Ministry for Primary Industries
Manatū Ahu Matua

Guidance Document

Equivalence of Veterinary Medicine Trade Name Products

Providing equivalence information to support an application for registration under the ACVM Act

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Title

Guidance Document: Equivalence of Veterinary Medicine Trade Name Products

About this document

This document explains the minimum information needed for MPI to consider equivalence to a reference product in support of an application to register a veterinary medicine trade name product under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

Related Requirements

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

Document history

Version Date	Section Changed	Change(s) Description
11 July 2018	New document	This document replaces ACVM Standard and Guideline for Therapeutic Equivalence of Trade Name Products.
29 May 2024		Includes information requirements for intramammary products, updates to external document links and editorial changes to improve readability of content.

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1 Purpose

This document explains the minimum information needed to support the equivalence of test and reference veterinary medicines under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997. Demonstration of equivalence enables cross reference of efficacy data held for the reference product.

This document provides guidance for:

a) the design, conduct and analysis of bioequivalence studies; and
b) dosage forms for which demonstrating pharmaceutical equivalence may be sufficient to confirm equivalence to a reference product.

This document is applicable to chemical pharmaceutical products. Equivalence cannot be used to obtain registration for vaccines and other immunobiologicals.

2 Background

Before being imported, manufactured, sold or used in New Zealand, agricultural compounds and veterinary medicines (ACVMs) must be authorised under the ACVM Act. Authorisation is required:

a) to manage risks to trade in primary produce, public health, animal welfare, and agricultural security; and
b) to make sure that the use of ACVMs does not result in breaches of domestic food residue standards; and
c) to ensure the provision of sufficient consumer information.

Authorisation of veterinary medicines usually takes the form of product registration. To register a veterinary medicine trade named product (TNP), sufficient information must be provided to enable MPI to evaluate your estimates of all the risks under the Act posed by the use of your product. There are two ways to provide the required information in your application for registration:

d) You can generate efficacy, target animal safety and residue data for your product. These data are then submitted with your risk analysis which clearly identifies risks posed by your product under the ACVM Act and how these are managed or mitigated. This guidance document is not relevant if you choose this option.
e) You can base your risk analysis on information/data that is already held by MPI for a similar product registered under the ACVM Act. This is known as cross-referencing. This option requires you to provide a robust case demonstrating that your test product is equivalent to the reference product (or products) you have specified. This may be relevant for a new product registration that is similar to an existing registration, or where a change to the formulation of an existing registered product necessitates demonstration of equivalence between the approved and new formulations. If you nominate more than one reference product, you must provide a case for equivalence for each reference product and your test product.

   Data and information held by MPI for the reference product that is confidential and protected under provisions of the ACVM Act may not be cross-referenced until either:

   i) expiry of the protected period; or
   ii) provision of appropriate authority from the registrant of the reference product.

3 Definitions and abbreviations

API means active pharmaceutical ingredient

AUC means area under the curve of plasma drug concentration against time

bioavailability means the rate and extent of absorption into the systemic circulation of active ingredient(s) or active metabolites of a trade name product. The rate and extent of absorption are typically measured by the C_{max} (peak concentration) and AUC (area under the curve), respectively

biobatch means the batch or batches of test product used in a bioequivalence study

bioequivalence: two veterinary medicine trade name products (TNP) are bioequivalent when the rate and extent of absorption of the same molar dose of the active ingredient(s) or therapeutic moiety as determined by comparison of measured parameters (e.g. active concentration in blood or pharmacological effect) is demonstrated to be similar (within predefined acceptable limits), when administered under similar experimental conditions

Biopharmaceutics Classification System (BCS) means a scientific system utilised in human pharmaceutics for classifying active ingredients based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the active ingredient the BCS may be used to predict intestinal absorption as it takes into account three major factors that govern the rate and extent of absorption from immediate release solid oral dosage forms: dissolution, solubility, and intestinal permeability. The BCS classifies substances as follows:

Class 1: High Solubility – High Permeability
Class 2: Low Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

chemical equivalence: trade name products are considered to be chemically equivalent if the quantity and quality and source of formulation ingredients are the same -- the final product is formulated at the same manufacturing plant using the same manufacturing procedures, equipment and quality controls, and packaged in the same container material(s). For such products the only difference is the trade name. Therefore, chemically equivalent products are deemed to be identical products with respect to their ACVM Act relevant risk profiles

closely similar products means similar trade name products that also contain non-active ingredients that are the same or equivalent at the same or equivalent concentrations or, if non-active ingredients are not the same or equivalent, that differences are minor and will not affect product quality or biological activity, and the product specifications and physicochemical properties are the same or equivalent or, if different, will not adversely affect product quality or biological activity

