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Proposed changes to the existing guidance:

- Added text is highlighted in yellow
- Deleted text is marked in grey with a strikeout

Chemistry and manufacture of veterinary active constituents (Part 2)

1. Introduction

All veterinary actives must be approved before they can be used in the manufacture of a registered veterinary product unless they have been specifically exempted from approval (as listed on Active constituents exempt from the requirements of APVMA approval for use in agricultural or veterinary chemical products, for example bentonite, pyrethrins and sulfur).

This is a guidance document about the types of information you may submit to address the safety criteria for veterinary active constituents and information that you must submit as stated in the Agvet Code Act and or the Regulations. The information that you must submit is indicated throughout this guidance document along with the relevant section of the Agvet Code or Regulation.

This guideline does not apply to immunobiologicals. The chemistry and manufacturing data that should be provided for immunobiological actives can be found on the Guideline for the registration of new veterinary vaccines

The APVMA has adopted the quality guidelines of International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH (link is external)), with certain variances to reflect particular Australian requirements. Where the VICH guideline specifies that it is for new veterinary drugs substances (active constituents), such as VICH GL10(R) and GL39, we consider that it should be applicable to all veterinary active constituent applications.

You should provide a valid scientifically based justification for any deviation from the VICH guidelines.

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The APVMA will also consider data that has been submitted to other regulatory authorities and associated assessment reports. If you are going to submit such data packages and/or assessments you should consider our *Guidance for applicants – submission of international data, standards and assessments*.

For further guidance on submitting chemistry and manufacturing data in support of active constituent approval you may also wish to view the guidance for industry documents for active constituent (drug substance) submissions available from the websites of:

- the US Food and Drug Administration, Center for Veterinary Medicine (link is external)
- the veterinary medicines area of the European Medicines Agency (link is external)
- the Veterinary Drugs Directorate (link is external) of Health Canada.

This document attempts to clarify some ambiguities regarding what you may provide and what information you must provide to address and satisfy specific aspects of the Agvet Code and Regulations.

If after reading this document you are unsure as to the information that you may provide to support your application it is recommended that you request Pre-Application Assistance to obtain clarification of any points you may have.

Applications for a new source of an already approved active may qualify for reduced data requirements as outlined in section 11.

2. Identification of the active constituent

You should provide details of the nomenclature, structure, identity and general properties of the new or existing active constituent.

2.1. Common name (Must provide)

(Agvet Regulation Subdivision 2.1.3, Regulation 15)

You should nominate the common names for new active constituents. ~~The preferred common name will be the name specified in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). If the active constituent is not listed in the SUSMP~~

Suitable common names may be found in the following compendia:

- World Health Organization—International Non-proprietary Names (INNs)
- Therapeutic Goods Administration—Approved terminology for medicines—Chapter 1—Australian Approved Names (AANs) for therapeutic substances
- Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)
- British Pharmacopoeia (BP)
- British Pharmaceutical Codex
- Australian Pharmaceutical Formulary and Handbook
- British Pharmacopoeia (Veterinary) (BP (Vet))
- European Pharmacopoeia (Ph. Eur.)
- United States Pharmacopoeia (USP)
- Chemical Abstracts Services (CAS)

If no common name has been established you may submit:

- The name established by the International Union of Pure and Applied Chemistry (IUPAC)
- The name descriptive of the true nature and origin of the constituent.

There are some actives that may also be used as pesticides (e.g. abamectin, piperonyl butoxide) and the suitable common names may be available from

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- Standards Australia (AS 1719-1994: Recommended common names for pesticides),
- International Organization for Standardization (ISO) standard for pesticide common names (ISO 1750:1981),
- British Standards Institution (BSI) common names for pesticides

A trademark or trade name cannot be used as an approved name of an active constituent.

2.2. Chemical name (Must provide)

(Agvet Regulation Subdivision 2.1.3, Regulation 15)

The full chemical name, in accordance with the International Union of Pure and Applied Chemistry (IUPAC) must be provided and the Chemical Abstracts Services (CAS) nomenclature, should be provided.

