Changes to these critical excipients would directly impact the risk profile of the product: failure of a preservative in a parenteral injection poses an animal safety risk; failure of a penetrant would mean decreased absorption of the active ingredients in the pour-on and the risk of under-dosing, inefficacy, or resistance; and failure of a viscosity modifier in a topical would mean the product runs off quickly and could also cause under-dosing, inefficacy, or resistance.

(1) The identity of an excipient as critical will be product-specific and directly related to the indications, claims, and use of the product in the target animal. That means an ingredient considered critical in one product or formulation type would not necessarily be critical in another. Registrants are expected to evaluate the risk profile of their product, and the purpose and importance of each excipient, to determine whether the ingredient is critical to the individual product.

(2) If an excipient is considered critical to the therapeutic function of the product, provide a discussion of the potential impact of the ingredient on the product's risk profile. This discussion should be related back to how the function of the critical excipient will be assured through manufacturing and quality controls.

   a) The formulated product release and shelf life specifications are expected to incorporate parameters that will manage the critical excipient and its impact on the risk profile of the product. This may be a parameter to directly ensure that an acceptable amount of a critical excipient is present in the formulation throughout its shelf life such as preservative content, or a parameter that monitors the function of the critical excipient throughout the product's shelf life such as viscosity or sterility testing.

(3) Additional information may also be required to support the applicant's assessment of the critical excipient's risk profile and provide a complete understanding of its use. This may include ingredient manufacturing information, batch analyses, and/or further discussion.

(4) Details about the critical excipient manufacturer(s) are not required in the PDS, but are expected to be provided in the dossier.

6.4.4 Food grade excipients

(1) Colouring additives, proprietary flavourings, perfumes and other food-grade excipients must comply with a recognised standard such as the Food Standards Code (FSANZ). If these additives comply with a recognised standard, reference the standard.

6.4.5 Excipient batch analysis

(1) Provide a certificate of analysis or CEP (as applicable) from at least one recent batch of excipient ingredient to demonstrate that it meets the chosen pharmacopoeial monograph or manufacturer's specification.

   a) If an excipient is identified as a critical excipient, provide certificates of analysis or CEPs from three batches of ingredient to ensure conformance to the chosen specification and batch to batch consistency.

(2) The batch analysis results should include:

   a) batch number, date of manufacture, and date of analysis;

b) identity and quantity (if appropriate) of impurities; and
c) results of analytical determinations. For quantitative tests (e.g. ingredient assay, pH, impurities), provide the actual numerical results rather than vague statements such as “within limits” or “conforms”.

(3) If the excipient undergoes additional processing, such as milling or sterilisation, provide a brief overview of these processes.

(4) If an excipient is sourced as a sterile ingredient for aseptic addition into a sterile formulated product (with no further sterilisation steps), provide evidence of site-specific test method validation for the test used to confirm sterility.

(5) MPI reserves the right to enquire into the manufacturing process of excipient ingredient(s) if it needs to satisfy issues relating to suitability of the process or adequacy of Quality Assurance procedures that may impact on the risks under the ACVM Act.

6.5 Formulated product manufacturing

6.5.1 Manufacturer identity

A **formulated product manufacturer** is an entity that undertakes any step of the manufacturing process. These also include manufacturers of intermediate or incomplete formulated products used in the production of the final trade name product, quality control testing, contracted sterilisation entities, packing from bulk, secondary packers, relabellers, and release for market entities.

(1) Provide the following details for each site of formulated product manufacture:

a) name of organisation;
b) physical address;
c) site telephone number and email address; and
d) all steps of the manufacturing process conducted at each site, including identification of each release test performed at each site when applicable.

6.5.1.1 Formulated product manufacturers and GMP conformance

(1) The following types of formulated product manufacturers must have evidence of conformance to GMP for the manufacturing activities and product types for which they are responsible:

a) sites that manufacture and perform analysis of the formulated product (including sites that perform individual manufacturing steps and/or manufacture an intermediate product used in the production of the final trade name product);
b) contracted sterilisation entities; and
c) repackers, relabellers.

(2) Evidence of GMP conformance must be current and have been obtained from either MPI or a competent regulatory authority that is recognised by MPI. These include approvals from the following:

a) MPI;
b) New Zealand Medicines and Medical Devices Safety Authority (Medsafe), if a facility manufactures both human and veterinary medicines and the veterinary medicines are covered in the Medsafe audit;
c) a Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) member;
d) a recognised agency under the European Union Mutual Recognition Agreement; or
e) a recognised agency with a technical agreement with MPI.

Refer to Appendix 5 for more information on the evidence required from international authorities for GMP and other types of independent certification. If you are unsure whether approval from a particular authority or certificate will be accepted, please contact MPI for advice.

(3) Evidence of GMP conformance from an international authority not recognised by MPI, or evidence of conformance to another set of appropriate requirements such as FAMI-QS certification, can be considered for certain product types on a case-by-case basis.

(4) Manufacturers identified as sites performing secondary packaging and/or relabelling steps for trade name products must only be involved in processes that do not breach the primary packaging, e.g. packing the primary unit into separate/additional secondary packaging, addition of New Zealand specific leaflets, or adding or changing product labelling.

a) It is not considered 'repacking' if product is packed from bulk storage into primary market packaging, or transferred from one primary package to another. Packing of product into market packaging from bulk is part of the manufacturing process and the manufacturer's evidence of GMP conformance should identify this.

6.5.1.2 Contracted testing and quality control laboratories

(1) If testing and quality control is contracted to a separate laboratory, identify each laboratory in the PDS as a manufacturer with details of the tests undertaken by that laboratory.

(2) Testing and quality control laboratories should have evidence of GMP conformance. Evidence of an applicable current ISO accreditation is also currently accepted for contracted testing and quality control laboratories if they do not have evidence of GMP conformance from a MPI-recognised authority.

(3) Provide details for contracted testing and quality control laboratories in the PDS as per section 6.5.1 (1).

6.5.1.3 Release to market entities

(1) Identify the entity responsible for release of the trade name product to the New Zealand market.

a) The entity must ensure that, before release of the product to the New Zealand market:

i) the product conforms to the approved product and manufacturing specifications, including formulation and manufacturing particulars in the approved PDS;
ii) the product is labelled with the correct approved New Zealand product label, and all parts of the product label are present;
iii) transport of the product has been conducted as required to manage product-specific risk such as cold chain transport;
iv) all final checks related to distribution and supply of the trade name product have been completed; and
v) all distribution and sales restrictions such as those applied to RVM products are adhered to.

b) For products manufactured outside of New Zealand, the entity responsible for release to market must ensure that the product has arrived in New Zealand without any negative impacts on product conformance and quality in addition to all of the requirements above in a).

(2) Release to market entities do not require evidence of conformance to GMP.

(3) The release to market entity should be present in New Zealand.

a) If the release to market entity is outside of New Zealand, they must assign an entity present in New Zealand to perform the applicable final checks on the product before release. The entity in New Zealand will perform those parts of (1) a) above that cannot be checked remotely by the release to market enitity, and provide the results of those checks to the the release to market entity for review. The release to market entity will then be responsible for authorising release of the product to the New Zealand market after all information has been reviewed.

i) For example, if the release to market entity is present in Australia, they will assign a New Zealand supplier to perform checks on the product once it has been imported. The Australian entity will have direct authority over and communications with the New Zealand

supplier performing the checks, and after review of the information from the checks authorises release to the New Zealand market.

(4) Registrants may nominate themselves as the release to market entity for their own products, or nominate a third party to perform this function.

(5) The release to market entity or any nominated third party must have an appropriate documented system in place to manage all applicable steps of the release to market process.

(6) Provide details for the release to market entity in the PDS as per section 6.5.1 (1).

6.5.1.4 Non-sterile, single-component formulation manufacturers

Non-sterile, single-component formulations are those formulations comprised of a single ingredient that functions as both the active ingredient and the full formulation, such as a zinc-based facial eczema product formulated without a carrier or other additional ingredients. The manufacturer of such a product is considered both the active ingredient manufacturer and the formulated product manufacturer.

(1) As a formulated product manufacturer, it is expected that the entity will manufacture the trade name product with procedures and quality controls in place to conform to the expectations of GMP.

(2) If the manufacturer has not been or cannot be verified to comply with GMP by a recognised regulatory authority, a conditional registration requirement for product testing may be considered in lieu of evidence of GMP compliance on a case-by-case basis. The condition of registration would require randomised sampling and testing of each batch or lot of product imported into New Zealand to confirm compliance with the established release specification prior to release to market.

a) The testing must be performed in a GMP or ISO 17925 accredited laboratory according to pharmacopoeia or test methods approved for the single-component formulation.
b) Completed assay results must be retained for MPI audit purposes.

(3) Imported product must also be inspected on arrival to ensure it is labelled correctly and can be traced back to the retained sampling and testing results.

6.5.2 Manufacturing information

(1) The manufacturing batch formula is the complete list of formulants used in the manufacture of the final trade name product, including all intermediates, solvents, and stabilisers that are partially or completely consumed or removed during the manufacturing process. If the manufacturing process is staged, two or more tables may be used to ensure that the information presented is clear and accurately represents the manufacturing processes.

Table 2: Example of batch formula table

Typical Batch Size	**100-300kg**	
Component	**Quality Standard**	**Amount (kg) per batch**
Core tablet formulation		
Active ingredient	MS	500
Excipient X	USP	310
Excipient Y	EP	280
Magnesium stearate	EP	15 (range 14.5 – 15.5)
Purified water	USP	(200)[a]
Film coat solution[b]		
Hydroxymethylcellulose	USP	10
Purified water	USP	(200)[a]

Typical Batch Size	**100-300kg**	
Component	**Quality Standard**	**Amount (kg) per batch**
Colour red	Food grade	10
Print ink solution		
Colourant	Food grade	0.15
Solvent	BP	10
Total batch size		Z
[a] Water is removed during processing [b] Film coat weight variability is 80 - 120% target		

(2) Ensure the batch formula includes all components, with a reference to their quality standards to be used in the manufacturing process. Provide details on the amounts on a per batch basis, including ingredients consumed during the manufacturing process. Identify any gases used in manufacture and packaging (e.g. nitrogen gas), and state at what point in the process the gases are used.

(3) If a manufacturing-related overage is used, state the overage included for each affected ingredient. The information and discussion expected regarding stability-related overages are detailed in section 6.2.2.

(4) Process validation should be performed across the batch size range and between equipment (if different equipment is used for different batch sizes). This is to verify the entire batch size range can be produced consistently across a batch and between batches.

6.5.3 Manufacturing Process

(1) Provide a flow diagram of the manufacturing process from ingredient dispensing to labelling. The diagram must represent the sequence of steps and the process controls used during the manufacture of the product to monitor and, if appropriate, adjust the process to ensure the trade name product meets its release specification.

(2) Specify the entire manufacturing process in the flow diagram, and include details (as applicable) of:

a) where each starting material enters the manufacturing process;
b) all critical control points, and where they occur in the process;
c) sampling points;
d) all heating, cooling, and blending steps, including associated timing/duration (qualitative and/or quantitative description, as applicable, e.g. “30 minutes or until dissolved,” “until solution is clear”)
e) the production, use and storage of intermediates, if applicable;
f) details of bulk storage of product, including information on the physical characteristics (e.g. size, material, presence/absence of a stirrer) of the storage vessel or container;
g) time frame of bulk storage post-manufacture;
h) storage conditions, such as temperature control;
i) duration of storage prior to packaging into the final market packs;
j) the filling process into the final product container, application of, and sealing of the closure system (e.g. “vials are stoppered and crimped”); and
k) how market labels are attached to the product packaging, and the application of the required batch number and expiry date.

(3) Ensure each manufacturer performing each step of the process, including all quality control and critical control points, is identified.

(4) If alternative manufacturing processes can be used to manufacture the same formulation, provide full manufacturing process information for each alternative process.

(5) State typical production batch size or batch range if applicable.

(6) For sterile products, detail the method of sterilisation and how it is appropriate for the product.

(7) Any time in storage prior to packing or repacking into market packaging should be incorporated into the final shelf life of the product.

(8) Include ingredients that are partially or completely consumed during the manufacturing process (i.e. ingredients that are still present but in smaller quantities, or undetectable in the finished product) in the batch formula table. Examples of this would include the addition of two precursor compounds that are expected to mix in situ to create an active ingredient (e.g. barium chloride and sodium selenate to make barium selenate), or pH adjustors that are added until the desired pH is reached.
Note: List ingredients that are entirely consumed in the manufacturing process (i.e. completely absent from the final formulation) in the batch formula table but not the formulation composition table.

6.5.4 Manufacturing-related overages

(1) If an overage of active ingredient is deliberately added to compensate for loss during the manufacturing process, state the actual total quantity (nominal content plus overage) in the batch formula table. Explain the reason for the overage with respect to the manufacturing process.

(2) Address overages added to compensate for loss during the storage of the formulated product in the final formulation table – see section 6.2.2.

6.5.5 Manufacturing process validation

Manufacturing process validation is the procedure employed to ensure that the manufacturing process can produce a trade name product that is capable of consistently meeting the established minimum quality parameters and specifications. Conducting manufacturing process validation is a requirement for all veterinary medicines as part of the manufacturer's good manufacturing practice (GMP) approval. Refer to EMA/CHMP/QWP/BWP/70278/2012-Rev1, Corr1 for further guidance. Process validation should not be viewed as a one-off event. Process validation must incorporate process developments and amendments. Except in exceptional circumstances a manufacturing process should be validated before a product is placed on the market.

(1) Provide evidence of manufacturing process validation from each formulated product manufacturer approved to manufacture a trade name product, even if the process used is identical to another site producing the same trade name product. This is because site-specific variations in the manufacturing processes, monitoring procedures, and/or equipment used from site to site can impact the quality and consistency of a product, making validation non-transferrable.