C_{max} means maximum plasma concentration of an ingredient in a pharmacokinetic study

Good Laboratory Practice (GLP) means an international quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported

immediate release dosage forms means drug forms for which the release of the active ingredient(s) is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid pharmaceutical form, the dissolution profile of the active substance depends essentially on its intrinsic properties

pharmaceutical equivalence: two trade name products are pharmaceutical equivalents if they contain the same active ingredient(s) manufactured to meet the same or comparable compendial standards, and are of the same dosage form and administered via the same route, and are identical in active concentration or strength

pharmaceutical alternative means two trade name products that contain the same active moiety but that may differ in chemical form (i.e. salt, ester etc.) of that active compound or in dosage form (capsule, tablet, oral suspension) or strength

reference product means a trade name product nominated by the applicant with which the 'test' product is compared

similar products means trade name products that contain the same API(s) at the same concentration, are administered in the same dosage form using the same formulation type, at the same dose rate, to the same target animal, for the same clinical indications. The non-active ingredients in the formulation are likely to have similar properties and be present in similar proportions as the reference product

simple aqueous solution means a solution that contains the active ingredient(s), water, buffers, preservatives, colouring or flavouring agents, and no other types of constituents. A simple aqueous solution can be further defined as a homogenous mix in which the solute is in molecular dimensions. Simple aqueous solutions do not include emulsions or suspensions

same active ingredient: for two active ingredients to be considered the same, they must contain the same salt, ester, ether, isomer, mixture of isomers, complex or derivative of the active substance

test product means the product for which equivalence is sought to be proven, in the final formulation in which it will be sold

therapeutic equivalence: two trade name products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration of the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined by appropriate *in vivo* bioequivalence or *in vitro* studies

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

4 Information needed

(1) An explanation of the minimum information MPI considers necessary is numbered in each section, while any further guidelines are given (without numbers) at the end of a section under '**Additional guidance**'. This guideline 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.

(2) Applicants are responsible for providing all information required by MPI to make a decision on the acceptability of the case for equivalence and, consequently, to allow the information/data to be cross-referenced in the application. If further advice is required to generate an adequate case for equivalence, you are advised to contract the services of an appropriate consultant prior to submitting your application.

(3) MPI will only consider an application as complete and able to be appraised if it contains all of the necessary information to undertake a risk assessment. This includes completed applicable application forms, up-to-date product and manufacturing specifications (product data sheet) and label, a product specific risk analysis completed by the registrant with all the necessary data and argument to support cross-reference, the necessary independent data assessments and all other supporting information and data.

5 Equivalence between test and reference product

5.1 Methods to demonstrate equivalence

(1) Depending on the product class and formulation type, equivalence may be demonstrated via one or more of the following mechanisms:

a) demonstrating that your test product is chemically equivalent to the nominated reference product; or
b) demonstrating that your test product is pharmaceutically equivalent to the nominated reference product and, after administration in the same molar dose, their effects with respect to efficacy are essentially the same, as determined from appropriate *in vitro* studies and/or peer reviewed literature and scientific argument; or
c) demonstrating that your test product is biologically equivalent to the nominated reference product by conducting a blood level, pharmacological or clinical end point bioequivalence study.

5.2 Chemically equivalent products

(1) The most straightforward case for equivalence is between products that are identical. The test and reference products must contain the same quantity and quality of formulation ingredients sourced from the same manufacturers. They must be formulated at the same manufacturing plant using the same manufacturing procedures, equipment and quality controls, and utilise identical packaging materials and specifications. For these test products the registrant, all label claims and consumer advice, dose rates and regimes, and assigned withholding periods are identical. The *only* aspect that is different is the trade name under which the product is marketed.

(2) In this circumstance all the information held by MPI for the reference product may be cross-referenced as the risk profiles will be the same. (This is known as a B1 application.)

(3) If a different registrant applies to register a test product that is identical to a nominated reference product in all but trade name, this is not classified as a B1 application. However, all information may be cross-referenced if the reference product registrant provides authorisation confirming that the products are identical in all respects.