~~You should include all accepted and proposed non-proprietary names for the active constituent – for example, the International non-proprietary name (INN), United States adopted name (USAN), British approved name (BAN) – along with the names of the approving authorities.~~

2.3. Chemical Abstracts Service registry number (CAS RN)

You should provide the Chemical Abstracts Service (CAS) number of the active constituent. If the CAS number has not been allocated, state 'Not yet allocated'.

2.4. Manufacturer's code numbers and synonyms

Manufacturer or laboratory code numbers and synonyms should be provided.

2.5. Molecular and structural formula and molecular mass

You should provide the molecular formula, molecular mass and structural formula of the active constituent. For active constituents existing as salts or hydrates, you should also provide the molecular mass of the free base/acid or anhydrous form. For polymeric compounds, you should provide the molar mass distribution in the form of the mass average molar mass (Mm) and number average molar mass (Mn).

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

2.6. Elucidation of structure and other characteristics

You should provide confirmation of the chemical structure of the active constituent. The elucidation of structure should be based on appropriate physical and chemical test results. This may include:

For actives that comply with a recognised pharmacopoeial standard this may include:

- The identity tests specified in the pharmacopoeial standard

For all other actives this may include:

- a description of the synthetic route as evidence of structure
- an elemental analysis with theoretical values
- a discussion on ultraviolet (UV) spectroscopic characteristics, including pH dependence shifts
- infrared (IR) spectrometry
- ^{1}H, ^{13}C, ^{19}F or ^{31}P nuclear magnetic resonance (NMR) spectrometry

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- mass spectrometry (MS)
- any other relevant information to confirm the structure (for example, X-ray diffraction).

3. Physical and chemical properties

You should provide all relevant physical and chemical properties of the active constituent. The information should include the purity of the substance used to generate the data. The information should include, as appropriate:

- purity (or information sufficient to determine the purity)
- composition (or information sufficient to determine the composition)
- a general description (for example, appearance, colour, odour and physical state)
- when a new active constituent contains one or more chiral centres, whether the active is a pure enantiomer, racemate or fixed combination of non-enantiomeric isomers
- specific optical rotation
- melting point (for solids)
- boiling point (for liquids)
- condensation point (for gases)
- refractive index (for liquids)
- density/specific gravity (for liquids)
- UV absorption maxima and molar absorptivity
- pH and/or pKa values
- solubilities in common solvents
- n-octanol/water partition coefficient (P_{ow}or log P_{ow})
- dissociation constant, if appropriate
- if the active constituent can exist in more than one physical form (for example, polymorph, solvate or hydrate), information for the form (or forms) of the constituent that will be used in the manufacture of the product
- particle size distribution (including nanoscale particles).

A nanomaterial is any substance intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale—that is, in a size range typically between 1 nm (nanometre) and 100 nm—and that is either a nano-object (that is, confined in one, two, or three dimensions at the nanoscale) or a nanostructure (having an internal or surface structure at the nanoscale).

Aggregates and agglomerates are considered to be nanostructured substances. Where size distribution shows that, by number of particles, 10 per cent or more of a substance is at the nanoscale, the substance will be considered a nanomaterial for risk assessment purposes.

To allow us to identify and assess the potential risks of nanomaterials, you should provide the following characteristics and physical chemical properties:

- purity (or information sufficient to determine the purity)
- composition (or information sufficient to determine the composition)
- identity
- morphology
- structural integrity
- catalytic or photocatalytic activity
- particle size/size distribution
- electrical/mechanical/optical properties
- surface-to-volume ratio
- chemical reactivity
- surface area/chemistry/charge/structure/shape
- water solubility/dispersibility

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- agglomeration/aggregation (or other properties)

Definitions of purity and composition
Purity: the amount of the active substance as a per cent or in grams per kilogram expressed on a dry weight basis.
Composition: the amount of related impurities present in the active constituent

- These impurities are either pre-cursor chemicals that were not fully consumed in the manufacture process and are in excess.
- Or are a product of side chemical reactions that took place during the primary synthesis of the main compound.
- Or the impurities are present in the pre-cursor chemicals used in the synthesis of the active constituent.

Appropriate description of all methods used for determining the characteristics as listed above should be provided so the APVMA can have confidence in the results obtained (references to compendial methods such as OECD, US EPA OPPTS, CIPAC, BP, USP, Ph.Eur., etc. where these were used, are acceptable in lieu of method descriptions).