(2) Validation should include all strengths, batch sizes and pack sizes, for each manufacturing site. A bracketing approach may be acceptable for different strengths, batch sizes, and pack sizes when strengths are identical or very closely related in composition (e.g. one formulation used to produce a range of tablet sizes for different dosing strengths).

(3) If validation has not been completed for a specific product at the time an application is made, approval of the registration based on the validation plan and, in these instances, the provision of a validation protocol or equivalent can be considered. The document provided must include:

a) a description of the entire manufacturing process, with a summary of the critical processing steps or critical process parameters to be monitored during validation;
b) in-process controls and analytical methods proposed for the process, with justification, acceptance criteria, and analytical validation, if appropriate;
c) additional testing intended to be carried out, with justification, acceptance criteria, and analytical method validation, if appropriate;
d) the sampling plan that will be used during validation, including what, when, and how the samples will be taken, and justification for the sampling plan relative to the product-specific risks;
e) number of batches (usually a minimum of **three** consecutive batches are expected);
f) details of the methods for recording and evaluating the results;
g) the proposed formulated product release specification;

h) the validation acceptance criteria; and
i) a proposed time frame for completion of process validation.

(4) For those products where process validation has been completed prior to submission of a registration application, or when evidence of process validation is supplied to satisfy a conditional requirement for the provisional of additional data, the report must include all of the following:

a) a copy of the protocol or equivalent plan followed during validation;
b) analytical data from three production-scale batches of product manufactured following the proposed manufacturing process, representative of the proposed batch size range;
c) certificates of analysis for each batch of product, including batch size;
d) batch production records to demonstrate conformance to the protocol or equivalent validation plan and established process, including results from all in-process and additional analytical testing performed;
e) a discussion of batch to batch variations, even if all results are within established parameters;
f) a report on any and all unusual findings, modifications, deviations, or changes necessary during the process, with appropriate justification and discussion; and
g) conclusions of the validation process.

(5) If the trade name product has been registered before validation has been completed and results of the validation have demonstrated significant deviations from the protocol (or equivalent validation plan) or manufacturing process from those expected, notify MPI immediately. Submit a variation application to discuss these deviations and propose changes to the product quality characteristics and manufacturing processes for assessment as soon as an application with the relevant information can be compiled.

Note: To be compliant with GMP principles it is expected that process validation in the form of continuous process verification will be conducted regularly during the life of a trade name product to ensure processes and established parameters remain fit for purpose. If it is determined during regular validation that a change is required, submit an application to vary the registration of the product before that change is implemented in the normal commercial production of the trade name product. Evidence of continuous process verification is not required to be submitted, but if a formulation, process or equipment change necessitates re-validation, and the change necessitates a variation to the TNP registration, evidence of this re-validation may be necessary. Refer to the variation section for specific details.

(6) For sterile products, evidence of validation should include confirmation that the intended sterilisation process is capable of producing entire batches that are sterile. A bracketing or similar approach providing evidence from a similar product using the same sterilisation process can be accepted if justified. Provision of a sterility test in the final product release specification cannot be used as evidence of a sterile manufacturing process.

6.6 Formulated product quality control

6.6.1 Finished product specifications

The **finished product specification** establishes the criteria to which a formulated product must conform to be considered acceptable for its intended use. “Conformance to specification” means that the product, when tested according to the listed analytical procedures, will meet the established and justified acceptance criteria.

(1) Consider formulation type when determining appropriate parameters and acceptance criteria for a particular parameter. Examples of parameters that must be addressed by formulation type are:

a) sterility testing for formulations being administered by injection or by intramammary infusion, and powders for injection after reconstitution;
b) suspendability, uniformity of dose, and particle size testing for suspensions (including pastes);
c) uniformity of dose for tablet formulations, especially if the tablet is scored for doses less than a whole tablet; and
d) microbial limits for aqueous-based emulsions, solutions and suspensions.

A complete list of expected specification parameters by product and formulation type can be found in Appendix 3.

6.6.1.1 Formulated product release specification

(1) The release specification must include:

a) the identity of the testing parameter, acceptance criteria, and the analytical procedures used to perform each assay or test including method numbers or other identifiers, when applicable;
b) suitable upper and lower limits for each active ingredient and preservative agent included in the formulation;
c) suitable upper and lower limits for each quantitative physical or chemical characteristic considered relevant to the function and risk profile of the product (e.g. pH range, particle size);
d) suitable acceptable parameters for each qualitative physical or chemical characteristic considered relevant to the function and risk profile of the product (e.g. appearance, solution clarity); and
e) all testing parameters considered critical for the particular dose form and/or formulation type.

The expected parameters for each dose form and/or formulation type are listed in Appendix 3.

(2) The analytical methods used for each parameter should be fully validated. Provide evidence of method validation or equivalent for the active ingredient assay, or method verification from each testing laboratory. Validation or verification for the other parameters need not be supplied when pharmacopoeial standards, ISO, and other internationally recognised standards are employed. Document and validate any variations from nominated standards.

(3) The release specification of a sterile product must include a sterility parameter, and the test method used must be validated. Provide evidence of test method validation for each laboratory performing sterility testing.

(4) Explain omission(s) of any parameter usually required for a particular product type (e.g. omission of the hardness specification for tablets).

(5) Specification parameters must take any overages used in the manufacture of the formulation into account.

6.6.1.2 Formulated product shelf life specification

(1) The general requirements for shelf life specification parameters are as outlined in section 6.6.1.1 for the release specification.

(2) Include all appropriate parameters in the shelf life specification with upper and lower acceptable limits supported by technical rationale. The technical rationale should include justification of parameters and acceptance limits with respect to product quality, and link to efficacy, safety and residues.

(3) Setting specification parameters to provide for a particular shelf life duration or to allow for significant degradation without consideration of the impact on the risk profile will not be accepted. The specification, parameters, and ranges chosen should allow for a realistic and justifiable amount of degradation, but must still ensure there is no negative impact on the efficacy, safety, or residue profile of the product. For example, if the pH of an injectable solution decreases over its shelf life, the value set for the pH parameter is to ensure that the formulation will not result in any safety concerns such as injection site reactions.

6.6.1.3 Formulated product specification parameters for functional active ingredients

(1) Because functional active ingredients are not responsible for the primary therapeutic efficacy of the product, the formulated product release and shelf life specification parameters specific to functional active ingredients may be limited or absent provided the specifications as a whole are sufficient to ensure the efficacy of the ingredient.

a) For example, if an anthelmintic formulation is mineralised to provide nutritional supplementation, the overall release specification must ensure the mineral is delivered to the treated animal to ensure a nutritional benefit. Provided the stability of the mineral in the formulation can be sufficiently demonstrated throughout the nominated shelf life, management of the efficacy of the mineral may be achieved by establishing a minimum quantity of the mineral at release without a full release parameter range or the inclusion of a mineral-specific shelf life specification parameter. The minimum acceptable level for the release parameter, and how stability throughout the shelf life is evidenced, will depend on the ingredient and formulation being considered.

(2) If a product claim or claims to treat, manage, or alleviate disease are attributed to an ingredient that would otherwise be considered a functional active ingredient, the ingredient must be managed as per a therapeutic active ingredient in the formulated product release and shelf life specifications.

6.6.1.4 Specification rationale

(1) Provide a rationale explaining how the each specification proposed for the formulated product will manage the risks associated with the product's manufacture, storage, and use.

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

(3) The rationale should include a discussion of the parameters being chosen, the value or range proposed as acceptable for those parameters, and the frequency in which the parameters are tested (e.g. for every batch, every other batch, or another frequency).

a) If the frequency of testing is anything other than for every batch, discuss and justify the reduced frequency.

(4) Discuss the criticality of each chosen parameter in the specification, and how each on its own and in conjunction with the rest of the chosen parameters addresses the management of the critical quality attributes of the product. For example, the expected release and shelf life specifications for solid dose forms (tablets) include disintegration, disintegration, hardness, and friability. Although the quality control specification may include all four parameters, the release and shelf life specifications may only need to focus on dissolution if the acceptable range for dissolution and in-process controls sufficiently manage the other aspects.

(5) Base the value(s) chosen as the acceptable limits for each parameter on a risk assessment relative to the efficacy, safety, residue, and stability risk profile of the product and product type. For example, the viscosity of an intramammary antibiotic would be set at a range that would allow the product to be viscous enough to remain within the teat, but not so viscous as to hinder administration. It is not acceptable to set the acceptable specification value(s) based solely on the results of stability trial work without also linking it back to the use risk profile of the product.

(6) If applicable, consider stability data from production scale batches or validation batches in setting and justifying specifications.

If production scale batches are not available, smaller scale batches can be considered with the appropriate discussions regarding scale-up to set an interim specification for the formulated product.

The interim specification should be re-evaluated when confirmatory stability data on production scale batches has been generated, and any differences to set release and/or shelf life specifications discussed.

(7) If multiple manufacturing sites are proposed for the trade name product, present and evaluate data from all manufacturing sites when establishing the formulated product specification parameters and parameter acceptance criteria. This is to ensure that the specifications will be capable of ensuring product from all manufacturers will be consistent, equivalent, and compliant with the acceptance criteria for each parameter.

(8) Justification for exclusion of a test expected for a specific formulation type from the complete specification set should be based on formulation development and/or process validation data.

6.6.2 Quality control testing

In-process quality control testing refers to all quality control tests that are performed during the manufacture of the trade name product. These may include testing conducted during the manufacture to monitor conformance to the established processes, and tests that will determine whether formulation adjustments are needed (e.g. pH of the solution). In-process quality controls may also include any mixing adjustments, intermediate form specification parameters (such as hardness and friability of tablets which will then be coated, or a controlled-release formulation that will then be assembled into an administration device), or any other tests necessary to ensure the quality or consistency of formulated product before manufacture is complete.

Formulated product release testing refers to the quality control testing performed on each batch of product after manufacture is complete. The release testing is intended to confirm that the batch conforms to the product specification and is suitable for final packaging and market release and should be performed for every batch.

(1) Provide full details of the quality control testing processes used by the formulated product manufacturer(s) and/or contract testing laboratories to ensure the batch to batch consistency of the product.

   a) If details of the processes vary between manufacturers, manufacturing sites or laboratories, provide a separate outline of the quality control testing for each manufacturer and/or site.
   b) Details of the quality control testing must include all in-process and release testing and assays performed at various stages of the manufacture, processing, and packing of the product.

(2) For in-process quality control testing, provide the test method descriptions for all tests conducted during the manufacturing process, the parameters/expected results of those tests, and actual test results from a manufactured batch. This will provide an understanding of what the test is intended to achieve and how that aspect of the manufacturing process and product quality control is managed.

(3) For formulated product release testing, provide the test method descriptions of all tests conducted for each batch at release. Test methodology and descriptions are expected for all parameters included in the formulated product release specification as per section 6.6.1.2.

6.6.3 Formulated product batch analyses

(1) Provide a minimum of three batch analyses of the formulated product from each site of manufacture. The number of batches should be adequate to provide sufficient confidence of quality both within a batch and between batches.

   a) Production scale batch analyses are always preferred. If, however, three production scale batches have not yet been manufactured, pilot scale batches or smaller may be considered with appropriate technical discussion. The discussion supporting the use of smaller batches should address how these batches represent production scale manufacture with respect to processes and equipment used, and the analyses must demonstrate conformance to the parameters intended for as production scale manufacture.
   b) If batch analyses for production batches have not been supplied, MPI may require additional information post-registration as part of the conditions of registration.
   c) Ensure that the method used in the analysis matches the validated methods nominated for the release specification.

(2) Each batch analysis must include the following information:

   a) date of manufacture;
   b) date of testing;
   c) batch size;

d) site of manufacture; and
e) results for all the parameters included in the release specification, using the specified methods.

(3) Qualitative words like “conformed” or “qualified” are not considered acceptable for quantifiable parameters.

(4) Time zero stability trial analysis results may be used as the formulation batch analyses provided they meet the requirements in section 6.8.1. Batches that are pilot scale or smaller may be considered if appropriately justified.

(5) Report all results, including those that do not conform to established specification.

6.7 Product packaging

(1) For all packaging material to be marketed, supply details including schematics of the packaging materials. These details should include, as applicable:

a) size
b) shape
c) colour (if applicable, such as for light sensitive products)
d) construction material
e) lining.

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

(3) Discuss the suitability of the container in terms of its compatibility with the product (including adsorption to container, leaching, or transpiration), its performance in protecting the product physically, and the ability of the container to protect the product from moisture and light. Conformance to an appropriate pharmacopoeial standard, such as the USP packaging requirements for injections, may be considered sufficient evidence of packaging suitability.

(4) The integrity of the container must not be impaired by the product it contains, and the product must not be adversely affected by the packaging material.

(5) If the inherent chemical characteristics of the formulated product are such that the packaging must be designed to manage special or particularly high risks associated with the formulation or formulation type (e.g. high acidity, photosensitivity), identify and discuss these risks and the qualities of the packaging that specifically manage them.

a) Demonstrate suitability of the packaging for such formulations as part of the stability trial work, with risk-specific testing.
b) The discussion of the tests and results should include notes on the inherent chemical or physical characteristics that impact on packaging. Examples of special packaging characteristics that would need to be discussed include, but are not limited to, porosity, permeability, impact, strength, closure type, and specific stability considerations such as photolytic and hydrolytic stability of biodegradable packaging.

(6) Specify all pack sizes for which approval is sought.

(7) A pack size range may be considered acceptable for certain product types. A pack size range may be approved if it is considered that there is no additional risk associated with pack sizes within the assessed range after consideration of the product, its specifications, and packaging-specific details such as construction materials.