5.3 Similar products

(1) Most cases for equivalence are between products that are similar to each other.

(2) Trade name products are similar if they:

a) contain the same concentration of the same active ingredient(s) manufactured to the same or comparable compendial standard; and
b) have the same formulation type and dosage form; and
c) have the same use patterns (including target species, dose rate, administration route, and withholding period) and label instructions; and
d) have identical label claims or, if claims are different, the proposed claims of the test product do not exceed those approved for the reference product.

(3) For similar products the non-active ingredients, manufacturing process and product specifications may not be the same. Consequently, provide data and/or argument to confirm that any differences would not be expected to alter the efficacy profile of the test product and that information/data held for the reference product would be equally relevant for your test product.

5.3.1 Pharmaceutical equivalence

(1) For certain dosage forms active pharmaceutical ingredient (API) bioavailability is minimally dependent on the product formulation. Additionally, for some moderately formulation dependent dosage forms *in vitro* data may correlate well to *in vivo* bioavailability. For such products therapeutic equivalence may be able to be established via demonstration that your test and the nominated reference product are pharmaceutically equivalent.

(2) This method of establishing equivalence is relevant to applicable dosage forms of products that are defined as closely similar. Differences in product formulation, manufacturing process, specifications or physiochemical properties must be identified. Data and argument must be provided to clearly demonstrate that any differences will not adversely affect product quality or biological activity and that cross-reference of efficacy (and/ or safety and residue) data is supported.

(3) Arguments to support a conclusion that any differences are clinically insignificant must be technically sound, robust, and supported with reliable evidence.

5.3.2 Biological equivalence

(1) For many dosage forms differences in formulation, manufacturing process, specifications and physicochemical properties may significantly affect the bioavailability of the API, and *in vivo* studies are required to confirm if a test and reference product are biologically equivalent.

(2) *In vivo* bioequivalence studies are commonly conducted as pivotal studies to demonstrate that a proposed similar pharmaceutically equivalent test product will be equivalently effective and/or as safe as the registered reference product for which MPI holds information. However, bioequivalence studies may also be applicable in the following situations:

a) if you wish to register multiple veterinary medicine products containing the same new API using different dosage forms; or
b) as bridging studies between different formulations in product development (e.g., investigational formulations used to generate clinical data and final formulations); or
c) to support new or variation of registration applications for a veterinary medicine that has an alternative dosage form or active strength (i.e., pharmaceutical alternative) or route of administration; or
d) to support approval of a change in formulation or manufacturing processes that may impact API bioavailability.

6 Biological equivalence

6.1 General considerations

(1) Biological equivalence is typically demonstrated by conducting bioequivalence studies.

(2) In appropriately designed studies bioequivalence of a test and reference product is confirmed when there is no difference (within predefined acceptance criteria) in the bioavailability of the same molar dose of the same active ingredient(s) or its metabolite(s) at the site of action when administered under similar experimental conditions. A test and reference product demonstrated to be bioequivalent may be considered to be therapeutically equivalent and **efficacy** data generated for the reference product may be cross-referenced.

(3) Bioequivalence studies only demonstrate equivalent **safety** with respect to the active ingredient and cannot necessarily be extrapolated to support safety of the test formulation. Differences in excipients and product specifications may result in a different safety profile (e.g., increased tissue irritancy following administration of an injectable veterinary medicine). Therefore, you may need to address safety of the test product by providing data from target animal safety studies and/or relevant scientific literature and argument. (Refer to the ACVM information requirements for target animal safety.)

(4) Similarly, **residue data** needs to be addressed separately because you may not always conclude that demonstration of bioequivalence will result in a similar tissue residue profile to that of the reference product.

If you can show bioequivalence based on blood-level studies, which cover the absorption, distribution, and elimination phases of the active ingredient(s), and the assay method used is sensitive enough to measure the residue levels in blood for the entire withdrawal period established for the reference product, then you may not have to provide residue depletion data. Note that the correlation between the depletion of the active ingredient(s) or its metabolite(s) from plasma and residues in the tissue(s) of significance must be known.

(5) A tissue residue study will be required when bioequivalence is established via clinical end-point and pharmacologic end-point studies. (Refer to the ACVM Information Requirements for Determination of a Residue Withholding Period for Veterinary Medicines.)