The combined information provides clarification of specific aspects of the Agvet Code such as safety, toxicity, composition of degradation products and impurities.

4. Stability data (relates to Regulation 15(1)(d))

You should provide stability data to demonstrate the inherent stability of the active constituent. The content of the active constituent, any degradation products including toxicologically significant impurities and other critical characteristics should be monitored initially and at sufficient sampling frequency during storage that provides an accurate stability profile of the active constituent. It is this information that we will use to determine the appropriate composition and purity of the active constituent over the retest interval to determine the safety criteria as required by the Agvet Code section 5A.

The results of stability studies (long-term, accelerated, and under various conditions of stress such as heat, light, humidity, acid/base hydrolysis and oxidation) should be provided. You should propose a suitable re-test period based on the stability of the active constituent in an Australian climate. Australia has climatic conditions encompassing VICH zones I to IV. VICH GL3(R) (link is external),GL5 (link is external), GL10(R) (link is external), GL18(R) (link is external), GL39 (link is external), GL45 (link is external) and GL51 (link is external) provide information on stability design and testing protocols and data evaluation.

The stability data provides clarification of specific aspects of the Agvet Code such as section 5A and Regulation 15(1)(d).

You should also demonstrate the nanoscale stability properties of the active constituent, if relevant.

5. Method of manufacture of the active constituent

5.1. Manufacturer and site of manufacture (Must provide)

(Agvet Regulation Subdivision 2.1.3, Regulation 15(e)(f)

You must provide the name and business address of the manufacturer or manufacturers of the active constituent and the street address of the manufacturing plant(s) in which the active constituent is manufactured or is to be manufactured. If a toll or contract manufacturer is involved, their details must also be provided along with the step or steps of manufacture that the toll manufacturer undertakes in the manufacturing process.

If the active constituent is to be manufactured at multiple sites, with the same manufacturing process and to the same specification (composition and purity), you have the option of either submitting subsequent

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Item 17 applications referring to the file and application numbers of the primary application submitted, or requesting multiple site approvals under the one file and application number, depending on whether you wish to have a single approval covering all sites or an approval for each individual site. You are not required to submit the full data package again, only batch analysis results for each site.

Note: With regard to those approvals of an Active with multiple manufacture sites listed, if a compliance issue results in a cancelation, then all sites listed on that single approval number may also be cancelled (depending on the issue).

5.2. Description of the manufacturing process (Must provide for new active approvals) (Agvet Code 5A(2)(a)(ii)

5.2.1. Active constituents produced by chemical synthesis

You should provide a detailed description of the manufacturing process to allow us to establish that the process is capable of delivering a known quality active constituent in a process in which each step of the manufacturing is appropriately controlled and the active constituent meets all quality attributes set out by the manufacturer, including release specifications. The batch size (for example, in litres or kilograms) and scale (pilot or production) should be stated. You should provide full details of the quality control procedures that ensure batch-to-batch consistency of the active constituent. You should describe the in-process quality control checks performed at various stages of the manufacture, purification and packaging of the active constituent; testing should include the specifications and tests for pivotal and key/critical intermediates. It is this information that we will use to determine the appropriate composition and purity of the active constituent as required by Regulation 15(1)(d).

An example of an appropriate description of the manufacturing process will usually include:

- an introductory paragraph detailing the number of chemical steps, whether the process is a batch or continuous process, and significant purification steps
- a detailed description and flow diagram of the synthetic processes, including molecular formulae, chemical structures of starting materials, intermediates, reagents and chemical equations of the reactions involved, reflecting stereochemistry, and in-process quality control steps
- the relative amounts of each starting material and their order of addition
- reaction conditions (for example, temperature, pressure, pH and reaction times) and the duration and yield of each step of the process
- information on intermediates that are isolated and purified
- information on any catalysts used in the manufacturing process
- if a manufacturing concentrate is produced, details of the final concentration of the active constituent present, methods used to confirm the concentration, and details of the diluents and/or any additives used.

You should describe the nanoscale processes of the active constituent manufacturing process, if relevant.

