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 Requirements

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

Document history

This document replaces ACVM Registration Standard and Guideline for the Chemistry of Veterinary Medicines (ACVM 47 November 2003).

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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(s) means a substance(s) in a trade name product that is responsible for the biological or other effects that make the product a veterinary medicine

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

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

agricultural compound means any substance, mixture of substances, or biological compound, used or intended for use in the direct management of plants and animals, or to be applied to the land, place, or water on or in which the plants and animals are managed, for the purpose of:

- managing or eradicating pests, including vertebrate pests, or
- maintaining, promoting, or regulating plant or animal productivity and performance or reproduction, or
- fulfilling special nutritional requirements, or
- manipulating, capturing, or immobilising animals, or
- diagnosing the condition of animals, or
- preventing or treating conditions of animals, or
- enhancing the effectiveness of an agricultural compound used for the treatment of plants and animals, or
- marking animals

and includes:

- any substance, mixture of substances, or biological compound used for post-harvest pest control or disinfection of raw primary produce, and
- any substance, mixture of substances, or biological compound declared to be an agricultural compound

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

bioburden means the level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, active ingredient starting materials, intermediates or active ingredients. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected

BP means British Pharmacopoeia

BP (vet) means British Pharmacopoeia (Vet)

bracketing means the design of a stability schedule such that only samples on the extremes of certain design factors, e.g. strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system

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

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

climatic zone (New Zealand) see real time stability definition

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

critical manufacturing control point means a step at which control can be applied and is essential to prevent or eliminate an identified hazard, or reduce an identified hazard to an acceptable level

EP 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 formulants, inert or non-active ingredients

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

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

extraneous agent means a live biological agent (e.g. bacteria, virus, mycoplasma, or other organism) that may be present as a contaminant in any biologically-derived starting material

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

GLP means good laboratory practice (International Code: ISO/IEC 17025 General Requirements for the Competence of Testing and Calibration Laboratories)

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

GMP 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 specifications

ISO means International Standards Organisation

IUPAC means International Union of Pure and Applied Chemistry

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 for supply. 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 New Zealand 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. 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 I some cases, different container closure systems

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 filling would not normally be regarded as part of packing as it is considered part of the manufacturing process. This applies to the bulk product being the filled, but not finally packaged in the primary containers

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.) It is intended to protect not only the product, but also the primary packaging
>
> **outers and shippers** means those packaging materials used for transportation or shipment
>
> **recycled packaging** means new packaging that has been produced from recycled materials
>
> **reused packaging** means used packaging that has been cleaned and inspected as being fit for purpose

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

pilot scale batch means a batch of product manufactured by a procedure fully representative of and simulating that to be applied to full production scale. This includes equipment, manufacturing site, manufacturing procedures, in-process controls, post-production testing, and must be no less than 10% of the future production scale. For solid oral dose forms, pilot scale is at minimum, at least 10% or 100,000 units, whichever is greater

process validation means the documented evidence that the process operated within established parameters, can perform effectively and reproducibly to produce a trade name product meeting its predetermined specifications 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 I the application, at a volume sufficient to allow for the routine manufacturing of the trade name product for the commercial market

real time stability testing means testing of the final trade name product, in the container(s) and closure system intended for market, at the storage conditions intended for end user storage throughout the proposed shelf life. In New Zealand, MPI accepts data generated at 25°C + 2°C and 60% RH +/- 5% RH or at 30°C + 2°C and 65% RH +5% RH for veterinary medicines stored at 'room temperature', and 5°C for veterinary medicines stored in a refrigerator

ICH has assigned New Zealand to Climatic Zone II (Mediterranean/subtropical zone) with long term testing conditions of 25°C ± 2°C; 60% RH ± 5% RH. VICH GL3R provides guidance on stability testing of new veterinary drug substances and medicinal products for climatic zones I and II

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

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

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

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

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 specifications (where applicable), and physicochemical characteristics as specified at the time of manufacture and maintained throughout the shelf life of the trade name product within the specified range established by the expiry specification

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

USP means United States Pharmacopoeia

validation means the act of demonstrating and documenting that a procedure operates effectively. *Process validation* is the means of ensuring and providing documentary evidence that processes, within their specified design parameters, are capable of consistently producing a finished trade name product to the required quality. *Method validation* is the means of ensuring and providing documentary evidence that a particular test method or procedure is capable of producing consistent results to the required quality

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

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

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

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

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.

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

4.1 Units

All units should preferably be SI units.

4.2 Dossiers

When submitting a dossier for review to support the registration of a new product, the applicant must, in addition to the information outlined in this document, also take into account the current state of veterinary medicinal development and knowledge, and must include the most current methods and information available as applicable to the product and formulation type.