(6) **Palatability** is not addressed by bioequivalence data. This may require provision of additional data and/or argument when submitting the application. Consideration may also need to be given to physical characteristics of the TNP and how these may impact product performance in the field, e.g. Will viscosity of an injectable product or pour-on enable appropriate syringeability or product retention respectively under all practical field conditions?

(7) The **label claims** for the test product must be the same, or fewer, as approved for the reference product.

6.2 Bioequivalence studies

(1) The preferred hierarchy of bioequivalence studies (in descending order of sensitivity) is:

a) blood level study
b) pharmacological end-point study
c) clinical end-point study.

(2) The most sensitive study type should be used. Provide justification for choosing either a pharmacological or clinical end-point study in preference to a blood level study.

6.2.1 Blood level studies

(1) Blood level (or other biological fluid or tissue) bioequivalence studies are undertaken if systemic absorption of the active ingredient is sufficient to enable measurement of the concentration of the active ingredient and/or its metabolite(s) directly in the blood, plasma, serum (or other appropriate biological fluids or tissues) *and* the active ingredient and/or metabolite concentration level is correlated to the drug action.

(2) This study design is particularly applicable to dosage forms that deliver the active ingredient(s) into the systemic circulation (e.g., injectable drugs and most oral dosage forms). Generally, the study should encompass the absorption, distribution, and depletion (elimination) phases of the drug concentration vs time profiles.

(3) For detailed guidance on blood level bioequivalence studies, refer to the VICH guidance listed in clause 6.3 (1).

6.2.2 Pharmacological end-point studies

(1) If the measurement of the rate and extent of absorption of the active ingredient or metabolite in biological fluids cannot be achieved or is unrelated to the drug action, a pharmacological end point may be acceptable.

(2) Pharmacological end-point studies measure a drug induced physiologic change that is related to the approved indications for use. They require that there is a quantitatively measurable pharmacodynamic

substance (e.g., enzyme) in a biological tissue or fluid following administration of a veterinary TNP and this substance is directly correlated to the desired therapeutic action of the drug.

(3) For guidance on pharmacological end-point studies, refer to FDA Guidance for Industry #35 (see clause 6.3).

6.2.3 Clinical end-point studies

(1) Clinical end-point studies are a quantitative comparison of a clinical (therapeutic) effect between the test product and the reference product.

(2) If active ingredient concentrations in blood (or fluids or tissues) are not measurable or are inappropriate, and there are no appropriate pharmacological effects that can be monitored, then a well-controlled clinical endpoint study is an acceptable means of demonstrating bioequivalence. For example, pharmacokinetic and pharmacological end point studies may not be relevant for APIs that exert their action in the organ or tissue where the product is administered (e.g., skin or gut) and may also be absorbed. (e.g., topically applied ectoparasiticides and some oral anthelmintics).

(3) A clinical endpoint study is subject to a high degree of variability and requires a careful consideration of all aspects of design and data analysis. You must provide justification for the clinical outcome measures used in the study. The outcomes must be measurable and sensitive enough to enable assessment of whether there is a clinically significant difference in efficacy between the test and reference product.

(4) For guidance on clinical end-point studies, refer to FDA Guidance for Industry #35 (see clause 6.3).

6.3 Trial design, conduct and analysis

(1) The trial design, conduct and analysis of *in vivo* bioequivalence studies is to follow guidance described in the following internationally recognised guidelines:

a) Guidance for Industry #35 : Bioequivalence Guidance, Food and Drug Administration, Center for Veterinary Medicine (CVM) November 8, 2006
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052363.pdf

b) VICH GL52: Bioequivalence: blood level bioequivalence study
http://www.vichsec.org/guidelines/pharmaceuticals/pharma-efficacy/bioequivalence.htm

c) Guideline on the conduct of bioequivalence studies for veterinary medicinal products, European Medicines Agency, Committee for Medicinal Products for Veterinary Use (CVMP), 11 April 2011
Conduct of bioequivalence studies for veterinary medicinal products - Scientific guideline | European Medicines Agency (europa.eu)

Additional guidance
Additional useful information for pharmacokinetic studies may be found in:
Guidelines for the conduct of pharmacokinetic studies in target animal species, European Medicines Agency, Committee for Medicinal Products for Veterinary Use (CVMP) 8 Sept 2000
Conduct of pharmacokinetic studies in target animal species - Scientific guideline | European Medicines Agency (europa.eu)

6.3.1 Trial design

(1) Conduct bioequivalence studies using the most appropriate design available for the specific use of the test product.