(8) Additional pack sizes within the approved range and specifications can be chosen and marketed without submitting stability data for assessment. An amended Product Data Sheet and label(s) identifying the new pack sizes and any new relevant label information will be required at the next

variation or registration renewal to bring the product details current. If different from the container volume, specify the product fill volume.

(9) If additional product-specific administration devices or attachments are provided with the final packaged trade name product, provide details of these additional devices or attachments for assessment and approval. Product-specific administration devices would include specialised syringes and or administration equipment that is specifically designed or calibrated to deliver the product and is supplied with that product as part of the market packaging. The information on these additional devices or attachments should include a brief discussion of any associated risks to stability and/or the risk profile of the product when they are used.

a) Applicants are expected to provide schematics, use information, and calibration/validation data for product-specific administration devices when appropriate to characterise the associated risk.
b) Applicants are not required to provide information on commercially available administration devices (such as draw-off tubes, drench guns, bolus administration devices etc. that could be purchased separately by the end user to administer the product). Applicants are, however, expected to ensure that commercially available administration devices provided with the trade name product are fit for their intended purpose, have been evaluated to assess the potential impacts on the risk profile of the product, and that the risks associated with their use are managed appropriately.

(10) Use of new component packaging materials for the primary packaging of all products is expected, as use of recycled materials as the primary packaging for a trade name veterinary medicine product poses a significant amount of risk. Use of recycled materials can, however, be considered with sufficient data, information, and documentation of operating procedures to ensure that the risks associated with the use of such packaging are appropriately managed. If the use of recycled packaging or re-use is proposed, provide details including the method of recycling/re-use, the physical and chemical characteristics of the trade name product, the process for determining it is fit for purpose and the risk management procedures proposed for the management of such a practice.

6.8 Shelf life stability

VICH GL3R, GL4, GL5, GL8, GL45, GL51 and EMEA/CVMP/424/01 provide information on stability design, testing protocols and evaluation of data. The purpose of stability testing is to provide evidence on how the quality of the trade name product varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and to establish a shelf life for the product and recommended storage conditions.

6.8.1 Stability study requirements

6.8.1.1 Batch selection

(1) Stability studies should be performed on **three** batches of trade name product stored at real-time storage conditions and **one** batch of product stored at accelerated storage conditions.

(2) A minimum of three batches of formulation are expected to support the stability of a product, and the three batches chosen should be sufficiently similar in formulation details, size, and manufacturing process to be representative of production scale routine manufacture.

a) Note: in addition to establishing the shelf life, a stability study should provide confidence in the ability to manufacture of product consistently enough to ensure all batches are capable of meeting specification at the end of the nominated shelf life. More than three batches may be needed to achieve this.

(3) The formulation of the product used in the stability studies should be the same formulation as stated on the Product Data Sheet, and the same as that used to generate efficacy, safety and residue data. If the formulation is not identical, provide a technical discussion addressing why stability data using the alternate formulation will be representative of stability in the formulation proposed for registration.

(4) When possible, batches should be manufactured using different batches of the active ingredient(s).

(5) The product should be tested in the same containers (packaging material) and the same as (or simulates) the closure system proposed for registration.

(6) The batches should be production scale, or at a minimum pilot (≥10% production) scale.

a) For pilot scale batches, use a method of manufacture and procedure that simulates the final process to be used for production batches.

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

ii) If after assessment there are any concerns that scaling-up to production scale could negatively impact the stability of the product and thereby the risk profile of the product, further stability data may be required post-registration.

b) Laboratory scale batch data may be considered on a case by case basis if the presentation of laboratory scale data can be supported with a technical rationale for why this can be considered representative of manufacturing scale. If there is any doubt, additional post-approval data on larger batches may be required to confirm the laboratory scale data was sufficiently representative.

(7) The batches should be manufactured at a nominated site of manufacture.

(8) Uniquely identify each batch tested (including whether pilot or production scale).

6.8.1.2 Pack types and sizes

(1) If there is more than one primary container packaging type, demonstrate stability for each type (e.g. a product packed into HDPE plastic and Type II glass primary containers would require stability data for each packaging type).

(2) For homogenous formulations, generate stability data on the smallest pack size being proposed for registration or smaller if justified.

(3) For heterogeneous formulations (e.g. suspensions), provide data on both the smallest and the largest pack size. If stability testing on the largest size packaging would be impracticable, then provide other evidence of phase stability and discussion of how it applies to the largest pack size.

a) When applicable, discuss resuspension techniques for stored product such as shaking or mixing for all pack sizes.

6.8.1.3 Study conditions

(1) Provide data from batches stored at real-time storage conditions or a combination of data from studies conducted at real-time and accelerated storage conditions to support the proposed shelf life.

a) Data from studies conducted at accelerated storage conditions, in addition to real-time stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes (e.g. water loss).

b) Batches evaluated at accelerated storage conditions should include results from a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), for at least six months. If there is an expectation that results from accelerated testing are likely to deviate significantly from expectations (see section 6.8.1.5 (4)), increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

(2) The product label storage instructions relevant to the New Zealand climate and recommended temperature and relative humidity design for stability tests are as shown in Table 3.

Table 3: Product label conditions and temperature and humidity design for stability tests

Storage instruction on product label	Real-time stability test protocol	Accelerated stability test protocol
Store below -18°C (Deep freeze)	-20°C ±5°C	Not appropriate
Store below -5°C (Freeze)	-20°C to -5°C ±5°C	Not appropriate
Store between 2°C and 8°C (Refrigerate. Do not freeze)	5°C ±3°C	25°C ±2°C and 60% RH ±5% RH
Store below 25°C (Room temperature)	25°C ±2°C and 60% RH ±5% RH	40°C ±2°C and 75% RH ±5% RH
Store below 30°C (Room temperature)	30°C ±2°C and 65% RH ±5% RH	40°C ±2°C and 75% RH ±5% RH

(3) If real-time stability data has been generated overseas at a "room temperature" protocol using 30°C ±2°C and 65% RH ±5% RH, this data can be considered representative of "room temperature" in New Zealand. If this higher temperature is used, the final on-label storage conditions should reflect this (e.g. "store below 30°C" instead of the "store below 25°C").

(4) The length of the stability study and the storage conditions must be sufficient to cover storage, transport and subsequent use.

(5) The omission of certain stability study storage condition parameters can be considered provided it has been evidenced in another way that that they will have no effect on the final product's stability. For example, humidity conditions do not need to be controlled as outlined in Table 3 if the final trade name product will be marketed in non-permeable, air-tight packaging if information is provided in the dossier to demonstrate that the packaging will be and remain non-permeable and air-tight in the nominated storage conditions.

6.8.1.4 Testing frequency

(1) Frequency of testing should be sufficient to establish the stability profile of the product. At a minimum, generate the data at the following time points:

a) time zero, which must be set as soon as practicable following manufacture;

i) A delay between manufacture and the start of the stability testing representative of the expected bulk storage period must be included, if applicable (report the delay and/or storage period)

b) at least every three months over the first year;
c) at least every six months over the second year; and
d) 12-monthly intervals thereafter.

(2) If data has been generated at the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a 6 month study is recommended.

(3) Abbreviated trial designs such as bracketing or matrixing can be applied when the testing frequency is reduced or certain factor combinations are not tested at all, if justified.

a) Bracketing assumes that testing at the extremes is representative of testing any of the intermediate levels. It may be considered where a range of strengths are identical or very closely related in composition, or there are a range of container sizes or different fills with the same closure system.

b) Matrixing assumes that a selected subset of the total number of possible samples for all parameter combinations is representative of overall stability.The differences in the samples for the trade name product should be identified as, for example, covering the different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

6.8.1.5 Specification parameters

(1) Stability studies should include testing of those attributes of the trade name product that are susceptible to change during storage and are likely to influence quality, safety, efficacy and/or residues. If the outcomes of testing are likely to have an influence on the risk profile of the product, the testing should cover the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative) and functionality tests (e.g. for a dose delivery system).

(2) Data must conform to the formulated product release specification at time zero for all established parameters.

(3) Data must conform to the formulated product shelf life specification at the time point specified as the nominated shelf life for all established parameters.

(4) Discuss and justify any omitted parameters or results that differ significantly from what is expected.

a) What constitutes a significant deviation from what is expected can be product- or test-specific. These deviations can include a failure to meet specification at a particular time point or points, highly variable results over time, or significant changes of a particular parameter that remains within the nominated specification. If a result can draw the overall stability or batch-to-batch consistency of the product into question, address it in the submission.

b) Examples of a significant deviations would be:

i) a 5% change or more in assay from its initial value;
ii) any degradation product exceeding its acceptance criterion;
iii) failure to meet the acceptance criteria for appearance, physical attributes, and functionality tests such as colour, phase separation, resuspendibility, or hardness (it is understood however that some changes in physical attributes e.g. softening of gel capsules or reduced viscosity for otherwise viscous formulations may be expected under accelerated conditions); and
iv) failure to meet the acceptance criterion for pH, dissolution, sterility, or other risk-specific criteria as appropriate to the product and dosage form.

(5) Consider and address additional stability considerations for the following formulation types (specific specification parameters for each product type are listed in Appendix 3):

a) For liquid formulations, include cold temperature stability data unless the product label contains a warning against exposure to low temperatures and specifies a minimum temperature. This should include the effects of freezing and freeze/thaw data if such changes may impact the stability of the product.

b) For suspension formulations, address the potential for precipitation or separation by demonstrating the phase stability of the product. If a degree of separation is expected at storage, demonstrate that the product can be practically re-suspended under field conditions.

c) In-use stability data is expected for tablets removed from primary packaging (e.g. blisters) when removal could impact product quality. In those cases when the in-use shelf life of tablet fractions is relevant, data should be supplied to support the stability of the remaining tablet fractions for the expected period of time between the breaking of the tablet and its administration.

d) For formulations requiring refrigeration or storage in a freezer, include freeze/thaw data to ensure the stability of the product during cold chain distribution and storage.

i) Evaluation of the stability of products intended for storage in a refrigerator should be based on real time data obtained at 5°C ±3°C for a minimum of 12 months, and accelerated data conducted at 25°C ±2°C and 60% RH ±5% RH for a minimum of six months. If a

significant change occurs within the first three months of testing at the accelerated conditions, provide a discussion to address the effects of short-term excursions outside the proposed storage condition. This discussion can be supported by further testing at accelerated conditions for a shorter period than three months with more frequent testing intervals, when appropriate.

ii) Evaluation of the stability of products intended for storage in a freezer should be based on real time data obtained at -20°C ±5°C for a minimum of 12 months, and accelerated data at an elevated temperature (5°C ±3°C or 25°C ±2°C) for an appropriate time period to address the effect of short-term excursions outside the proposed storage conditions, e.g. during shipping or handling.

e) For formulations that may be particularly sensitive to changes in temperature, demonstrate stability within the applicable range of temperatures that may be expected in field conditions. If, for example, a refrigerated product develops precipitate if in room temperature for more than two hours, address the resuspendability of the precipitate and the effect of precipitation on the continued stability, efficacy, safety and residue profile of the product.

f) For formulations that may be particularly sensitive to storage position, demonstrate stability in both the upright and inverted positions, and address any potential interactions with the closure system.

g) For photosensitive formulations, include data evaluating the photostability of the product in the proposed market packaging.

(6) For products with a formulation that is altered before use (e.g. diluted, dissolved, or reconstituted before administration), demonstrate that any changes that may occur during storage over the nominated shelf life will not adversely affect the alteration process or the risk profile of the product.

6.8.1.6 Analytical methods

(1) Describe analytical methods employed in stability testing.

(2) The analytical methods must be fully validated within the testing laboratory. Copies of validation information need not be supplied when pharmacopoeial standards, ISO, and other internationally recognised standards are employed. Document and validate any variations from nominated standards.

(3) A study conducted to GLP is not a mandatory requirement. MPI requires stability studies to be accompanied by a signed declaration from a competent person that the results are true and accurate. The declaration would preferably be signed by someone not involved in the study.

6.8.1.7 Stability data analysis

(1) A systemic approach should be made in the presentation and evaluation of the stability information, which should include results from the physical, chemical, biological and microbiological tests when undertaken. This information should also include specific tests relevant to the formulation type (e.g. dissolution rate for tablets).

(2) If the data shows so little degradation and variability that it is apparent the requested shelf life is justified, it is unnecessary to provide a formal statistical analysis. Include this conclusion in the discussion of the data to address the omission of statistical analysis.

(3) If there is degradation and variability in the stability data, statistical analysis is appropriate. Refer to VICH GL51 for the approach to analysing data of a quantitative attribute over time.

6.8.1.8 Discussion of stability study results

(1) Provide a discussion on observed variations from the proposed shelf life specification, and the likely impact of these variations on the proposed shelf life of the trade name product.

6.8.2 Proposed product shelf life

(1) The proposed shelf life is to be based on the maximum time over which the product has been

demonstrated, through real time data or a combination of real time and accelerated data, to remain within specification. The proposed shelf life cannot be based solely on accelerated stability data.

(2) The maximum acceptable proposed shelf life will be the point at which product released at the low end of the acceptable release parameter range will still conform to the low end of the corresponding shelf life specification parameter range.

(3) If both real-time and accelerated data is available, accelerated data may be used to extrapolate a shelf life beyond that demonstrated in the real time studies. For example, nine months of real time data + nine months of accelerated data (if the results indicate that the product is within the given specification parameters during and on completion of the stability studies) could be used to support a shelf life of 18 months provided there are no significant changes in the stability profile over the nine month period.

a) The ability to extrapolate a shelf life beyond that demonstrated in the real-time data is based on the understanding of the mechanisms of degradation and the degree of change is as presented in the accelerated data. How far the shelf life may extend beyond the end of the real-time data depends on how well this profile is characterised in the accelerated data, and the modelling used for extrapolation.

b) If a significant deviation (see section 6.8.1.5 (4)) occurs in the accelerated data, the same test should be conducted at the real-time storage conditions to ensure the finding is related to the accelerated conditions. For example, a significant loss of water would not necessarily be an unexpected outcome for products evaluated at the accelerated storage conditions. If this occurs, however, it is expected that there would also be a water content assay conducted under real-time storage conditions to demonstrate there will not be a significant loss of water that may negatively impact the product at the proposed shelf life and storage conditions.