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, regardless of whether the information is favourable or unfavourable to the application. In particular, provide all relevant details of any

incomplete or abandoned test or trial relating to the trade name product, including any stability results that do not conform to specification.

If the product is currently or has previously been registered by an overseas authority, provide any pharmacovigilance information pertaining to chemistry or manufacture of the product.

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

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

5 Additional guidelines

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 must 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 of the formulation.

(5) For controlled-release devices:

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.

Table 1: Formulation composition table

Ingredient Name (Common or Chemical)	CAS Number	Standard	Quantity (g/kg or g/L)	Function

Specific gravity	
Other information about formulation (for example, overage, isomers)	

(3) If the active ingredient is not added in its pure state, state the potency of the active ingredient as part of the common name of the compound (e.g. [active ingredient] HCl, technical grade (90% w/w)).

(4) Include ingredients used to standardise the formulation, such as pH adjustors, in the formulation when used or possibly used in a formulation.

(5) If an ingredient remains in the formulation as a residue from manufacturing (e.g. gentamycin sulphate in vaccines), include it in the formulation table.

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

A quantity sufficient (qs) designation may be used in place of ingredient quantity if that ingredient is added to an endpoint rather than a set nominal content; state the endpoint (e.g. qs to 1mL, qs to pH 5.5).

(7) If a salt or hydrate form of an active ingredient is used, identify the salt. Clearly state the quantity of the active ingredient relative to the salt form (e.g. 1mg [active] base = 1.075 mg of [active ingredient] HCl).

(8) If an ingredient is added based on potency, state how the quantity of ingredient is calculated based on the potency assay.

For example, if the theoretical batch quantity of an active 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.

(9) 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.*

(10) If the product contains components with distinct formulations such as tablet coatings, show these components as a separate distinguishable formulation table.

6.2.2 Overages

(1) If an overage of active ingredient is deliberately added to compensate for storage loss, 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.

State the nominal content and the overage content in the notes on the formulation, along with the reason for the overage, in the product data sheet.

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
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.

6.3.2 Active ingredient specification

(1) Provide an active ingredient specification that lists all physical and chemical characteristics, qualitative and quantitative parameters including acceptance limits and validated test methods. All proposed and approved active ingredient manufacturers must produce active ingredient that conforms to the proposed active ingredient specification.

(2) Provide validation of all test methods detailed in the active ingredient specification. Any data obtained by measurements must meet the required specificity, precision and accuracy.

(3) If the efficacy, safety or residue profile of the final product is dependent on a particular characterisation 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, as with some complex plant/herbal extracts, it may be difficult to adequately control the ingredient through quantitative specifications. In this case, a combination of specifications and details of the manufacturing process must be established to adequately characterise the active ingredients.

(5) The minimum tests and limits expected in specification for an active ingredient include:

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. The information should include, as appropriate:
Physical characteristics:

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

Chemical characteristics:

- isomeric content (enantiomeric, rotational, diastereometric and/or geometric)
- solubility (in water and organic solvents)
- hydrolytic properties

- photolytic properties
- polymorphism
- pKa and/or (aqueous) pH values
- hygroscopicity
- n-octanol/water partition coefficient (P_{ow} or log P_{ow})
- chelating and/or encrypting properties.

(6) For vitamins and minerals present in products for nutritional purposes only (i.e. with no therapeutic claims or target animal safety/ residue risks), provide identity and impurity parameters only.

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

6.3.2.1 Active ingredients conforming to a pharmacopoeial monograph

(1) If a pharmacopoeial monograph is nominated, it must be from a pharmacopoeia recognised by MPI – i.e. BP, EP (Eur Ph), or USP. The nominated pharmacopoeial standard will apply to the ingredient in its entirety, and MPI expects that the active 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.

(2) 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 using different MPI-recognised pharmacopoeial standards, but the active ingredient sourced must conform to the active ingredient specification proposed for registration.

(3) Validation of test methods is not required for active ingredients conforming to a MPI-recognised pharmacopoeial monograph

6.3.2.2 Active ingredients conforming to a non-pharmacopoeial specification

(1) If a manufacturer's specification (MS) is used, explain the relevance of the parameters and limits selected.

6.3.3 Active ingredients impurities

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

(1) Identify, quantify, and report any impurities present at a concentration of 1g/kg or more. Explain both the relationship of the impurity to the active ingredient and its origin.

(2) Details of the impurities must include:

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

(3) Identify, quantify, and report any impurities of toxicological/residue concern present at any level, including those present at less than 1g/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.

(4) 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 specifications. The selection of batches to demonstrate routine compliance with the pharmacopoeial monograph or manufacturer's specifications should be the same as that described in VICH GL3(R).

(2) Batch analysis data must include:

a) batch size, 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. 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.