(2) The test product must be in the final formulation you want to register.

(3) If a product has more than one active ingredient, bioequivalence must be proven for all active ingredients in the test product.

6.3.2 Standard

(1) Conduct and report studies in accordance with the ACVM Research Standard.

(2) Conduct all bioequivalence studies in a manner that assures the reliability of the data generated. Studies should be conducted according to the principles of Good Laboratory Practice (GLP) and/or Good Clinical Practice (GCP), as appropriate.

(3) All analytical laboratory studies should be conducted by a GLP compliant laboratory.

6.3.3 Reference product

(1) Demonstration of bioequivalence should be conducted against a New Zealand registered reference product approved for the same clinical indications as intended for the test product. Wherever possible, the reference product selected should be the pioneer product as this product will have undergone a full registration appraisal and MPI will hold data on this product.

If the original pioneer product is no longer marketed, then the first approved generic product may be considered as a reference product. However, during product selection it is appropriate to identify if the proposed reference product has a history of effective and safe use in New Zealand. Use of a TNP which has been used in published clinical efficacy trials may help inform selection. Where selection of an appropriate reference product is unclear, options may be discussed with MPI only once potential candidates have been identified and all relevant data for these products sourced.

(2) The reference product should be similar to your test product. That is, they must:

a) have the same active ingredient(s) in the same concentration; and
b) have the same dosage form; and
c) be administered at the same dose rate to the same target animals; and
d) have the same use patterns.

However, use of reference products that are not similar may be applicable for some studies as outlined in clause 5.3.2(2).

(3) Clearly justify the choice of reference product in the trial protocol.

(4) Clearly identify the reference product in the final study report, including the batch number and expiry date of the batch. The reference product used in the bioequivalence study must be from a current batch.

(5) Batch results of the test and reference veterinary TNPs should be reported. Unless justified, the assayed content of the API(s) in the batch used as the test product should not differ by more than 5% from that of the batch used as the reference veterinary TNP as determined by the test method proposed for batch release of the test product.

6.3.4 Use of a non-New Zealand registered reference product

(1) If bioequivalence studies are conducted in another regulatory jurisdiction, use the ACVM registered reference product if possible.

(2) If the reference product used in the bioequivalence study is not registered in New Zealand but instead has been authorised by another regulatory authority, you must provide sufficient evidence to demonstrate that the reference product formulation is qualitatively and quantitatively the same as the ACVM registered nominated reference product. This includes meeting the same compendial standard or other applicable standards of active ingredient identity, strength, quality and purity, disintegration times, and dissolution rates. Information and data provided should include (as applicable):

a) documentation that the reference product used in bioequivalence studies contains the same active ingredient(s) in the same concentration as found in the ACVM registered product; and
b) documentation that the reference product is approved for marketing by a registration authority in a country using drug assessment criteria comparable to those used in New Zealand; and

c) documentation that the reference product is marketed in the country of origin by the same company or corporate entity that currently markets the same active ingredient in the same dosage form in New Zealand, or that is marketed in the country of origin through a licensing agreement with the company or corporate entity that currently markets the product in New Zealand; and
d) documentation for proof of purchase of the reference product including product trade name, expiry date, batch number, and manufacturer; and
e) copies of the approved labels for the reference product used in the bioequivalence studies and that of the ACVM nominated reference product; and
f) if possible, a side-by-side comparison of the product formulations (both qualitative and quantitative); and
g) certificates of analysis for both products, analysed using the specifications proposed for the generic product; and
h) information on additional testing of solutions, including pH, viscosity, specific gravity, and any other test that is relevant in establishing equivalency; and
i) for immediate release solid oral dosage forms, comparative dissolution profiles conducted as recommended in the appendix under dissolution testing; and
j) documentation that the reference product used in bioequivalence studies appears the same as the nominated ACVM reference product, with respect to colour and, in the case of immediate release tablets, shape, size, weight, and type of coating.

(3) There may be circumstances where pharmaceutical equivalence, *in vitro* data and additional documentation, and discussion of the information provided are insufficient to confirm that the non-New Zealand registered reference product is equivalent to the ACVM registered reference product. In these cases bioequivalence studies using the ACVM nominated reference product will be required.