5.2.2. Active constituents produced by fermentation

The information about an active constituent produced by fermentation should describe the fermentation process in detail, including:

- the source and strain of microorganism used in the fermentation process
- strain improvement procedures
- purity and stability checks
- cell banking arrangements
- storage
- propagation seeding procedures
- whether or not the microorganism has been deposited in a recognised culture collection, such as the American Type Culture Collection (link is external), the United States Department of Agriculture (link is external) or the World Federation for Culture Collections (link is external)
- the composition of the media and details of how the reaction conditions are controlled (for example, times, temperatures, pH, rates of aeration, and name and composition of preservatives)

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- a detailed description of the isolation and purification procedure for the active constituent, including in-process controls used to ensure freedom from potentially pathogenic agents, such as viruses and prions.

5.2.3. Semisynthetic active constituents derived from fermentation

If the starting material for a semisynthetic antibiotic is obtained by fermentation, the description of the starting material should be provided as detailed under section 5.2.2 (above). The information for the synthesis of the final active constituent from the starting material should be provided as described under section 5.2.1 (above).

5.2.4. Feed-grade active constituents produced from fermentation

Feed-grade active constituents are permitted as components of feed – additive drug premixes, which are used in the manufacture of medicated feeds. The feed-grade active constituent is usually derived from fermentation and is marketed as an unpurified or partially purified product. It commonly contains a large percentage of carbohydrates, amino acids, fatty acids and nucleotides, but it may also contain small amounts of toxic components that are not readily isolated or identified.

For this reason, the microbial fermentation should be described in detail, including specifications for all components of the media and all procedures and precautions employed to prevent contamination or abnormal fermentation. You should include a description of all in-process tests used to determine quality and yield.

5.2.5. Active constituents of plant origin

For an active constituent of plant origin, you should give full details of the manufacturing procedure (such as extraction and purification) of the constituent. Your submission should also include:

- a description of the botanical species and the part of the plant used (such as leaf, flower or root)
- the geographical origin and, where relevant, the time of the year harvested

If they are known, you should record the nature of chemical fertilisers, pesticides, fungicides and other agents used during cultivation. It may be appropriate to include limits for pesticide residues resulting from such treatments in the active constituent specifications. The absence of toxic heavy metals should also be confirmed.

Seasonal variabilities in plants and hence the composition of plant extracts needs to be considered, and as a result it is recommended that the batch analysis data covers plant extracts generated from plants harvested over multiple seasons (see section 7 below for further details).

5.2.6. Sterile active constituents

For sterile active constituents, the sterilisation process should be described in detail and appropriate parameters for microbial quality (i.e. sterility) included in the release specifications.

5.3. Quality control

You should provide the following information on the measures taken to assure the quality of the active constituent:

- control of all raw materials
- tests and acceptance criteria performed at critical steps of the manufacturing process to demonstrate that the process is controlled
- in-process quality control of intermediates and operations

5.4. Animal-sourced material

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For starting materials of animal origin used in the manufacture of the active constituent, you should provide information on:

- biological sources
- country of origin
- manufacturer
- specifications

You should also provide evidence that the material is free of bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathies (TSEs).

For information about importing biological agents, refer to the Department of Agriculture and Water Resources (link is external)website.

5.5. Genetically modified organisms

For starting materials that consist of, or contain genetically modified organisms (GMOs), the APVMA seeks advice from the Office of the Gene Technology Regulator (OGTR). For approval of a GMO, you should also refer to OGTR guidelines on data for a risk analysis relating to the use of the GMO.

6. Active constituent specification

A specification is a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active constituent should conform. You should provide active constituent specifications to allow the APVMA to assess whether the constituent is of an acceptable quality for its intended use.

If a relevant pharmacopoeial or APVMA standard exists, the active constituent should comply with the current monograph or standard. If a pharmacopoeial standard is not available, you should provide a manufacturer's specification. VICH GL39 (link is external)and GL40 (link is external) provide test procedures and acceptance criteria for active constituents, raw materials and excipients. The tests and limits in the manufacturer's specification for an active constituent should include the universal and specific tests described in VICH GL39 (as appropriate). You should consider inclusion of limits for impurities according to VICH GL10(R) (link is external) and GL40 (link is external) and residual solvents according to VICH GL18(R) (link is external).