6.3.5 Active ingredient test methods and validation

(1) Provide full details of the analytical methods used. 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, and
g) worked examples of the calculations, if applicable.

(2) Provide validation data 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), and
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.

(3) For sterile active ingredients, provide the analytical method and test method validation data, of the test used to confirm sterility.

6.4 Active ingredient manufacturers

An active ingredient manufacturer is any site of manufacture that produces an ingredient defined as an active ingredient and that complies with the active ingredient specification in the proposed trade name product.

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

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

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

(3) Any manufacturer listed must conform to the stated active ingredient specification (parameters and acceptance limits), although test methods may vary.

(4) Manufacturers who produce sterile active ingredients must have a current GMP approval. Provide details of the sterilisation facility and a brief description of the sterilisation process(es) used to produce the active ingredient at that facility.

(5) If active ingredients are sterilised at a secondary facility, provide details for both the manufacturer and the sterilisation facility. GMP approval is required for the sterilisation facility if the active ingredient is not further sterilised as part of the formulated product manufacturing process.

(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.

6.5 Excipient ingredients

(1) Clearly identify each excipient, including:

a) the chemical or IUPAC, ISO or common name
b) CAS registry number
c) the form in which the ingredient is used in the formulation
d) its specific purpose in the formulation with respect to the purpose of the product in the New Zealand context (e.g. a solvent in a pour-on product enables transdermal absorption of the active ingredient, and is critical to efficacy, target animal safety and residues), and
e) the standard with which the excipient complies.

(2) If an excipient is considered critical to the function of the final product, more information on that excipient may be required. An example of such an excipient would be an adjuvant in a vaccine intended for use in food-producing animals which may pose a residue risk.

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

(4) Nominate 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), or USP. 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) Colouring additives, proprietary flavourings, perfumes and other additives must comply with a recognised standard such as the Food Standards Code (FSANZ). If these additives comply with a recognised standard, reference the standard and provide the supplier name, postal and physical address.

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

a) details of the manufacturer's specifications for the compound, and

b) a description of chemical and physical characteristics of the compound.

(7) 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.

(8) Batch analysis
Provide batch analysis data (e.g. certificate of analysis, CEP) for at least one recent commercial-scale production batch of the excipient to demonstrate the excipient is manufactured consistently to meet the proposed pharmacopoeial monograph or manufacturer's specifications.

The batch analysis results should include:

a) batch number, date of manufacture and date of analysis, and
b) 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".

(9) Identify, quantify (if appropriate), and report any other impurities of toxicological/residue concern. Specify whether these impurities occur as a result of manufacture or storage.

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

(11) For excipients sourced as sterile ingredients that are used in a manufacturing process where there is no terminal sterilisation of the final product, MPI regards these as similar risk to sterile active ingredients. Provide the same information required for sterile active ingredients (see 6.3.5 (3)).

(12) 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.

6.5.1 Ingredients of biological origin

(1) If materials (active and non-active) of biological origin are used, also provide a current MPI Biosecurity approval.

6.6 Formulated product manufacturing

6.6.1 Manufacturer identity and GMP

A formulated product manufacturer is a site where any step of the manufacturing process is occurring. This includes sites that manufacture an intermediate product used in the production of the final trade name product, contracted testing and quality control laboratories, contracted sterilisation entities, repackers, relabellers, and entities responsible for release for supply of the trade name product.

(1) The following types of formulated product manufacturers must have the appropriate GMP approval to conduct the portions of the manufacturing process for which they are responsible:

a) sites that manufacture 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 testing and quality control laboratories
c) contracted sterilisation entities, and
d) repackers, relabellers.

(2) GMP approval must be current and have been obtained from either MPI or a competent regulatory authority that is recognised by MPI. Provide evidence of GMP approval for all manufacturers that have not been approved by MPI (i.e. international manufacturers).

(3) Manufacturers approved to repackage and/or relabel trade name products must only be involved in processes that do not breach the primary packaging, e.g. packaging the primary unit into

separate/additional secondary packaging, addition of New Zealand specific leaflets, or adding or changing product labelling. It is not considered 'repackaging' if product is packaged from bulk storage into primary market packaging.

(4) Identify entities responsible for release for supply of the trade name product to the New Zealand market. This entity must be directly responsible for confirming the product is suitable for release to market, including ensuring that all final checks are performed, testing of the product has verified that the trade name product meets approved specifications and that the labelling/packaging meets the approved conditions. This entity must be present in New Zealand, or have direct authority over New Zealand distribution and/or entities performing final checks or functions such as labelling/packaging in New Zealand (e.g. present in Australia with direct contact with New Zealand suppliers).

Registrants performing release for supply to the New Zealand market activities currently do not require GMP approval.

If the registrant contracts a New Zealand third party to perform release for supply activities, that third party must hold a GMP approval for that function.