(4) Extrapolation of stability data is expected to follow the statistical evaluation and extrapolation methods set out in VICH GL51: Quality: statistical evaluation of stability data.

(5) If data extrapolation is performed, confirmatory real time data demonstrating conformance to the established specification up to and including the approved shelf life must be provided as soon as it is available. If the data provided is considered insufficient to establish an approved shelf life for the product, an interim shelf life may be approved by MPI to allow the product to be marketed while further data is generated. This will be considered on a case by case basis in exceptional circumstances, taking into consideration any impacts on the risk areas managed under the ACVM Act the setting of an interim shelf life may have.

6.8.3 Proposed storage conditions

(1) State the proposed storage requirements of the product (i.e. label and product literature storage directions).

(2) State the proposed maximum temperature or temperature range for storage.

(3) If applicable, state any specialised storage conditions or requirements needed. This is particularly important for products for which the storage conditions pose a particular risk, e.g. freezing, high temperatures, or exposure to moisture, light or oxygen (air).

6.8.4 Ongoing stability commitment

(1) MPI expects applicants to provide a commitment that an ongoing stability programme will be put in place to monitor the stability of all marketed products over time. This would generally be presented as a declaration in the overall application summary. See Appendix 6 for further detail on MPI's expectations of an ongoing stability programme.

(2) MPI reserves the right to request a review of the stability programme and data during a site audit or on request.

6.9 In-use stability

6.9.1 In-use stability for multi-dose containers

(1) In-use stability data must be provided for trade name products that are parenteral formulations supplied in multi-dose containers.

(2) In-use stability data is also expected for all other types of trade name products supplied in multidose containers when, by nature of their physical form and composition, the first opening of the container may pose a risk to its contents with regard to microbiological contamination or proliferation and/or physiochemical degradation.

a) If in-use stability data is not provided for these trade name products, other data or information must be provided to support the in-use stability of the product for the period of time between first broaching and complete use.

(3) A minimum of two batches of at least pilot scale should be tested. Batch number, date of manufacture, and batch size should be stated for each batch.

(4) At least one of the batches used in in-use stability testing should be approaching the end of its shelflife. If results on the older batch are not available at the time the application is made, data on an aged batch can be provided after registration provided no significant change has been observed following six months of unbroached stability testing at real time and accelerated conditions.

(5) If the proposed product packaging includes more than one container size, product packaged in the size that poses the greatest risk (e.g. a solution packaged in the smallest pack size) should be used in the trial work.

(6) Provide the rationale for the test design and study duration. The test design should simulate the use of the product in practice, taking into account the fill volume of the container and any dilution or reconstitution performed before use. At intervals comparable with those that occur in practice, volumes of the product as per the label recommendations, should be withdrawn.

(7) Sampling should take place under normal environmental conditions.

(8) For products that are altered before use (e.g. reconstitution or dilution), the alteration procedures and diluent(s) must be identical to that proposed for product use as per label. If more than one diluent is proposed for use and the diluents are significantly different, generate in-use stability data for each diluent.

(9) Final label storage and use instructions should reflect the findings of the multi-dose container in-use stability studies when required to manage the risks. Refer to EMEA/CVMP/424/01 for further guidance.

6.9.2 In-use stability for trade name products administered in feed or water

(1) For in-feed products, demonstrate that the trade name product can remain evenly distributed in feed during transportation and in storage for the duration of the time expected for that product in the treatment of the target species.

a) The choice of feed used to demonstrate in-feed stability should be representative of the most likely feed type(s) in which the product will be administered. If the product is intended for use in multiple species (e.g. pig and poultry, cattle and sheep) where feed types vary considerably, infeed stability may need to be demonstrated in multiple feed types.
b) Conduct sampling at multiple points (top, middle, and bottom) in a batch of feed at all testing time points.

(2) For in-water products, demonstrate that the product is sufficiently soluble in water and will remain in solution or suspended for the duration of the storage and/or treatment period for the target species.

a) For products that form a solution, demonstrate that the product will remain in solution and bioavailable, and not form sediments that negatively impact the efficacy, safety or residue profiles

of the product, over the intended administration period. The trial design should take the frequency of water changes into consideration.

b) For products that form a suspension, demonstrate that the product will remain in suspension over the intended administration period. If the product requires agitation, mixing, or re-suspension, address this as part of the trial.

(3) Final label storage and use instructions should reflect the findings of the in-feed and in-water stability studies when required to manage the risks, particularly agitation and re-suspension instructions for suspension products.

7 Variations to a registered trade name product

(1) The registrant must assess the effects of every manufacturing change to a registered trade name product.

(2) Applications to vary the details of a registered trade name product are required whenever there is a change to the approved product information.

(3) Applications must be submitted and approved prior to the implementation of the associated change, and prior to release of the changed product for sale in New Zealand. It is not acceptable to retrospectively apply for a variation to the registration unless prior permission has been granted by MPI in exceptional cases (e.g. corrective actions to manage an issue identified during post-registration management).

(4) Most changes will require data and/or technical rationale to be provided. An acceptable technical rationale will include discussion of the proposed change relative to the information or parameter currently approved, and potential impacts on quality, stability, efficacy, safety, residue profile of the product. If there is little or no impact, explain why you have determined this to be so.

(5) If the change is administrative in nature but affects the technical details of the product (e.g. changes to the storage conditions statement on the label, which may impact the interpretive meaning of the statement relative to providing sufficient consumer information), a technical discussion or justification may be required to support the change.

7.1 Changes to approved formulation details

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

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

Changing the concentration of an existing active ingredient and/or a functional active ingredient can be considered as a variation to the approved formulation details. Please note, however, that for this kind of change further stability, manufacturing process, efficacy, target animal safety, and/or residue data may be required to support the revised risk profile of the formulated product.

(2) Provide:

Technical rationale for the change
Table of the current and proposed formulation details, with differences highlighted
Updated manufacturing process flow chart and description if the manufacturing process has changed. • Provide discussion on any areas affected by the process change: i.e. physical and chemical properties, stability, residues, animal safety and efficacy • Provide process validation data (minimum validation protocol or equivalent) if the change is considered significant
Updated outline of the new QC parameters/test methods/method validation if the details have changed • Provide discussion on any areas affected by the QC changes: i.e. physical and chemical properties, stability, residues, animal safety and efficacy
Batch analysis data on minimum of **one** batch representative of production scale
Release specification, with any changes from that currently approved highlighted

Shelf life specification, with any changes from that currently approved highlighted
Discussion of any areas affected by the formulation change: i.e. physical and chemical properties, stability, residues, target animal safety and efficacy
Stability data to support formulation changes that impact on the stability of the product
Updated Product Data Sheet. Ensure all areas of the PDS affected by the change are updated, as applicable: • final formulation table • batch formula table, and • manufacturing process information
Current/amended product label

7.2 Changes to approved active ingredient manufacturer(s)

For the purposes of section 7.2, "active ingredient" can refer to either therapeutic active ingredients or functional active ingredients as the requirements are the same.

7.2.1 Adding or replacing an active ingredient manufacturer /active ingredient sterilisation site; change in active ingredient manufacturer /active ingredient sterilisation site address

(1) Submit a variation application to add an additional active ingredient manufacturer or sterile active ingredient sterilisation site, or to replace a currently approved active ingredient manufacturer or sterilisation site with another. This applies to all active ingredients, and all new manufacturers and sterilisation sites, to demonstrate their ability to conform to the approved active ingredient specification.

(2) Provide:

Amended Product Data Sheet and label
Details of the proposed manufacturing site(s): • name of organisation • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
Batch analysis data from three (minimum pilot scale) batches of active ingredient from the proposed manufacturer to provide evidence that the active ingredient from the proposed manufacturer will conform to the approved active ingredient specification. The data should include test results from all parameters listed in the approved specification. The results should include: • Batch number, date of manufacture, date of analysis • Manufacturing site (including the site for further processing such as micronisation and testing site, if different to manufacturing site) • Parameters tested, acceptance criteria and test results
Analytical test methods, and validation of test methods conducted at the testing site for non-pharmacopoeial active ingredients Note: confirmatory evidence of test method validation is not required for active ingredients conforming to BP, EP (Eur Ph), USP, or JP
GMP is required for sterile active ingredient manufacturers and secondary sterilisation facilities when the active ingredient is not further sterilised as part of the formulated product manufacturing process

Technical rationale and/or data to confirm equivalence of the proposed source of the active ingredient to currently approved sources, when stability, physical and chemical properties, stability, residues, target animal safety and efficacy are affected

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

(1) Submit a variation application to remove the sole active ingredient manufacturer and/or QC testing site.

a) Note that data and information will need to be provided to support the addition of a new manufacturer as per section 7.2.1 if one has been chosen. This data and information will be expected to demonstrate that the nominated manufacturer will produce the active ingredient, or test the active ingredient if a QC testing site, to ensure the formulated product will still conform to approved specifications and risk profile. If equivalence cannot be established, additional data and information may be needed to re-evaluate the risk profile of the product.
b) MPI will assess this change, and likely apply a condition to the registration approval to require additional information at a later date.
c) The product must not be manufactured if there is no approved manufacturer for a particular ingredient or testing activity.

(2) Provide:

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

7.2.3 Change in name only of a sterile active ingredient manufacturer

(1) Submit a variation application to change the name/address of a sterile active ingredient manufacturing site.

(2) Provide:

Declaration of new name and/or address with updated GMP certificate
Amended Product Data Sheet and label

7.2.4 Change in name only of a non-sterile active ingredient manufacturer

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

(2) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.2.5 Removing an active ingredient manufacturer /active ingredient testing site (if two or more sites are approved)

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

Note: The sole primary manufacturer and/or QC testing site cannot be removed as a self-assessable change. If the sole manufacturer or testing site is removed, a variation application for a change to the approved manufacturers must be submitted.

(2) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.3 Changes to approved active ingredients and functional active ingredients

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

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

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

(2) Provide:

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

7.3.2 Narrowing only of active ingredient specification parameters within the currently approved range

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

(2) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.3.3 Adding, deleting, changing a pharmacopoeial standard

This section applies to the addition of, deletion of, or change to an approved BP, EP (Eur Ph), USP or JP monograph as stated in the active ingredient specification and/or formulation table in the Product Data Sheet.

Note:

a) *There is no need to advise of a monograph update for BP, EP, USP, or JP in the case that reference is made to the 'current edition' in the dossier and Product Data Sheet.*
b) *A self-assessable change can only be progressed if the active ingredient conforms to a pharmacopoeial monograph in its entirety. An active ingredient that conforms to specification comprised of a combination of parameters from multiple monographs is to be treated like a manufacturer's specification.*

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

(2) To be considered a self-assessable change, the chemical identity and characteristics of the active ingredient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

(3) A specification must always apply to the active ingredient. If proposing to delete a MPI-recognised pharmacopoeial standard, at least one other pharmacopoeial monograph or a manufacturer's specification must remain applicable to the ingredient.

(4) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.3.4 Change in name of the active ingredient(s)

(1) Submit a C9 variation. The chemical identity, characteristics, and risk profile of the active ingredient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

Note: a change in name of the active ingredient cannot be considered a self-assessable change due to the need to update and amend the product label and the potential impacts on providing sufficient consumer information.

(2) Provide:

Relevant application forms
Amended Product Data Sheet and label
Proof of acceptance by WHO or a copy of the INN list

7.4 Changes to approved excipient ingredients

7.4.1 Adding or removing a critical excipient

(1) Submit a variation application for changes to formulation involving the addition, removal, or change in quantity of a critical excipient.

(2) Provide:

Amended Product Data Sheet and label
Technical rationale for the change, including the impact on the bioavailability of the active ingredient(s) and/or function of the product leading to the classification of the ingredient as a critical excipient
Batch analysis data on minimum of one batch of ingredient. The data should include: • batch identification, date of manufacture and date of analysis • site of manufacture (if not tested by the actual site, then evidence of origin from the site is required) • results of all analytical determinations. For quantitative tests (e.g. ingredient concentration) provide the actual numerical results. Vague statements such as “within limits” or “conforms” is not considered acceptable
Copy of the monograph to which the ingredient complies
Discussion on any other areas affected by the proposed change: efficacy, target animal safety, and residue profile of the TNP, as applicable
Stability data to support the proposed change if the quality or stability of the product is impacted, or a technical discussion of why these aspects of the product would not be impacted

7.4.2 Adding or removing a non-critical excipient

(1) Submit a variation application for changes to formulation involving the addition, removal, or change in quantity of a non-critical excipient.

(2) Provide:

Amended Product Data Sheet and label
Technical rationale for the change, including the impact on the quality or stability of the reformulated product relative to the approved shelf life
Batch analysis data on minimum of one batch of ingredient. The data should include: • batch identification, date of manufacture and date of analysis • site of manufacture (if not tested by the actual site, then evidence of origin from the site is required) • results confirming conformance to the nominated specification. Ensure the actual numerical results for quantitative tests are reported. Vague statements such as “within limits” or “conforms” is not considered acceptable
Copy of the monograph to which the ingredient complies

7.4.3 Adding, deleting, or changing a MPI -recognised pharmacopoeial standard for a critical excipient

This section applies to the addition of, deletion of, or change to a MPI-recognised pharmacopoeial standard (i.e. BP, EP (Eur Ph), USP, and JP) for a critical excipient as stated in the formulation table in the Product Data Sheet.