For actives of plant origin; specification of the main components will generally suffice (see section 7 below).

The nanoscale properties of the active constituent, if relevant, should be incorporated into the active constituent specification.

7. Batch analysis data

You should provide batch analysis data to allow us to validate the processes (manufacturing and quality control) and determine whether the active constituent is manufactured consistently to meet the proposed quality standard. The data should include test results for all parameters listed in the 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) (link is external). You should consider the presence of impurities according to VICH GL10(R) (link is external), GL39 (link is external) and GL18(R) (link is external).

The results should include:

- batch size, batch number, date of manufacture and date of analysis

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- analytical determinations (for quantitative tests, such as active constituent contents, individual and total impurities, provide the actual numerical results rather than imprecise statements such as ‘within limits’ or ‘conforms’)
- information on the analytical procedures used to generate the data, and validation of those procedures
- where applicable, chromatograms of the batches, showing the separation of impurities (chromatograms should be clearly labelled with batch numbers, peak identity, peak integration data and X and Y axis labels and scales)a copy of all raw data used to generate the final results.
- raw data used to generate the final results must be available on request. ~~a copy of all raw data used to generate the final results.~~

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

As introduced in section 5.2.5 above in relation to plant extract actives, seasonal variation occurs with plants. It is recommended that at least 5 batches spanning at least 3 years be provided to provide a reasonable understanding of the variation of individual components that may be present and a valid base in which to base the limits of related compounds.
Normalisation of the chromatograms can be undertaken to gain an upper and lower concentration variation of the components present. As actives derived from a plant origin are expected to have a significant number of components equal to or greater than 1g/kg it is reasonable to characterise the main components. It is recommended that you apply for Pre Application Assistance to clarify any questions that may arise regarding information that is required prior to generating this information.

If there is a pharmacopoeia standard for the plant origin active, then it should comply with all aspects as stated in that international standard.

You should demonstrate the nanoscale properties of the active constituent, if relevant.

8. Analytical methods and validation data

You should provide analytical methods and validation data to allow us to assess the quality and adequacy of the control processes. Compendial methods, such as those found in the European, United States and Japanese pharmacopoeia, should be used where applicable. You should provide a full description of the analytical procedures used for the testing of the product, including:

- full details of the analytical methods (including method numbers)
- the purity of the reference standards or Certified Reference Material (CRM) along with the Certificate of Analysis for the CRM
- where chromatographic (such as HPLC or GLC) and spectroscopic (such as NMR or FTIR) techniques are used, representative chromatograms and spectra of the reference standard, veterinary chemical product and placebo (labelled with batch number, peak identity and peak integration data, if appropriate)
- worked examples of the calculations

You should provide method validation data to allow us to assess the suitability of the method for its intended use. Typical analytical validation methodologies and characteristics are provided in VICH GL1 (link is external)and GL2 (link is external).

You should describe the nanoscale aspects of the active constituent analytical methods, if relevant.

9. Analytical reference standards

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If you are applying for approval of new active constituents, you should provide the following samples to the Australian Government National Measurement Institute (NMI) (Agvet Code section 157 and section 169):

- 1 gram of analytical reference standard of each pure active constituent or, if the active constituent is a mixture of major isomers that can be separated, 1 gram of each isomer
- 100 grams of the active constituent as manufactured (the percentage purity and the method used to determine purity should be provided)

  You may provide justification that you should supply less than 1 gram analytical reference standard and/or less than 100 grams of active constituent as manufactured. We will consider your argument on its merits.
- 10 mg of analytical reference standards for the toxicologically significant impurities present in the active constituent
- 100 mg of analytical standard for all metabolites identified and for which a maximum residue limit (MRL) applies (metabolites included in the residue definition for enforcement).

You should also submit storage instructions and information on the shelf life of the analytical reference standard and active constituent, especially if degradation is likely to occur during transport or storage.

If those amounts of material are excessive please discuss this with the APVMA to negotiate an appropriate amount of material to be provided.