(5) Provide the following details for each site of manufacture:

a) name of organisation
b) postal address
c) physical address
d) site telephone number and email address (to enable MPI to quickly contact the site if necessary), and
e) step(s) of the manufacturing process conducted at each site, as described in 6.6 (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".

6.6.2 Manufacturing information

(1) Provide the batch formula that includes a list of all the 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 overages, ingredients consumed during the manufacturing process, and gases used in manufacturing and packaging (e.g. nitrogen gas).

Table 2: Example of batch formula table

Component	Quality Standard	Amount (kg/L) 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]
Total batch size		X
Film coat solution[b]		
Hydroxymethylcellulose	ISP	10
Purified water	USP	(200)[a]
Colour red	Food grade	10

Component	Quality Standard	Amount (kg/L) per batch
Total batch size		Y
Print ink solution		
Colourant		0.15
Solvent		10
Total batch size		Z
[a] Water is removed during processing [b] Film coat weight variability is 80 - 120% target		

(2) Provide a narrative description of all stages of the manufacturing process from dispensing to labelling.

(3) Provide a narrative description of the essential steps and critical processes. This includes the point(s) at which the product or its ingredients are exposed to heating or cooling, blending times, sterilisation, and any processes likely to lead to toxic impurities. Include all critical in-process quality control steps.

(4) Provide a flow diagram of the manufacturing process from dispensing to labelling – this 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 release specification.

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) all heating, cooling, and blending steps, including associated timing/duration
d) the production and use of intermediates, if applicable
e) details of bulk storage of product, including information on the storage vessel or container
f) time frame of storage post-manufacture
g) storage conditions, such as temperature control
h) duration of storage prior to repackaging into the final market packs.
i) the filling process into the final product container, application of, and sealing of the closure system, and
j) the attachment of market labels, and the application of the required batch number and expiry date.

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

(6) State typical production batch size, and batch range if appropriate.

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

(8) If an overage of active ingredient is deliberately added to compensate for manufacturing loss, state the actual total quantity (nominal content plus overage). Explain the reason for the overage.

(9) State ingredients that are partially consumed during the manufacturing process, such as water that is later extracted. Ingredients that are entirely consumed in the manufacturing process (e.g. completely absent from the final formulation) are not to be listed in the formulation composition table.

(10) Any time in storage prior to repackaging into market packaging should be incorporated into the final shelf life of the product.

6.6.3 In-process quality control testing

In-process quality control testing is all tests that may be performed during the manufacture of the trade name product for the purpose of adjusting formulation and/or process parameters within the specified range. These may include certain tests conducted during the manufacturing process, if the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution), if the test result

can be used as a formulated product specification. In-process quality controls may also include any mixing adjustments, intermediate form parameters (such as hardness and friability of tablets which will then be coated, or assembled into a slow-release bolus), or any other tests necessary to ensure the quality or consistency of manufacture but are not included in the formulated product specifications.

(1) Provide full detail of the quality control processes used by the formulated product manufacturer(s) to ensure the batch to batch consistency of the product. If these details vary between manufacturers, provide a separate outline of the quality control procedures for each manufacturer.

a) Details of the in-process quality control procedures must include all tests and assays performed at various stages of the manufacture, processing, and packaging of the product.
b) Provide the test method descriptions and numbers for all in-process tests.

6.6.4 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 manufacturing process validation data 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 data non-transferrable.

(2) Validation should include all strengths, batch sizes and pack sizes. However, a bracketing approach may be acceptable.

(3) If validation data has not been generated 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 can be considered. The validation protocol must include:

a) a description of the entire manufacturing process, with a summary of the critical processing steps or critical 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 3 consecutive batches are expected)
f) details of the methods for recording and evaluating the results
g) the proposed formulated product release specification, and
h) a proposed time frame for completion of process validation.

(4) For those products requiring completion of process validation at the time of the application or to meet a condition, the report must include all of the following:

a) a copy of the protocol 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 and established process, including results from all in-process and additional analytical testing performed

e) a report on any and all unusual findings, modifications, deviations, or changes necessary during the process, with appropriate justification and discussion, and
f) 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 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 the validation data should include evidence 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.

6.7 Finished product specification

The finished product specification establishes the criteria to which a formulated product must conform to be considered acceptable for its intended use. "Conformance to specifications" 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
b) suspendability, uniformity of dose, and particle size testing for suspensions (including pastes), and
c) uniformity of dose for tablet formulations, especially if the tablet is scored for doses less than a whole tablet.

Find a complete list of expected specifications by product and formulation type in Appendix 3.

6.7.1 Fitness for purpose rationale

(1) Provide a rationale explaining how the specification proposed for the formulated product is fit for purpose. This includes both the parameters being chosen and the value or range proposed as acceptable for those parameters.