Note:

a) *There is no need to advise of a monograph update for BP, EP, USP, or JP in the case that reference is made to the 'current edition' in the dossier and Product Data Sheet.*
b) *A self-assessable change can only be progressed if the ingredient conforms to a pharmacopoeial monograph in its entirety. An ingredient that conforms to a specification comprised of a combination of parameters from multiple monographs is to be treated like a manufacturer's specification.*

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

(2) To be considered a self-assessable change, the chemical identity, characteristics, risk profile, and function of the excipient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

(3) A specification must always apply to the excipient. If proposing to delete a MPI-recognised pharmacopoeial standard, at least one other pharmacopoeial monograph or a manufacturer's specification must remain applicable to the ingredient.

(4) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.4.4 Adding, deleting, or changing a manufacturer's specification for a critical excipient

(1) Submit a variation application for changes to the excipient ingredient(s) specification(s) when a manufacturer's specification applies. This includes changes to the parameters, acceptance criteria and analytical test methods for critical excipients.

(2) A specification must always apply to the excipient. If proposing to delete a manufacturer's specification, at least one other pharmacopoeial monograph or a manufacturer's specification must remain applicable to the ingredient.

(3) Provide:

Amended Product Data Sheet and label
Technical rationale for the change
Table of the current and proposed specification tables, with differences highlighted
Batch analysis data on minimum of one batch of critical excipient. The data should include: • batch identification date of manufacture and date of analysis • site of manufacture (if not tested by the actual site, then evidence of origin from the site is required) • results of all analytical determinations. For quantitative tests (e.g. ingredient concentration) provide the actual numerical results. Vague statements such as "within limits" or "conforms" is not considered acceptable
Details of any new analytical test methods and validation, if applicable
Discussion on any areas affected by the proposed change: i.e. quality, stability, residues, target animal safety and efficacy of the TNP
Stability data to support critical excipient specification changes that impact on the stability of the product

7.4.5 Adding, deleting, or changing a specification for a non-critical excipient

This section applies to the addition of, deletion of, or change to either a MPI-recognised pharmacopoeial standard or a manufacturer's specification for a non-critical excipient as stated in the formulation table in the Product Data Sheet.

Note: There is no need to advise of a monograph update for BP, EP, USP, or JP in the case that reference is made to the 'current edition' in the dossier and Product Data Sheet.

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

(2) To be considered a self-assessable change, the chemical identity, characteristics, risk profile, and function of the excipient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

(3) A specification must always apply to the excipient. If proposing to delete a specification, at least one other pharmacopoeial monograph or a manufacturer's specification must remain applicable to the ingredient.

(4) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.4.6 Change in name of an excipient(s)

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

(2) To be considered a self-assessable change, the chemical identity, characteristics, and function of the excipient must remain the same, and there must be no other change to the information previously supplied for that ingredient.

(3) To update the product registration following a self-assessable change at the next variation or renewal, provide:

Details of the change made, and declaration that the change has been self-assessed to have no significant impact on the risk profile of the product, in a covering letter or email
Amended Product Data Sheet and label
Evidence of name change (e.g. CoA, letter from the manufacturer, evidence the new name being a recognised CAS synonym)

7.5 Changes to approved formulated product manufacturers

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

7.5.1 Additional manufacturers of the formulated product

(1) Submit a variation application to add an additional manufacturing site, or to replace a currently approved manufacturing site with another; or to transfer a specific activity (e.g. sterility testing) from one site to another.

(2) Provide:

Amended Product Data Sheet and label
Details of the proposed manufacturing site(s): • name of organisation • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
GMP certificate Provide evidence of current GMP approval for the proposed formulated product manufacturing site(s) for scope of the manufacturing process for which they are responsible. If there is a current MPI-issued GMP approval for the proposed site(s) and the approved manufacturing categories are applicable, there is no need to provide a GMP certificate - just refer to that approval Manufacturer approval is site-specific, and must be granted for all individual sites involved in the manufacturing process. If a manufacturer is currently approved to manufacture a trade name product and the manufacturer changes sites, a variation application with a current GMP approval for the new site must be submitted and approved before the new site can commence manufacture
Step(s) of the manufacturing process conducted at each site, as described in 6.5.1 above. If one manufacturer manages the entire process from procurement of raw materials to filling of the market packaging, it is appropriate to state “all steps”
Data to demonstrate the proposed manufacturing site(s) will manufacture the product equivalent to that currently approved. This data must include: • Evidence of completed manufacturing process validation as per section 6.5.6 confirming that manufacturing process at the proposed site(s) will be capable of producing the trade name product consistently and to the specifications approved for the product. If validation has not yet been completed, a validation protocol may be accepted with a conditional requirement that evidence of process validation will be provided post-approval • If any portion of the manufacturing process at the new site differs from that currently approved for the product, outline and explain the differences
Batch analysis data from three (minimum at least pilot) scale batches of TNP from the proposed manufacturer. (Refer to 6.7). The results should include: • date of manufacture • date of testing • batch size • site of manufacture • evidence that the batches conformed to approved release specification, using the specified and validated methods performed by the approved testing laboratory If batch analyses are not available when the application is submitted, approval of the new manufacturer may be made based on an assessment of the validation protocol, manufacturing process and equipment information, and specifications applied to the formulated product. Post-approval submission of batch analyses, evidence confirming process validation, and any related information relevant to the approval may be required as a condition of registration
If it is determined that the risk profile of the product, including stability, may be significantly altered by the differences in manufacturing at the new or additional site, stability data and/or data directly addressing one of the other risk areas may be required

7.5.2 Addition of or changes to secondary packaging and relabelling manufacturers

(1) Submit a variation application to add an additional secondary packaging and relabelling site, or to replace a currently approved secondary packaging and relabelling site with another.

(2) Provide:

Amended Product Data Sheet and label
Details of the proposed repacker/relabelling site(s): • name of organisation • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
GMP certificate Provide evidence of current GMP approval for scope of the manufacturing process for which they are responsible. If there is a current MPI-issued GMP approval for the proposed site(s) and the approved manufacturing categories are applicable, there is no need to provide a GMP certificate, just refer to that approval Manufacturer approval is site-specific, and must be granted for all individual sites involved in the manufacturing process. If a manufacturer is currently approved to repack/relabel a trade name product and the manufacturer changes sites, a variation application with a current GMP approval for the new site must be submitted and approved before the new site can commence repacking/relabelling

7.5.3 Addition of or changes to QC testing sites

(1) Submit a variation application to add an additional QC testing site, or to replace a currently approved QC testing site with another.

(2) Provide:

Amended Product Data Sheet and label
Details of the proposed QC testing site(s): • name of organisation • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
GMP certificate, evidence of ISO accreditation, or equivalent Provide evidence of current GMP approval/ISO accreditation or equivalent for the quality tests for which they are responsible. If there is a current MPI-issued GMP approval for the proposed site(s) and the approved manufacturing categories are applicable, there is no need to provide a GMP certificate, just refer to that approval Manufacturer approval is site-specific, and must be granted for all individual sites involved in the manufacturing process. If a testing site is currently approved to conduct QC tests and the company changes sites, a variation application with a current GMP approval for the new site must be submitted and approved before the new site can commence testing
Provide data and/or other information to confirm that the proposed QC testing site will perform the testing as per validated procedures, and that are identical or equivalent to those used by the currently approved testing site

Provide evidence of the method validation or method transfer validation, as applicable. If evidence of method validation is not available at the time the application is submitted, approval of the testing site can still be considered. Evidence of method validation would be required as a condition of registration post-approval

7.5.4 Change in details for an approved formulated product manufacturer or manufacturing site

(1) Submit a variation application to change the name and/or address of an existing manufacturer or manufacturing site, including details for formulated product manufacturers, repacker/relabellers, QC laboratories, and testing sites.

(2) Provide:

Amended Product Data Sheet and label
Details of the manufacturing site(s), outlining what has changed in the details previously listed in the product data sheet
GMP certificate Provide evidence of current GMP approval for the manufacturer or manufacturing site, confirming that site approval has been granted under the new name/details. If there is a current MPI-issued GMP approval for the proposed site(s) with the updated name/details and the approved manufacturing categories are applicable, there is no need to provide a GMP certificate - just refer to that approval Approval is manufacturer- and site-specific, and must be granted for all individual sites involved in the manufacturing process under the correct details. If the details of a particular manufacturer or manufacturing site changes, a variation application with a current GMP approval for the new site must be submitted and approved before the new site can commence manufacture
Confirm the step(s) of the manufacturing process conducted at each site, as described in 6.5.1 above If one manufacturer manages the entire process from procurement of raw materials to filling of the market packaging, it is appropriate to state “all steps”
If only the name of the manufacturer is changing, provide: • confirmation of GMP approval under the new name as above • a declaration that all other processes, equipment, and procedures remain as previously assessed for the manufacture of the product If the site address is changing, provide: • confirmation of GMP approval for the new site • evidence of completed manufacturing process validation as per section 6.5.6, confirming that manufacturing process at the new site will be capable of producing the trade name product consistently and to the specifications approved for the product. If validation has not yet been completed, a validation protocol may be accepted with a conditional requirement that evidence of process validation will be provided post-approval • if any portion of the manufacturing process at the new site differs from that currently approved for the product, outline and explain the differences
Batch analysis data from three (minimum at least pilot) scale batches of TNP from the proposed manufacturer. (Refer to 6.7). The results should include: • date of manufacture • date of testing • batch size

• site of manufacture • evidence that the batches conformed to approved release specification, using the specified and validated methods performed by the approved testing laboratory If batch analyses are not available when the application is submitted, approval of the new manufacturer may be made based on an assessment of the validation protocol, manufacturing process and equipment information, and specifications applied to the formulated product. Post-approval submission of batch analyses, evidence confirming process validation, and any related information relevant to the approval may be required as a condition of registration
If it is determined that the risk profile of the product, including stability, may be significantly altered by the differences in manufacturing at the new or additional site, stability data and/or data directly addressing one of the other risk areas may be required

7.5.5 Removal of a formulated product manufacturer, repacker/ relabeller, or QC testing site (if two or more of that type of site are approved)

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

Note: The sole primary manufacturer and/or QC testing site cannot be removed as a self-assessable change. If the sole manufacturer or testing site is removed, a variation application for a change to the approved manufacturers must be submitted.

(2) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.6 Changes to manufacturing process

7.6.1 Change to manufacturing process

(1) Submit a variation application if it is proposed to change the details of the currently approved manufacturing process. This includes changes to any point of the manufacturing process itself, in-process critical control points and/or analytical methods, equipment used, sterilisation processes, increase or decrease in batch size or range and any details in the process and control procedures that may impact the risk profile or quality of the product.

The data requirements will be dependent on the significance of the change and its impact on the product.

(2) If the change will have a minimal impact on the ability of the process and controls to ensure the process is able to meet minimum quality and consistency requirements for the product, provide a technical discussion of the change relative to the risk profile of the product, supported by evidence to confirm the justification. This evidence may be comparative or product-specific results from the affected method or assay, batch analysis results, validation reports or other quantitative evidence as relevant and appropriate to the change.

(3) If the change could have an impact on the ability of the process to result in a product that meets minimum quality and consistency requirements, provide evidence of manufacturing process validation.

(4) If manufacturing process validation has not been completed for the product at the time the variation application is made, approval of the variation based on the provision of a validation protocol can be

considered. A validation protocol must be supplied from each site at which the change is being implemented.

Information expected in a manufacturing process validation protocol and subsequent report can be found in section 6.5.6.

(5) If the change involves changes to the test methods or analysis of a product, provide evidence of method validation to support the proposed change.

(6) Examples of manufacturing process/quality control testing changes where MPI would expect a variation application to be made are:

a) technical changes to the details of the currently approved manufacturing process and/or QC procedures
b) change in manufacturing parameters or critical control point
c) change in formulation impacting manufacturing process
d) change in sterilisation method for a sterile product
e) introduction or increase in the overage that is used for the active ingredients(s)
f) increase or decrease in batch size and/or batch size range
g) addition of new in-process tests or limits
h) addition, replacement or deletion of an in-process test
i) widening of in-process test limits.

(7) Provide:

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

7.6.2 Tightening of batch size ranges

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

(2) To be considered self-assessable, the change must be limited to a tightening of the currently approved range (i.e. within the limits of the currently approved lower and upper bounds) at the currently approved site in the same equipment previously confirmed to have been used in process validation.