The samples should be sent to:

National Measurement Institute
105 Delhi Road, North Ryde NSW 2113, Australia
PO Box 138, North Ryde NSW 1670, Australia
Phone: (02) 9449 0111
Fax: (02) 9449 1653
Email: info@measurement.gov.au (link sends e-mail)

Samples should be accompanied by a letter stating:

- the reason for submitting the samples
- the purity of the materials supplied, with the certificate of analysis
- storage instructions
- acute oral and dermal toxicities of the materials, or the appropriate safety data sheet (SDS)
- where the samples are regarded as commercial in confidence material, it is recommended that you include this information when providing your documentation. It is not uncommon to enter into a confidentiality agreement with the NMI prior to submitting any reference material. It is recommended that you contact the NMI to discuss any concerns you may have.

Take care to ensure that samples are properly packed. Samples that arrive leaking or otherwise damaged will be destroyed and replacement samples will be requested.

Samples should be provided to the NMI before approval of a new active constituent. When standards are supplied to the NMI, documentation to that effect should be forwarded to the APVMA.

From time to time, the APVMA may request replacements for some or all of the above samples to maintain the inventory.

> Note: The National Measurement Institute (NMI) store and maintain the physical storage of these chemical materials. They are used as required by the APVMA, and by the National Residues Survey (NRS) to monitor residue levels in food producing crops and animals. The NRS may contract out the analytical testing when undertaking residues testing. These reference material will not be released to any other party for any other use. The APVMA may use these materials when undertaking testing as we see fit.

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10. Packaging

The packaging or storage/shipping containers should be appropriate for the characteristics of the active constituent. You should provide a description of the packaging materials used for the active constituent and information about the corrosive effect, if any, of the active constituent on the packaging materials. This information is not required if the active constituent is formulated into a product at the site of manufacture.

11. Reduced data for existing actives (new source)

Data requirements for new sources of existing actives may be reduced to following requirements listed below only where there are no limitations on the use of the information associated with existing actives.

All applications for new sources of active will require the following information (Agvet Regulation Subdivision 2.1.3, Regulation 15):

- Identity – common name
- Identity – chemical name (IUPAC name)
- Composition and purity (as included in requirements described below)
- Name and address of the manufacturer of the active constituent

11.1. New source of an existing active that meets (or exceeds) the requirements of a recognised pharmacopoeial standard

Application to approve a new source of an already approved active may qualify for reduced data requirements if:

- the active is listed in the BP, EP or the USP and
- the active complies to all aspects of the relevant pharmacopoeial standard

If this is the case then you are required to submit three (3) certificates of analysis (COA) that demonstrate compliance with the relevant pharmacopoeial standard.

Alternatively you may submit a certificate of suitability to the European monograph (CEP) as granted by the European Directorate for the Quality of Medicines (EDQM).

11.2 New source of an existing active that does not comply with a pharmacopoeial standard

Applications to approve a new source of an already approved active that does not comply with a pharmacopoeial standard published for that active.

- the active is listed in the BP, EP or the USP and
- the active does not comply to all aspects of the relevant pharmacopoeial standard

As this active does not comply with a published standard in the BP, EP or USP, it cannot be classified as being manufactured to that standard. You are required to provide data/argument to support the approval of that the proposed site of manufacture.
Note that a non-compendial standard may not be suitable for specific types of veterinary products, such as injections or oral medications such as tablets, although such a standard might be appropriate for products such as feed premixes.

The following data points will need to be addressed by data or scientific argument:

- 2. Identification of the active constituent
- 5. Method of manufacture of the active constituent
- 6. Active constituent specification

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- 7. Batch analysis data/certificates of analysis for three batches
- 8. Analytical methods and validation data

11.3 New source of an existing active where there is no pharmacopoeial standard

Applications to approve a new source of an already approved active where there is no pharmacopoeial standard published for that active in the BP, EP or the USP.
You are required to provide data/argument to support the approval of the proposed site of manufacture.

The following data points will need to be addressed by data or scientific argument:

- 2. Identification of the active constituent
- 5. Method of manufacture of the active constituent
- 6. Active constituent specification
- 7. Batch analysis data/certificates of analysis for three batches
- 8. Analytical methods and validation data

Scientific argument used to support applications under sections 11.2 may include, for example, documentation of particular points of difference where the active does not comply with a particular pharmacopoeial standard with reasoning provided as to why these differences would not affect the safety, stability or efficacy of the active constituent.