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

(3) 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. It is not acceptable to set the acceptable value(s) based on the results of stability trial work without technical justification and risk analysis.

(4) 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 interim specifications for the formulated product.

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

(5) If multiple manufacturing sites are proposed for the trade name product, present and evaluate data from all manufacturing sites when establishing formulated product specifications and 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.

(6) 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.

6.7.2 Formulated product release specification

(1) The release specification must include:

a) the identity of the testing parameter, acceptance criteria, and the method used to perform each assay or test including version numbers or other identifiers, if 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) testing parameters considered critical for the particular dose form and/or formulation type.

Select applicable parameters from the list provided in Appendix 3.

(2) The release specification of a sterile product must include a sterility parameter. The exception is if sterility is managed by a validated terminal sterilisation process that is appropriate for the product type and packaging. Evidence of validation of all sterilisation processes is required – see 6.6.4 (6).

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

(3) Specifications must take any overages used in the manufacture of the formulation into account.

6.7.3 Formulated product expiry specification

(1) The general requirements for expiry specifications are as outlined in clause 6.7.2(1) for release specifications.

(2) Include all appropriate parameters in the expiry 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) Justification of the specifications based on stability results alone will not be accepted.
For example, expiry specifications must not be set to justify degradation if the degradation may have a negative impact on the efficacy, safety or residue profile of the product.

6.8 Formulated product batch analyses

(1) Provide a minimum of three batch analyses of the formulated product from each site of manufacture.

Production scale batch analyses are always preferred. If, however, three production scale batches have not yet been manufactured, pilot scale batches may be considered with appropriate technical discussion addressing how they represent production scale manufacture with respect to processes and equipment used. If batch analyses for production batches have not been supplied, MPI may require additional information post-registration under conditions of registration 86 and/or 101.

(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 (2).

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

(6) Discuss and justify use of an alternative test method.

6.9 Product packaging

(1) For all packaging material to be marketed, supply details of:

a) size
b) shape
c) colour (where applicable for light sensitive products)
d) construction material, and
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.

(4) The integrity of the container must not be impaired by the product it contains, nor must the product 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 the associated risks (e.g. high acidity, photosensitivity), identify and discuss the associated risk and its management.

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.

a) Additional pack sizes within the approved range and specifications can be chosen and marketed without submitting stability data for assessment. An application to amend the approved product details (e.g. product data sheet and label) will, however, still be required to maintain approved product details as current.

(8) 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. 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 not required to provide information on commercially available administration devices (such as draw-off tubes, drench guns, bolus administration devices etc that may be purchased by the end-user to administer the product).

(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.

6.10 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.

6.10.1 Proposed shelf life

(1) Nominate a proposed shelf life.

(2) The proposed shelf life should not exceed the shelf life that is directly supported by data. The maximum acceptable proposed shelf life will be the point at which product released at the low end of the acceptable release parameter range will still conform to the low end of the corresponding expiry specification.

6.10.2 Proposed storage conditions

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

(2) State the proposed temperature range for storage, together with any other special conditions (e.g. protect from light).

(3) If applicable, state specific storage requirements. This is particularly important for products where the risk inherent in the product is one that is affected by storage conditions, e.g. freezing, high temperatures, and exposure to moisture, light or oxygen (air).

6.10.3 Stability study requirements

Batch selection

(1) Data from formal stability studies should be provided on a minimum of **three** batches of the trade name product. This means the formulation of the product used in the stability studies should be the same formulation as stated on the Product Datasheet, and the same as that used to generate efficacy, safety and residue data.

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

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

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

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

(5) The batches should be manufactured at the nominated site of manufacture.

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

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).

(2) Generate stability data on the smallest pack size being proposed for registration. Additionally, for heterogeneous formulations (e.g. suspensions), provide data on the largest pack size. If stability testing on the largest size packaging would be impracticable, then provide evidence of phase stability.

Storage conditions

(1) Provide real time studies or a combination of real time and accelerated studies to support the proposed shelf life.

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

(3) 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 2°C (Refrigerate)	5°C ± 3°C	25°C + 2°C and 60% RH +/-5% RH
Store below 25°C (Air conditioning)	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

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. 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 6 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) Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

Specifications

(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. The testing should cover, as appropriate, 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 expiry 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. Examples of significant changes can be found in VICH GL3.

(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.
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 where tablets are broken or removed from primary packaging (e.g. blisters) if product quality could be impacted. In those exceptional cases where in-use shelf life of tablet fractions is relevant, data should be supplied to support the stability of the remaining tablet fractions.
d) For formulations requiring refrigeration, include freeze/thaw data to ensure the stability of the product during cold chain distribution and storage.
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 photosensitive formulations, include data evaluating the photostability of the product in the proposed market packaging.