(3) To update the product registration following a self-assessable change at the next variation or renewal, provide:

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

7.7 Changes to finished product specification or test methods

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

(5) Provide:

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

7.8 Changes to product packaging

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

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

(1) Provide:

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

7.8.2 Change in pack size

(1) Provide:

Amended Product Data Sheet and amended label(s) with changes in place relevant to the new pack size(s)
Packaging specification data on the new pack size(s)
Data and justification appropriate for the product type and its practical use in the market relative to the risk profile of the product. For example: • For the introduction of a 50L drum pack size for a suspension product when the currently approved largest pack size is 20L, provide data to demonstrate that the product will remain stable in the nominated pack size with respect to storage stability, phase stability, and use as a multi-dose package • For the introduction of a 50mL vial pack size for a solution product when the currently approved smallest pack size is 1L, include full stability data because the 50mL size now becomes the worst case scenario for product stability. Introduction of a 5L pack size for the same product may only

require justification and discussion to establish how and why the 1L stability data is sufficient evidence to support the 5L pack size • For all suspension formulations, provide evidence to support that any proposed label statements for the management of the new pack size (e.g. shaking, reconstitution, special storage information, or any other product-specific or pack size-specific instructions) will be sufficient to manage the stability of the product and any associated risks.
Technical rationale explaining the reason for the change(s) and the expected impact(s) the change(s) will have on the quality and stability profile of the product. Relate these impacts to any potential impacts on the efficacy, safety and residue risk profile of the product
Stability data to demonstrate that the product will remain equivalently stable throughout the approved shelf life, if any packaging materials or closures differ from those approved for the pack size range, even if the volume of the proposed packaging falls within the approved range
In-use stability data if the proposed change introduces a multi-use package when one did not previously have approval, or if the new multi-use pack size presents a different efficacy, safety, residues, or stability risk profile than that previously assessed

7.8.3 Addition of a new pack size within currently approved size range and packaging material(s), or marketing of a new pack size within the currently approve size range

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

(2) To be considered self-assessable:

a) the new pack size must be packaged in the same packaging materials and closure system as approved for the pack size range; and

b) the product must have a pack size range approved, and the new pack size to be manufactured or marketed must be within the bounds of that range. For example, if a product is approved for packaging in a 10L container only and the registrant wishes to add a 5L pack size, this cannot be considered self-assessable as there is no range approved. However, if 1L and 10L pack sizes are approved, the addition of a 5L can be considered self-assessable provided the requirements in a) are met.

(3) To update the product registration following a self-assessable change at the next variation or renewal, provide:

Details of the change made, and declaration that the change has been self-assessed to have no significant impact on the risk profile of the product, in a covering letter or email
Amended Product Data Sheet and amended label(s) with changes in place relevant to the new pack size(s).

7.8.4 Change in secondary packaging

(1) Provide:

Amended Product Data Sheet and label
Details of the change including packaging specification information as applicable
• If the secondary packaging **serves to protect or preserve product quality** (e.g. photosensitive product), provide a technical rationale explaining the reason for the change(s) and the expected impact(s) the change(s) will have on the quality and stability profile of the product (e.g. such as photosensitivity, temperature sensitivity, and any other relevant parameters). Relate these impacts to any potential impacts on the efficacy, safety and residue risk profile of the product. Provide stability data and information to support the change if appropriate

• If the secondary packaging **does not have a direct impact on product preservation or quality**, provide a summary of the change proposed with a declaration that the change will have no significant impact on the risk profile of the product

7.9 Changes to formulated product shelf life and storage conditions

Refer to VICH Guidelines (as appropriate):

GL3(R): Stability: stability testing of new veterinary drug substances (revision)

GL4: Stability testing for new dosage forms

GL5 (Stability 3): Stability testing: photostability testing of new veterinary drug substances and medicinal products

GL8: Stability testing for medicated premixes

GL45: Quality: bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products

GL51: Statistical evaluation of stability data

(1) Conduct the stability study in accordance with the stability protocol used to produce data to support the initial shelf life approved at registration. If there are any variations between the original protocol and that used for the shelf life extension data, discuss and technically explain each variation.

(2) Conduct testing using appropriately validated analytical methods, and include all testing parameters in the approved product specifications.

7.9.1 Extension of the currently approved shelf life

(1) Submit a variation application for any proposed extension of the product's shelf life and/or in-use shelf life.

(2) Provide:

Amended Product Data Sheet and label
Stability data from real time and/or accelerated stability studies conducted as per section 6.8..

7.9.2 Change in the storage conditions for the product

(1) Submit a variation application for any proposed change in storage conditions.

(2) Provide:

The reason for the change to the storage conditions
Stability data to support the new storage conditions as per section 6.8 of this guidance
Amended Product Data Sheet and label

7.9.3 Shortening of the currently approved shelf life

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

(2) To update the product registration following a self-assessable change at the next variation or renewal, provide:

Amended Product Data Sheet

Justify the change in shelf life with an explanation for the change, including whether the change is due to a change to another aspect of the product such as post-registration monitoring, or to address a product non-conformance
Stability data may be required to support and justify the proposed shelf life if it is determined that there is significant risk associated with the reason for the change

Appendix 1: Product Types

Anaesthetic	A substance administered to bring about partial or complete loss of sensation.
Analgesic	A substance administered to relieve the sensation of pain.
Antibiotic	A naturally occurring, semi-synthetic, or synthetic antimicrobial substance that kills or inhibits the growth of bacteria to prevent or treat bacterial infections in an animal or plant.
Anticonvulsant agent	A substance that inhibits convulsions by depressing the central nervous system. This can include specific motor depressants, narcotics, and sedatives.
Antidote	A substance that counteracts the effect of a poisonous substance or drug. These can be chemical, physiological, mechanical, or universal agents, and include anti-toxins, anti-sera, and reversal agents.
Antiemetic	A substance that treats or prevents nausea and vomiting.
Antifungal	A substance that has the capacity to kill or suppress the growth and reproduction of fungi.
Antimicrobial	A naturally occurring or semi-synthetic substance which may be derived from a microorganism, or synthetic substance, that kills or inhibits the growth of microorganisms in or on the treated animal or plant. Substances classed as disinfectants, and substances that kill macro-organisms such as anthelmintics and nematocides, are excluded from this definition.
Antineoplastic agent	A substance which prevents, inhibits, or halts the development of a neoplasm (tumour).
Anti-inflammatory	A substance administered to reduce the inflammatory response to infection, trauma, surgery, or musculoskeletal disease.
Antiprotozoal	An antimicrobial substance that kills or inhibits the growth of protozoa to prevent or treat protozoal infections in an animal or plant.
Antiseptic	An antimicrobial substance that is applied externally to living tissue to inhibit the growth of or kill microorganisms and prevent infection.
Antiviral	A substance that eliminates the presence of or inhibits the replication of viruses, to prevent or treat viral infections in an animal.
Behaviour modifier	A substance administered to alter or regulate behavioural patterns. This group includes psychotropic and tricyclic medicines.
Bloat remedy	A substance administered to prevent or alleviate tympany of the rumen, abomasum, stomach, or caecum.
Cardiovascular agent	A substance administered to alter or enhance the activity of the cardiovascular system. This group includes inotropes, vasodilators, and angiotensin converting enzyme (ACE) inhibitors.
CNS stimulant	A substance which acts to increase activity in the brain.
Coccidiostat	A substance administered to inhibit the growth and reproduction of coccidian parasites.
Diagnostic antigens	A substance comprised of a single type or mixture of antigens intended for administration to an animal to diagnose allergy.
Ectoparasiticide	A substance administered to kill or inhibit the growth and reproduction of external parasites.
Endocrine agent (hormone)	A naturally-derived or synthetic analogue of a hormone administered to alter or enhance the function of the body system managed or affected by that hormone.
Endocrine agent (non-hormone)	A substance administered to treat dysfunction caused by altered function of the endocrine system. This group includes substances such as methimazole, trilostane, and pergolide mesylate.

Endoparasiticide	A substance administered to kill or inhibit the growth and reproduction of internal, usually gastrointestinal, parasites.
Euthanasia agent	A substance administered to cause a humane death by cessation of cardiac and central nervous system activity.
Gastrointestinal tract modifier	A substance administered to alter or enhance the activity of the gastrointestinal tract, usually by altering the motility or secretions of the system. This group includes therapeutic probiotics.
Growth promotant	A substance other than hormones administered to influence protein, carbohydrate and lipid metabolism to alter or enhance the rate of skeletal and visceral growth.
Hormonal growth promotant (HGP)	A hormone administered to influence protein, carbohydrate and lipid metabolism to alter or enhance the rate of skeletal and visceral growth.
Immune stimulant	A substance administered to enhance or increase an immunological response.
Immunomodulator	A substance administered to alter or enhance the function of the immune system or an immune response.
Ketosis remedy	A substance administered to treat or prevent the metabolic disorder and subsequent illness associated with abnormal fat metabolism.
Musculoskeletal modifier	A substance administered to influence the activity of the musculoskeletal system, including polysulphated aminoglycans.
Obstetric aid	A substance intended to be used during birth or the processes associated with it (such as sterile lubricant intended for use in a cervical examination).
Oral nutritional compound	A substance ingested by an animal as feed, or a nutritional preparation intended for oral administration to an animal to achieve a nutritional benefit. Oral nutritional compounds require registration when their ingestion results in a therapeutic benefit to the animal instead of or in addition to the nutritional benefit.
Parenteral nutrient/Electrolyte	A substance containing ions which are essential to the normal function of cells, or that provides nourishment from minerals, vitamins, fats, protein, carbohydrates and alter administered in an injectable formulation. Parenteral nutrients and electrolytes require registration when they are intended for administration to companion animals and/or are administered to achieve a therapeutic effect.
Renal and urinary tract modifier	A substance administered to alter or enhance the function of the kidneys or urinary tract. This group includes urinary pH modifiers.
Respiratory tract modifier	A substance administered to alter or enhance the function of the respiratory tract (includes bronchodilators, antitussives).
Sedative	A substance administered to depress the activity of the central nervous system to calm nervousness, irritability and excitement This group includes pre-anaesthetic agents.
Skin/Coat conditioner	A substance administered to improve or enhance condition of the skin and coat. Skin and/or coat conditioners require registration when they are intended to achieve a therapeutic effect (such as in the management of severe eczema) or are intended for use on the teats of lactating animals.
Teat Sealant	A substance administered to the teats of dairy animals at the end of lactation to prevent mastitis during the dry period by creating a physical barrier against bacterial entry. In New Zealand, these are usually internal teat sealants in the form of cerates injected into the teat canal to form a plug-like barrier.

Vaccine	A suspension of attenuated live or killed micro-organisms (bacteria, viruses, or rickettsiae) administered for prevention, amelioration or treatment of infectious diseases.
Other	Specify in the product data sheet.

Appendix 2: Formulation Types

Aerosol	A pressurised dose form where fine solid or liquid pharmaceutical preparations are released upon activation as a plume of fine particles or droplets.
Aqueous solution	A formulation of particles dissolved in water.
Aqueous suspension	A formulation of particles suspended in water.
Block	A prepared mixture of salt and minerals formed into blocks for oral consumption by groups of animals as a feed supplement.
Bolus	A rounded concentrated mass of pharmaceutical or nutritional preparation ready to be swallowed, usually formulated to be dissolved over time.
Capsule	A soluble structure containing a single dose of a pharmaceutical preparation.
Cerate	A pharmaceutical preparation of wax-like consistency, usually for intramammary use.
Cream	An oil-in-water emulsion, generally used topically.
Gel	A semi-solid material in which there is a physical or covalent interaction between colloidal particles within a liquid vehicle.
Granule	Solid formulation comprised of smaller powder particles processed to adhere into larger multi-particle entities. Granules are usually administered without further dilution.
Impregnated material	Any solid pharmaceutical preparation inserted into intact tissues or body cavity, or attached to an animal externally, which releases a pharmaceutical preparation over time.
Meal	A solid / semi-solid fine particulate material derived from animal or plant material.
Non-aqueous solution	A formulation of particles dissolved in a solvent other than water.
Non-aqueous suspension	A formulation of particles suspended in a solvent other than water.
Oily solution	A formulation of particles dissolved in oil.
Oily suspension	A formulation of particles suspended in oil.
Ointment	A semi-solid pharmaceutical preparation for external application to the skin or mucous membranes.
Paste	A highly viscous, semi-solid pharmaceutical preparation containing a high percentage of finely dispersed solids.
Powder	A solid dose form comprised of a large number of finely divided particles.
Syrup	A viscous liquid dose form where the vehicle for the pharmaceutical preparation is a concentrated sugar-based solution.
Tablet/Pellet	A solid unit dose form containing a pharmaceutical preparation, usually a powder, prepared by either moulding or compression.
Vapour releasing product	A formulated product containing one or more volatile ingredients, the vapours of which are released into the air. Evaporation is usually controlled by the formulation components and/or dispensing systems.
Other	Specify in the product data sheet.

Appendix 3: Expected Release and Shelf Life Specifications by Product and Formulation Type

These are the expected specifications for each product type, but this list is not exhaustive. There may be some additional parameters necessary for individual products within each product type, and some parameters may not be applicable to all individual products.

Product Type	Parameter for Release	Parameter for Product Expiry
Aerosols (pressurised pharmaceutical preparations)	Description	Description
	Identification (when appropriate)	Identification (when appropriate)
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Preservative content (when appropriate)	Preservative content (when appropriate)
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Delivered dose or dose per actuation	Delivered dose or dose per actuation
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Number of metered doses	Number of metered doses
	Loss in weight	Loss in weight
	Leakage	Leakage
	Pressure test	Pressure test
	Valve corrosion	Valve corrosion
Capsules	Description	Description
	Identification (when appropriate)	Identification (when appropriate)
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, physical dimensions)
	Degradation products	Degradation products
	Moisture content	Moisture content
	Mass variation	Mass variation
	Average weight	Average weight
	Capsule integrity (leakage for soft gelatin capsules, brittleness for hard gelatin capsules)	Optional with justification
	Disintegration time	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
	Dissolution profile (when appropriate)	Optional with justification
Collars	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, physical dimensions)
	Degradation products	Degradation products
	Uniformity of content / mass Dissolution profile (release of active constituent from the inert matrix)	Optional with justification
Controlled release devices	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	Type of or materials of construction	Optional with justification
	Shape and dimensions of device	Optional with justification
	Dose delivery specifications (e.g. dissolution)	Dose delivery specifications (e.g. dissolution)
	Microbial limits	Microbial limits
Dipping / jetting formulations	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity)	Physicochemical (e.g. colour, appearance, odour, specific gravity)
	Degradation products	Degradation products
	Water dispersibility	Optional with justification
	Suspendability	Optional with justification
	Wet sieve (suspensions)	Optional with justification
	Persistent foam	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
Emulsions	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity)	Physicochemical (e.g. colour, appearance, odour, specific gravity)
	Degradation products	Degradation products
	Homogeneity (extent of separation, ease of reconstitution)	Optional with justification
	Preservative content (when appropriate)	Preservative content (when appropriate)
	pH	Optional with justification
	Viscosity	Optional with justification
	Effect of freezing	Optional with justification
Granules	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, physical dimensions)
	Degradation products	Degradation products
	Particle size distribution / dustiness	Optional with justification
	Moisture content	Optional with justification
	Dissolution profile (when appropriate)	Optional with justification
Implants (subcutaneous, intravaginal)	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of content/mass	Optional with justification
	Hardness	Optional with justification
	Friability	Optional with justification
	Moisture content (when appropriate)	Optional with justification
	Dissolution profile (release of the active constituent	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
Intramammary medicines (including teat sealants)	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	pH	pH
	Sterility	Sterility
	Endotoxins/Pyrogens	Endotoxins/Pyrogens
	Water content (non-aqueous products)	Water content (non-aqueous products)
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Functional testing of delivery systems	Optional with justification
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Rheological properties e.g. viscosity (viscous solutions/suspensions)	Rheological properties e.g. viscosity (viscous solutions/suspensions)
	Syringeability (when appropriate)	Optional with justification
	Effects of freezing	Optional with justification
Medicated shampoos	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Viscosity (when appropriate)	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
Oral liquid medicines	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity)	Physicochemical (e.g. colour, appearance, odour, specific gravity)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	pH	pH
	Microbial limits	Microbial limits
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Extractables (re container/closure systems)	Optional with justification
	Dissolution (resuspended products)	Dissolution (resuspended products)
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Redispersibility (suspensions)	Redispersibility (suspensions)
	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)
	Reconstitution time	Reconstitution time
	Water content (for reconstituted products)	Water content (for reconstituted products)

Product Type	Parameter for Release	Parameter for Product Expiry
Parenteral medicines (injectables)	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of dosage units (powders for reconstitution)	Optional with justification
	pH	pH
	Sterility	Sterility
	Endotoxins/Pyrogens	Endotoxins/Pyrogens
	Particulate matter	Particulate matter
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Water content (non-aqueous products/products for reconstitution)	Water content (non-aqueous products/products for reconstitution)
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Extractables (re container/closure systems)	Optional with justification
	Functional testing of delivery systems	Optional with justification
	Osmolarity	Optional with justification
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Resuspensibility (when appropriate)	Resuspensibility (when appropriate)
	Redispersibility	Redispersibility
	Reconstitution time	Reconstitution time
	Related substances (antibiotics)	Related substances (antibiotics)
	Syringeability	Optional with justification
	Effects of freezing	Optional with justification
	Interactions with closure (some containers in the inverted position)	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
Pour-on medicines	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity)	Physicochemical (e.g. colour, appearance, odour, specific gravity)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	pH	pH
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Redispersibility (suspensions)	Redispersibility (suspensions)
	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)
Powders	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Moisture content (when appropriate)	Moisture content (when appropriate)
Powders for injection	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Moisture content (when appropriate)	Moisture content (when appropriate)
	pH value for reconstituted solution	pH value for reconstituted solution
	Completeness of solution or dispersion	Completeness of solution or dispersion

Product Type	Parameter for Release	Parameter for Product Expiry
Products delivered via drinking water	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	pH	pH
	Microbial limits	Microbial limits
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Dissolution (resuspended products)	Dissolution (resuspended products)
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Redispersibility (suspensions)	Redispersibility (suspensions)
	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)
	Reconstitution time	Reconstitution time
	Water content (for reconstituted products)	Water content (for reconstituted products)
Premixes and medicated feeds	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	Water (moisture) content	Water (moisture) content
	Microbial limits	Microbial limits
	Particle size and distribution	Particle size and distribution
	Antimicrobial preservative content (when applicable)	Antimicrobial preservative content (when applicable)
	Antioxidant preservative content (when applicable)	Antioxidant preservative content (when applicable)

Product Type	Parameter for Release	Parameter for Product Expiry
Solid oral medicines (tablets)	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, physical dimensions)
	Degradation products	Degradation products
	Dissolution	Optional with justification
	Disintegration	Optional with justification
	Hardness/Friability	Optional with justification
	Uniformity of dosage units	Optional for non-scored tablets with justification
	Uniformity of dosage units	Required for scored tablets
	Water content	Water content
	Microbial limits	Microbial limits
Solutions	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity)	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity)
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Degradation products	Degradation products
	Sterility (when appropriate)	Sterility (when appropriate)
	pH	pH
	Preservative efficacy (when appropriate)	Preservative efficacy (when appropriate)
	Viscosity (when appropriate)	Viscosity (when appropriate)
	Effects of freezing	Effects of freezing
Suppositories	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Softening range	Optional with justification
	Dissolution	Optional with justification

Product Type	Parameter for Release	Parameter for Product Expiry
Suspensions	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity)	Physicochemical (e.g. colour, appearance, odour, specific gravity)
	Degradation products	Degradation products
	Sterility (when appropriate)	Sterility (when appropriate)
	pH	pH
	Resuspensibility	Resuspensibility
	Viscosity (when appropriate)	Viscosity (when appropriate)
	Particle size (when appropriate)	Particle size (when appropriate)
	Effects of freezing	Effects of freezing
Topical, oral and ophthalmic powders, ointments, creams, lotions, gels, and pastes	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Uniformity of dosage units	Optional with justification
	pH	pH
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Sterility (for eye preparations)	Sterility (for eye preparations)
	Antimicrobial preservative content	Antimicrobial preservative content
	Antioxidant preservative content	Antioxidant preservative content
	Particle size distribution (suspensions)	Particle size distribution (suspensions)
	Resuspendibility (suspensions, especially lotions)	Resuspendibility (suspensions, especially lotions)
	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)	Rheological properties e.g. viscosity/specific gravity (viscous solutions/suspensions)

Appendix 4: Checklist for New Product Submissions

6.1	**Product details**	
	Product type	
	Formulation type	
	Pharmaceutical development summary	
6.2	**Formulation of the TNP**	
	Formulation table (incl. stability overages and potency calculations)	
6.3	**Active ingredient(s)**	
	Identity	
	Specification and impurities	
	Batch analyses x3	
	Analytical test methods and validation data	
	Active ingredient manufacturer(s) identity and details	
	GMP for sterile active manufacturers	
6.4	**Excipient Ingredients**	
	Identity	
	Standard	
	Batch analysis x 1	
	Impurities (if applicable)	
	Ingredients of biological origin has current Biosecurity approval/ conform to IHS	
6.5	**Formulated product manufacturing**	
	Manufacturer identity, details, activities and GMP scope	
	Manufacturing process	
	Batch formulation table (incl. manufacturing overages and potency calculations)	
	In-process quality control testing	
	Manufacturing process validation – preferably report, at minimum protocol	
6.6	**Formulated product quality control**	
	Specification rationales	
	Release specification	
	Shelf life specification	
	Formulated product quality control testing information	
	Formulated product batch analyses x3	
6.7	**Product Packaging**	
	Primary container and closure system	
	Secondary packaging	
	Product specific administration device/attachment specifications	
	Recycled packaging (when applicable)	
6.8	**Shelf Life Stability**	
	Proposed shelf life	
	Proposed storage conditions	
	Specification parameters	
	Testing storage conditions	
	Testing frequency/ time points	
	Analytical test methods and validation	
	Discussion of stability study results	
	Stability commitment	
6.9	**In Use Stability**	
	Multi-dose products	
	In Feed and/or In Water products	

Appendix 5: Acceptable Evidence of GMP Compliance for Formulated Product Manufacturers

As discussed in section 6.5.1, formulated product manufacturers must operate in compliance with current Good Manufacturing Practice (GMP). New Zealand manufacturers included in MPI's GMP Programme do not need to provide evidence of GMP compliance as part of an application. If a New Zealand manufacturer is not included in MPI's GMP Programme, they must first apply to be considered and need to be verified as compliant before they are added as a manufacturer of a registered product. More information on the application process can be found on the Manufacturing Veterinary Medicines under the ACVM Act 1997 page of MPI's website.

Evidence must be provided from a recognised overseas competent authority to confirm current GMP compliance before an international manufacturer will be authorised to manufacture a New Zealand registered veterinary medicine. Because the GMP programmes administered by overseas authorities may differ from the programme administered in New Zealand, the information required to provide assurance of GMP compliance can vary. If appropriate evidence from a recognised overseas authority cannot be provided, an audit by a MPI auditor may be required to confirm GMP compliance.

All documents submitted to MPI as evidence of GMP compliance must be in English.

MPI accepts GMP certification from recognised overseas authorities and organisations. Recognition means that the regulatory GMP programme administered by that authority can be considered sufficiently similar to MPI's programme to accept their existing evidence of conformity as assessed by their auditors. The recognised regulatory authorities are those authorities that are members of PIC/S, have a mutual recognition agreement on GMP Assessment with MPI, or have a technical agreement with MPI for acceptance of GMP certification.

The following regulatory authorities are currently recognised by MPI:

Country	Recognised Regulatory Authority
Argentina	National Institute of Drugs **aka** Instituto Nacional de Medicamentos (**INAME**)
Australia	Therapeutic Goods Administration (**TGA**) Australian Pesticides and Veterinary Medicines Authority (**APVMA**)
Austria	Austrian Agency for Health and Food Safety (**AGES**) Federal Office for Safety in Health Care **aka** Bundesamt für Sicherheit im Gesundheitswesen (**BASG**)
Belgium	Federal Agency for Medicines and Health Products (**FAMHP**) **which includes** *Agence Fédérale des Médicaments et des Produits de Santé* (**AFMPS**) and *Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten* (**FAGG**)
Brazil	National Health Surveillance Agency **aka** Agência Nacional de Vigilância Sanitária (**ANVISA**)
Bulgaria	Bulgarian Drug Agency (**BDA**) Bulgarian Food Safety Agency (**BFSA**)
Canada	Health Canada / Santé Canada **which includes** Regulatory Operations and Enforcement Branch (**ROEB**) **and** Direction générale des opérations réglementaires et de l'application de la loi *(***DGORAL***)*

Country	Recognised Regulatory Authority
Chinese Taipei	Taiwan Food and Drug Administration (**TFDA**)
Croatia	Agency for Medicinal Products and Medical Devices of Croatia **aka** Agencija za lijekove i medicinske proizvode (**HALMED**) Ministry of Agriculture - Veterinary and Food Safety Directorate **aka** Ministarstvo Poljoprivrede – Uprava Za Veterinarstvo (**MPS-UZV**)
Cyprus	Ministry of Health - Pharmaceutical Services (**CyPHS**) Veterinary Services, Ministry of Agriculture, Natural Resources and Environment (**MoA-Cy**)
Czechia (formerly known as Czech Republic)	State Institute for Drug Control **aka** Státní Ústav pro Kontrolu Léčiv (**SÚKL**) Institute for State Control of Veterinary Biologicals and Medicines (**ISCVBM**)
Denmark	Danish Medicines Authority (**DKMA**)
Estonia	State Agency of Medicines (**SAM**)
Finland	Finnish Medicines Agency (**FIMEA**)
France	French National Agency for Medicines and Health Products Safety **aka** Agence nationale de sécurité du médicament et des produits de santé (**ANSM**) Agency for Food, Environmental and Occupational Health Safety **aka** Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (**ANSES**)
Germany	Central Authority of the Laender for Health Protection Regarding Medicinal Products and Medical Devices **aka** Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (**ZLG**).* The following are German Regional State Authorities: **BADEN-WÜERTTEMBERG** Regierungspräsidium Tübingen (Referat 25) Leitstelle Arzneimittelueberwachung Baden-Wuerttemberg; Sachgebiet Pharmazeutische Angelegenheiten Sachgebiet 3 Arzneimittel-, Apotheken- und Medizinproduktewesen Pharmazeutische Angelegenheiten Regierungspräsidium Freiburg (Referat 25) Regierungspräsidium Karlsruhe (Referat 25) Regierungspräsidium Stuttgart (Referat 25) **BAYERN** Regierung von Oberbayern Sachgebiet 53.2 – Pharmazie Regierung von Oberfranken

Country	Recognised Regulatory Authority
Germany (cont.)	**BERLIN** Landesamt für Gesundheit und Soziales Berlin (LAGeSo), Referat I F 3 Arzneimittelwesen (Pharmazeutisches Inspektorat) **BRANDENBURG** Landesamt für Umwelt, Gesundheit und Verbraucherschutz Referat G4 Apotheken, Arzneimittel Medizinprodukte **BREMEN** Senator für Gesundheit Referat 44 Pharmazie, Toxikologie, Gentetechnik **HAMBURG** Behörde für Gesundheit und Verbraucherschutz **HESSEN** Regierungspräsidium Darmstadt Dezernat II 23.1 und 23.2 **MECKLENBURG-VORPOMMERN** Arzneimittelüberwachungs- und –prüfstelle Mecklenburg-Vorpommern LALLF Rostock **NIEDERSACHSEN** Staatliches Gewerbeaufsichtsamt Braunschweig Staatliches Gewerbeaufsichtsamt Hannover Staatliches Gewerbeaufsichtsamt Lüneburg Staatliches Gewerbeaufsichtsamt Oldenburg Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit **NORDRHEIN-WESTFALEN** Bezirksregierung Arnsberg Bezirksregierung Detmold Bezirksregierung Düsseldorf Bezirksregierung Köln Bezirksregierung Münster Gesundsheitamt der Stadt Landesamt für Natur, Umwelt und Verbraucherschutz **RHEINLAND-PFALZ** Landesamt für Soziales, Jugend und Versorgung Kreisverwaltung Mainz-Bingen **SAARLAND** Ministerium für Soziales, Gesundheit, Frauen und Familie Referat E3 / Referat E4