Analytical methods

(1) Describe analytical methods employed in stability testing.

(2) The analytical methods should be fully validated within the testing laboratory, and stability indicating. Copies of validation need not be supplied when pharmacopoeial standards, ISO, and other internationally recognised standards are employed. Any variations from nominated standards must be documented and validated.

(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.

Stability data analysis

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

(2) If the data shows so little degradation and so little variability that it is apparent the requested shelf life is justified, it is unnecessary to provide a formal 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.

Discussion of stability study results

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

Interim shelf life

(1) 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, taking into consideration any impacts on the risk areas managed under the ACVM Act.

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 the product over time.

6.11 In-use stability for multi-dose containers

(1) In use stability data should be provided for trade name products that are parenteral formulations supplied in multi-dose containers trade name products, and other types of trade name products supplied in multi-dose containers where 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.

(2) A minimum of two batches, at least pilot scale batches, should be tested.

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

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

(5) For products that undergo reconstitution prior to use, the reconstitution 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, generate in-use stability data for each diluent.

Refer to EMEA/CVMP/424/01 for further guidance.

6.12 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 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, in-feed 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 or form sediments that negatively impact the efficacy, safety or residue profiles of the product over the intended administration period, taking into consideration frequency of water changes.
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.

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 label wording that may impact the interpretive meaning of the label relative to providing sufficient consumer information), a technical discussion or justification may be required to support the change.

7.1 Changes to approved formulation details

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

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

(2) Provide:

Amended Product Data Sheet
Technical rationale for the change
Current formulation table and proposed formulation table, with differences highlighted
Updated manufacturing process flow chart and description if the manufacturing process has changed. Provide discussion on any areas affected by the process change: i.e. physical and chemical properties, stability, residues, animal safety and efficacy Provide process validation data (minimum validation protocol) if the change is considered significant
Updated outline of the new QC procedures/test methods/method validation if the quality control procedures have changed. Provide discussion on any areas affected by the QC changes: i.e. physical and chemical properties, stability, residues, animal safety and efficacy
Batch analysis data on minimum of 1 batch representative of production scale
Release specification, with any changes from that currently approved highlighted
Expiry specification, with any changes from that currently approved highlighted
Discussion on any areas affected by the formulation change: i.e. physical and chemical properties, stability, residues, target animal safety and efficacy
Stability data to support formulation changes that impact on the stability of the product

7.2 Changes to approved active ingredient manufacturer(s)

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

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

(2) Provide:

Amended Product Data Sheet
Details of the proposed manufacturing site(s): • name of organisation • postal address • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
Batch analysis data from three (minimum at least pilot) scale batches of active ingredient from the proposed manufacturer, and one batch from the currently approved manufacturer(s) as 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 size, 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
GMP is required for sterile active ingredient manufacturers and secondary sterilisation facilities where 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, where 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 1 site is approved)

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

MPI will assess this change, and likely apply condition 101 to the registration approval.

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

(2) Provide:

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

7.2.3 Change in name and/or address 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

7.2.4 Removing an active ingredient manufacturer /active ingredient testing site (if 2 or more sites are approved)

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

Note: You cannot remove the sole primary manufacturer and/or QC testing site and have no listed manufacturer for an active ingredient as a self-assessable change.

(2) Provide:

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

7.2.5 Change in name and/or address 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) Provide:

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

7.3 Changes to approved active ingredient(s)

7.3.1 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
Technical rationale for the change
Current active ingredient specification table and proposed specification table, with differences highlighted
Batch analysis data on minimum of one batch of active ingredient. The data should include: • batch size, number, date of manufacture and date of analysis • site of manufacture (if not tested by the actual site, then evidence of origin from the site is required) • results of all analytical determinations. For quantitative tests (e.g. active ingredient concentration, individual and total impurities) provide the actual numerical results. Vague statements such as “within limits” or “conforms” is not considered acceptable.
Details of any new analytical test methods and validation, if specification is non-pharmacopoeial
Copy of pharmacopoeial monograph active ingredient complies with (where 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 active ingredient specification changes that impact on the stability of the product
Toxicology and/or safety data may be required where the proposed change in 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 Adding, deleting, changing an MPI -recognised pharmacopoeial standard

The addition of, deletion of, or change to a MPI-recognised pharmacopoeial standard (i.e. BP, EP (Eur Ph), and USP) for an active ingredient as stated in the active ingredient specification and/or formulation table in the Product Data Sheet.

Note: there is no need to advise of an updated monograph of BP, EP or USP in the case that reference is made to the 'current edition' in the dossier and Product Data Sheet.

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

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

(2) Provide:

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

7.3.3 Change in name of the active ingredient(s)

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

(1) Submit a C9 variation.