Country	Recognised Regulatory Authority
Germany (cont.)	**SACHSEN** Landesdirektion Sachsen Referat 24L Pharmazie, GMP-Inspektorat **SACHSEN-ANHALT** Landesverwaltungsamt Sachsen-Anhalt Referat 604 Gesundheitswesen, Pharmazie **SCHLESWIG-HOLSTEIN** Landesamt für soziale Dienste des Landes Schleswig-Holstein **THÜRINGEN** Thüringer Landesamt für Verbraucherschutz Federal Ministry of Health **aka** Bundesministerium für Gesundheit (**BMG**) Federal Office of Consumer Protection and Food Safety (**BVL**) Paul Ehrlich Institute (**PEI**) * All German Regional State Authorities, which are listed on the **ZLG** website are represented by **ZLG**.
Greece	Greek National Organisation for Medicines **aka** Εθνικός Οργανισμός Φαρμάκων (**EOF**)
Hong Kong	Pharmacy and Poisons Board of Hong Kong (**PPBHK**)
Hungary	National Public Health and Pharmaceutical Center (**NCPHP** or **NNGYK**) National Food Chain Safety Office – Directorate of Veterinary Medicinal Products (**NEBIH**)
Iceland	Icelandic Medicines Agency (**IMA**)
Indonesia	Indonesian Food and Drug Authority **aka** Badan Pengawas Obat dan Makanan Republik Indonesia (**Badan POM**)
Iran	Iran Food and Drug Administration (**IFDA**)
Ireland	Health Products Regulatory Authority (**HPRA**)
Israel	Institute for Standardization and Control of Pharmaceuticals (**ISCP**)
Italy	Italian Medicines Agency **aka** Agenzia Italiana del Farmaco (**AIFA**) Directorate General for Animal Health and Veterinary Medicinal Products **aka** Direzione generale della sanità animale e dei farmaci veterinari (**DGSAF**)
Japan	Ministry of Health, Labour and Welfare (**MHLW**) Pharmaceuticals and Medical Devices Agency (**PMDA**)
Korea	Ministry of Food and Drug Safety (**MFDS**)
Latvia	State Agency of Medicines **aka** Zāļu valsts aģentūra (**ZVA**) Food and Veterinary Service (**PVD**)

Country	Recognised Regulatory Authority
Liechtenstein	Office of Healthcare (**AG**)
Lithuania	State Food and Veterinary Service (**VMVT**) National Food and Veterinary Risk Assessment Institute (**NMVRVI**)
Luxembourg	Ministry of Health / Ministere Sante (**MS**)
Malaysia	National Pharmaceutical Regulatory Agency (**NPRA**)
Malta	Malta Medicines Authority (**MMA**) Veterinary and Phytosanitary Regulation Department (**NVL** within the **AHWD**)
Mexico	Federal Commission for the Protection Against Sanitary Risks **aka** Comisión Federal para la Protección contra Riesgos Sanitarios (**COFEPRIS**)
Netherlands	Health and Youth Care Inspectorate **aka** Inspectie Gezondheidszorg en Jeugd (**IGJ**) Medicines Evaluation Board **aka** College ter Beoordeling van Geneesmiddelen **which includes** Veterinary Medicinal Products Unit (**CBG-MEB**)
Norway	Norwegian Medical Products Agency (**NOMA**)
Poland	Chief Pharmaceutical Inspectorate (**CPI**)
Portugal	National Authority of Medicines and Health Products, IP **aka** Autoridade Nacional do Medicamento e Produtos de Saúde IP (**INFARMED IP**) National Authority for Animal Health **aka** Direção-Geral de Alimentação e Veterinária (**DGAV**)
Romania	National Agency for Medicines and Medical Devices of Romania (**NAMMDR**) Institute for Control of Biological Products and Veterinary Medicines **aka** Institutul Pentru Controlul Produselor Biologice Si Medicamentelor De Uz Veterinar (**ICBMV**)
Saudi Arabia	Saudi Food and Drug Authority (**SFDA**)
Singapore	Health Sciences Authority (**HSA**)
Slovak Republic	State Institute for Drug Control (**SIDC**) Institute for State Control of Veterinary Biologicals and Medicaments Nitra **aka** Ustav statnej kontroly veterinarnych biopreparatov a Lieciv Nitra (**USKVBL**)
Slovenia	Agency for Medicinal Products and Medical Devices **aka** Javna agencija Republike Slovenije za zdravila in medicinske pripomočke (**JAZMP**)
South Africa	South African Health Products Regulatory Authority (**SAHPRA**)
Spain	Spanish Agency of Medicines and Medical Devices **aka** Agencia Española de Medicamentos y Productos Sanitarios (**AEMPS**)

Country	Recognised Regulatory Authority
Sweden	Sweden Medical Products Agency (**MPA**)
Switzerland	Swiss Agency for Therapeutic Products (**Swissmedic**)
Thailand	Food and Drug Administration (**Thai FDA**)
Turkey	Turkish Medicines and Medical Devices Agency (**TMMDA**)
Ukraine	State Service of Ukraine on Medicines and Drugs Control (**SMDC**)
UK	Medicines and Healthcare Products Regulatory Agency (**MHRA**) Veterinary Medicines Directorate (**VMD**)
USA	U.S. Food and Drug Administration (**US FDA**) U.S. Department of Agriculture (**USDA**)

1 Evidence from Australia

New Zealand has a memorandum of understanding (MOU) in place with the Australian Pesticides and Veterinary Medicines Authority (APVMA)). MPI and the APVMA recognise each other's certificates of GMP compliance. A GMP certificate of manufacture or a licence to manufacture issued to a manufacturer in Australia by the APVMA can be submitted to MPI as evidence of GMP compliance without additional supplemental information. The certificate or license should include:

- name and street address of the manufacturer;
- the authorised manufacturing steps; and
- the scope for which the approval was granted must be relevant to the activities the manufacturer will undertake in the production of the New Zealand registered product.

For Certificates of Manufacture, the date of the most recent inspection must be within the previous three years of the application. For a Licence to Manufacture, the delegated authority must have been signed within the last three years of the application. If this cannot be obtained, evidence of the most recent audit performed can be provided in the form of an audit closure letter or equivalent. Alternatively, evidence obtained from the APVMA's online register can be provided to show evidence that a license is still in place. However, this must be provided alongside the current License to Manufacture which stipulates any additional conditions placed on the license.

For international manufacturers inspected by the APVMA, a letter confirming overseas site GMP compliance may be accepted on a case by case basis if the product type and scope is applicable to the product registered in New Zealand.

2 Evidence from EU Mutual Recognition Agreement (MRA) Partners or PIC/S Members

2.1 Sterile veterinary medicines, non-sterile veterinary medicines, and ectoparasiticides

A current GMP certificate from a recognised authority will be accepted as evidence of compliance with GMP without additional supplemental information. The certificate should include:

- name and street address of the manufacturer; and
- the scope for which the approval was granted must be relevant to the activities the manufacturer will undertake in the production of the New Zealand registered product.

The certificate must clearly state that the approval is valid and be within the validity period.

The certificate must be applicable to veterinary medicines.

EudraGMP Certificates will be accepted if they meet the requirements above.

2.2 Registered feeds and feed supplements

If a GMP certificate is not available, MPI will also consider acceptance of FAMI-QS certification confirming the manufacturer complies with requirements. If FAMI-QS certification is being provided, it must include the following:

- name and street address of the manufacturer;
- the scope for which the approval was granted must be relevant to the activities the manufacturer will undertake in the production of the New Zealand registered product; and
- an original statutory declaration from the company confirming that quality control testing is being performed on each batch of the product and reviewed before its release.

3 Evidence from the United States

3.1 Sterile and non-sterile veterinary medicines

The evidence provided should be a current Certificate to Foreign Government from the US Food and Drug Administration (US FDA). The US FDA evidence should state:

- the name and street address of the manufacturing site and the products involved;
- that the product and the manufacturing site are subject to the jurisdiction of the FDA;
- that the manufacturing site is subject to periodic GMP-type inspections or audits;
- that the manufacturing site is in compliance with GMP;
- that the certificate has been recently issued, or that a recent audit has been performed (within the last three years and/or the certificate is specified as valid (these generally specify as expiring 24 months from date of notarisation); and
- the scope of the audit performed (product type or product name).

If a current certificate/license cannot be provided, MPI will consider a copy of the most recent manufacturer's audit report issued by the US FDA. The audit report must clearly indicate that the product has been included within the scope of the inspection, in addition to the previous license.

3.2 Sterile and non-sterile veterinary medicines that are either not marketed in the United States or not yet registered

The US FDA does not usually issue appropriate certificates for export-only veterinary medicines, or issue a certificate before a product is registered in the United States.

Certificates that refer to closely similar products manufactured at the same site, or a GMP certificate or an audit report from another MPI-recognised authority, may be considered on a case-by-case basis. If these are unavailable, an audit by a MPI auditor may be required to confirm GMP compliance.

3.3 Ectoparasiticides, registered feeds, and feed supplements

Recognised government agencies in the United States do not generally conduct GMP audits of these types of products. A GMP certificate or an audit report from another MPI-recognised authority may be considered on a case-by-case basis. If no such report is available, an audit by a MPI auditor may be required to confirm GMP compliance.

4 Evidence from Canada

4.1 Sterile and non-sterile veterinary medicines, registered feeds, and feed supplements

The evidence provided should be a Certificate of Compliance or an Establishment License issued by Health Canada. The evidence must be complete and include all pages, and must include evidence confirming that the product intended for New Zealand registration is covered by the GMP inspection programme. The documents should include:

- name and street address of the manufacturer; and
- the scope for which the approval was granted must be relevant to the activities the manufacturer will undertake in the production of the New Zealand registered product.

If the scope of approval or product type is not specified on the document, and/or the date on the license isn't recent, an Inspection Exit Notice or audit report can be provided to support the License to verify the date of the last inspection.

4.2 Ectoparasiticides

There are no Canadian authorities recognised to evaluate ectoparasiticide manufacturers. An audit report from another MPI-recognised authority may be considered on a case-by-case basis. If no such report is available, an audit by a MPI auditor may be required to confirm GMP compliance.

5 Overseas testing laboratories

Evidence of GMP compliance should be sought from MPI- recognised government authorities.

If evidence cannot be obtained from recognised authorities, MPI may consider evidence to confirm certification for compliance with the ISO/IEC 17025 Standard from an accredited organisation.

6 Evidence from authorities not recognised by MPI

If a product is manufactured in a country that does not have a MPI-recognised authority, a report from an audit conducted by a MPI-recognised authority may be considered on a case-by-case basis. Alternatively, the registrant company may request an audit of the overseas facility by MPI to grant GMP approval to allow the manufacture of a New Zealand registered product.

Appendix 6: MPI Expectations for an Ongoing Stability Programme

1 General expectations

(1) Once a trade name product has been registered and marketed, registrants are expected to monitor the stability of the product according to a continuous appropriate programme that will allow for the detection of any stability issue associated with the formulation in the approved market packaging. This includes changes in levels of impurities, changes to the dissolution profile of the product, or any other change that may signal an inability of the formulation to remain within specification for the duration of the approved shelf life.

(2) The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the approved storage conditions. To achieve this, the programme should include all marketed pack sizes and packaging types.

(3) The ongoing stability programme should also include the storage of product in bulk after manufacture and before final packing when bulk storage is used. This is particularly important if the product is stored in bulk for a long period before being packaged and/or shipped from a manufacturing site to a packaging site. The stability of bulk-stored product should be evaluated under ambient conditions to ensure it will not negatively impact the stability of the final marketed product.

(4) If manufacture of the product includes intermediates that are stored and used over prolonged periods, these should also be included in the programme.

(5) Ongoing stability studies on reconstituted product are not expected unless the stability profile of the product indicates this should be monitored.

2 Programme protocol and documentation

(1) The programme should be detailed in a written protocol following the expectations for shelf life stability as described in section 6.8, and results formalised as a report. All equipment used for the ongoing stability programme should be qualified and well maintained.

(2) The protocol should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

a) batch size;
b) batch strength (when applicable);
c) relevant physical, chemical, microbiological and biological test methods;
d) acceptance criteria;
e) reference to test methods;
f) description of the container closure system(s);
g) testing intervals (time points);
h) a description of the conditions of storage; and
i) any other applicable parameters specific to the product.

(3) The parameters, acceptable values, and methods included in the protocol must match those approved for the product and listed in the Product Data Sheet.

a) Although the protocol itself will not be approved by MPI, it is expected that the protocol will be available for review by the competent authority when requested.

(4) Details of the protocol that are not part of the product's registration, such as additional parameters or quality control processes, may differ from those used in the stability studies conducted for product registration provided that this is justified and documented in the protocol.

(5) The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type should be included in the stability programme.

a) If the product is manufactured infrequently (i.e. there are years when no product is manufactured), the frequency of testing may be reduced but still conducted such that the overall stability trends can be analysed.
b) If the product would normally require testing in animals and no suitable alternative validated methods are available, the determination of testing frequency should take a risk-benefit approach. Bracketing and matrixing may be used if scientifically justified in the protocol.

(6) If a variation to the formulation, manufacturing process, or packaging for the product has been approved, additional batches of the varied product should be included in the ongoing stability programme. Any batches that have undergone reworking, reprocessing or recovery should also be considered for inclusion.

(7) Results of the ongoing stability studies should be made available to key personnel and, in particular, to the release to market entity. If ongoing stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned.

(8) Results of ongoing stability studies should also be available for review by the competent authority.

(9) Any out-of-specification results or significant atypical trends should be investigated. Any confirmed out-of-specification result or significant negative trend affecting product batches released to the New Zealand market should be reported to MPI.

(10) A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.