(2) Provide:

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

7.4 Changes to approved excipient ingredient(s)

7.4.1 Adding, deleting, changing an MPI -recognised pharmacopoeial standard

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

Note: there is no need to advise of an updated monograph of BP, EP or USP in the case that reference is made to the 'current edition' in the dossier and Product Data Sheet.

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

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

(2) Provide:

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

7.4.2 Change in name of an excipient(s)

Self-assessable change. The active excipient's chemical identity must remain the same, and there must be no other change to the information previously supplied for that ingredient.

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

(2) Provide:

Declaration of self-assessable change made in covering letter/email
Amended Product Data Sheet and label
Proof of acceptance by WHO or a copy of the INN list

7.5 Changes to approved formulated product manufacturer(s)

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
Details of the proposed manufacturing site(s): • name of organisation • postal address • 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 6.6 (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 6.6.2 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 data is not yet available, a validation protocol may be accepted with a conditional requirement that validation data will be provided post-approval
Batch analysis data from three (minimum at least pilot) scale batches of TNP from the proposed manufacturer. (Refer to 6.8.1) 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 any portion of the manufacturing process at the new site differs from that currently approved for the product, outline and appropriately with an explanation of the differences and reason for the change with reference to the process validation data to support the changes
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 repackers and relabellers

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

(2) Provide:

Amended Product Data Sheet
Details of the proposed repacker/relabelling site(s): • name of organisation • postal address • 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
Provide data and/or other information to confirm that the proposed repacker or relabeller will use materials identical or equivalent to those used by the currently approved manufacturer responsible for packaging

7.5.3 Addition of or changes to 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
Details of the proposed QC testing site(s): • name of organisation • postal address • physical address • site telephone number and/or email address (to enable MPI to quickly contact the site if necessary)
GMP certificate, or 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

7.5.4 Removal of formulated product manufacturer/ repacker/ relabeller/ QC testing site (where 2 or more of that type of site is approved)

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

Note: You cannot remove the sole primary final product manufacturer and/or sole QC testing site and have no listed final product manufacturer for a Trade Name Product as a self-assessable change.

(1) Provide:

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

7.6 Changes to manufacturing process and quality control

7.6.1 Change to manufacturing process and/or quality control

(1) Submit a variation application if it is proposed to change the details of the currently approved manufacturing process or any quality control procedures. This includes changes to any point of the manufacturing process itself, in-process critical control points and/or analytical methods, equipment used, 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 validation data has not been generated 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.

Information expected in a manufacturing process validation protocol and subsequent report can be found in section 6.6.4.

(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
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

If the change is a tightening of the currently approved range (i.e. within the limits of the currently approved lower and upper bounds).

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

(1) Provide:

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

7.7 Changes to finished product specification or test methods

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

(2) Provide:

Amended Product Data Sheet
Reason for the proposed change
Current release / expiry specification table and proposed release / expiry specification table, with differences highlighted
For changes to analytical test methods, 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
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
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, 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, if the smallest approved 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 suspension formulations, provide information to support the 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 to manage the stability of the product in the market)
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 where 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)

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

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

(1) Provide:

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

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
Stability data from real time and/or accelerated stability studies conducted on at least three preferably production scale, or at a minimum pilot scale (e.g. greater than 10% production scale) batches of product

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 6.10 of this guidance
Amended Product Data Sheet and label

7.9.3 Shortening of the currently approved shelf life

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

(1) 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 substance containing an active ingredient, typically derived from bacteria or fungi, which has the capacity to kill or inhibit the growth and reproduction of micro-organisms. The term "antibiotic" usually refers to substances intended to kill or inhibit bacteria.
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 substance, chemical, or substance used to kill or inhibit the growth and reproduction of micro-organisms. Substances that are considered antimicrobials include surface disinfectants, antibiotics, parasiticides, anti-fungal and anti-viral agents.
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	A substance administered to kill or inhibit the growth and reproduction of protozoal parasites.
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.
Vaccine	A suspension of attenuated live or killed micro-organisms (bacteria, viruses, or rickettsiae) administered for prevention, amelioration or treatment of infectious diseases.
Other	Please specify.

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 topical 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	Please specify.

Appendix 3: Expected Release and Expiry 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 at Release	Parameter at Expiry
Aerosols (pressurised pharmaceutical preparations)	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
	Preservative content (where appropriate)	Preservative content (where 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	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
	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
	Dissolution profile (where appropriate)	Optional with justification
Collars	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities

Product Type	Parameter at Release	Parameter at Expiry
	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 Dissolution profile (release of active constituent from the inert matrix)	Optional with justification
Controlled release devices	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, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Water dispersibility	Optional with justification
	Suspendability	Optional with justification
	Wet sieve (suspensions)	Optional with justification
	Persistent foam	Optional with justification
Emulsions	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
	Homogeneity (extent of separation, ease of reconstitution)	Optional with justification
	Preservative content (where appropriate)	Preservative content (where appropriate)
	pH	Optional with justification
	Viscosity	Optional with justification
	Effect of freezing	Optional with justification
Granules	Description	Description

Product Type	Parameter at Release	Parameter at Expiry
	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
	Particle size distribution / dustiness	Optional with justification
	Moisture content	Optional with justification
	Dissolution profile (where 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	
	Hardness	
	Friability	
	Moisture content (where appropriate)	
	Dissolution profile (release of the active constituent	
Intramammary medicines	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 (where appropriate)	Optional with justification
	Effects of freezing	Optional with justification
Medicated shampoos	Description	Description

Product Type	Parameter at Release	Parameter at Expiry
	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 (where appropriate)	Optional with justification
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, 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
	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)
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)

Product Type	Parameter at Release	Parameter at Expiry
	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 (where appropriate)	Resuspensibility (where appropriate)
	Redispersibility	Redispersibility
	Reconstitution time	Reconstitution time
	Related substances (antibiotics)	Related substances (antibiotics)
	Syringeability	
	Effects of freezing	
	Interactions with closure (some containers in the inverted position)	
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, 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
	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 (where appropriate)	Moisture content (where appropriate)
Powders for injection	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent

Product Type	Parameter at Release	Parameter at Expiry
	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 (where appropriate)	Moisture content (where appropriate)
	pH value for reconstituted solution	pH value for reconstituted solution
	Completeness of solution or dispersion	Completeness of solution or dispersion
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 for 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 (where applicable)	Antimicrobial preservative content (where applicable)
	Antioxidant preservative content (where applicable)	Antioxidant preservative content (where applicable)

Product Type	Parameter at Release	Parameter at 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, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, 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, physical dimensions)	Physicochemical (e.g. colour, appearance, clarity, odour, specific gravity, physical dimensions)
	Residual solvent (if used during manufacture)	Residual solvent (if used during manufacture)
	Degradation products	Degradation products
	Sterility (where appropriate)	Sterility (where appropriate)
	pH	pH
	Preservative efficacy (where appropriate)	Preservative efficacy (where appropriate)
	Viscosity (where appropriate)	Viscosity (where 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
Suspensions	Description	Description
	Identification	Identification
	Assay of active constituent	Assay of active constituent
	Impurities	Impurities

Product Type	Parameter at Release	Parameter at Expiry
	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)	Physicochemical (e.g. colour, appearance, odour, specific gravity, physical dimensions)
	Degradation products	Degradation products
	Sterility (where appropriate)	Sterility (where appropriate)
	pH	pH
	Resuspensibility	Resuspensibility
	Viscosity (where appropriate)	Viscosity (where appropriate)
	Particle size (where appropriate)	Particle size (where appropriate)
	Effects of freezing	Effects of freezing
Topical and ophthalmic medicines (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 (lotions)	Resuspendibility (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 (for applicant's use)

Guidance Doc Reference	Description	For Applicant's Use
6.1	**Product details**	
	Product type	
	Formulation type	
	Pharmaceutical development summary	
6.2	**Formulation of the TNP**	
	Composition table (Q/QF)	
	Active ingredient potency calculation (where applicable)	
	Overages (storage)	
6.3	**Active ingredient(s)**	
	Identification	
	Specification	
	Impurities	
	Batch analyses x3	
	Analytical test methods and validation data	
6.4	**Active ingredient manufacturer(s)**	
	Identity and details	
	GMP for sterile actives	
6.5	**Excipients**	
	Identity	
	Standard	
	Batch analysis x 1	
	Impurities (if applicable)	
	Ingredients of biological origin must have current Biosecurity approval/ conform to IHS	
6.6	**Formulated product manufacturers**	
	Identity, details and scope	
	GMP	
	Manufacturing process	
	Batch formulation table	
	In-process quality control testing	
	Manufacturing process validation – preferably report, at minimum protocol	
6.7	**Finished product specification**	
	Fitness for purpose rationale	
	Release specification	

Guidance Doc Reference	Description	For Applicant's Use
	Expiry specification	
6.8	**Formulated product batch analyses x3**	
6.9	**Packaging specifications**	
	Primary container and closure system	
	Secondary packaging	
	Product specific administration device/attachment specifications	
	Recycled packaging (where applicable)	
6.10	**Stability – shelf life**	
	Proposed shelf life	
	Proposed storage conditions	
	Batch selection	
	Pack size/type	
	Storage conditions	
	Testing frequency/ time points	
	Analytical test methods and validation	
	Discussion of stability study results	
	Stability commitment	
6.11	**Stability – In Use** Multi-dose products	
6.12	**Stability – In Use** In Feed and/or In Water products	