6.3.5 Animal numbers and species

(1) In the trial design, justify animal numbers, which must be appropriate for the statistical analysis. Detailed advice is provided in guidance documents listed in clause 6.3 (1).

(2) Conduct bioequivalence studies for *each* major target species for which cross-reference of data is requested.

(3) Select animals that are clinically healthy and, if possible, from a homogenous group (e.g., age, breed, weight, hormonal and nutritional status, level of production) that represents the target population.

(4) Keep weight range to a minimum to allow for the same total dose to be administered across test animals.

Additional guidance
It may be possible to extrapolate blood level bioequivalence data from one species to another with the provision of scientific argument and/or peer reviewed literature that confirm only minor physiological and anatomical differences occur between the species that do not result in significant differences in the rate and extent of active ingredient absorption. For example, demonstration of bioequivalence in cattle using appropriate studies *may* support the assumption of bioequivalence in sheep for some dosage forms. The referenced TNP must have approval for the additional species nominated.

6.3.6 Product dose rate and route of administration

(1) Conduct bioequivalence studies using the same dose for the test and reference products. Generally, for single dose studies for which linear kinetics of the active ingredient has been demonstrated, the dose should be the highest dose rate approved for the reference product.

(2) Assay the active ingredient concentration of the test and reference products prior to conducting the bioequivalence study. The API concentration in the test product should not differ by more than 5% of that in the reference product.

(3) For active ingredients with a documented wide margin of safety and linear kinetics, *in vivo* bioequivalence studies at higher than the approved dose (two to three times the highest approved dose) may be conducted to achieve measurable blood levels and avoid splitting tablets.

(4) Splitting (or shaving or filing) tablets is not acceptable unless tablets are scored and dosing in halves is approved for the reference product. In this case, the study report should provide tablet uniformity data as supportive data.

(5) The route of administration should always be the same for a similar test and reference product. If the generic product is intended for use via more than one route of administration (e.g., both intramuscular and subcutaneous administration), test all different routes.

6.3.7 Presentation of data and statistical analysis

Blood level bioequivalence

(1) List all individual concentration data and pharmacokinetic parameters by product.

(2) Justify any withdrawal of data or test subjects.

(3) Describe the method used to derive the pharmacokinetic parameters from the raw data. Include summary statistics (e.g., geometric and arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum).

(4) Present data in a format that will enable the calculation of pharmacokinetic parameters and the statistical analysis to be repeated by MPI if required. Electronic submission in a spreadsheet is desirable.

(5) Present individual plasma concentration/time curves in linear/linear and log/linear scale.

(6) Logarithmical transformation of data for statistical analysis is recommended as distributions of AUC and C_{max} tend to be positively skewed. (If untransformed data are used, they must be demonstrated to be normally distributed.)

(7) The parameters to be analysed are AUC, C_{max} and C_{min} (if applicable).

(8) For AUC, C_{max} (and C_{min} if relevant), present both the point estimate and 90% confidence intervals.

(9) Present the ANOVA or other applicable statistical model used to calculate estimates of the error variance and the least square means used to calculate 90% confidence intervals.

Bioequivalence evaluation and acceptance criteria

(1) The assessment of bioequivalence is based upon calculation of 90% confidence intervals for the ratio of the geometric means (test/reference) for the parameters under consideration (transformed data) i.e., AUC and C_{max}. If untransformed data are used, 90% CI for the mean difference between the test and reference product are calculated. This is equivalent to two one-sided tests with the null hypothesis of bioequivalence at the 5% significance level.

(2) For AUC the 90% confidence interval of the ratio of the test/reference geometric means must be contained within the limits 0.80-1.25 (80-125%). If using untransformed data the limits are 80-120%.

(3) For C_{max} the 90% confidence interval of the ratio of the test/reference geometric means should also be contained within the limits 80-125% . Again, if using untransformed data the limits are 80-120%.

(4) Different confidence bounds for C_{max} may be *prospectively* proposed in the study protocol as C_{max} may exhibit greater intra-animal variability. The European Medicines Agency (EMA**)** proposes bounds of 70 - 143 % in this instance. Justify this with respect to both efficacy and safety in the trial protocol.

(5) For further advice on the statistical analysis, refer to guidance documents in clause 6.3 (1) and/or seek advice from an appropriate consultant.

Pharmacological and clinical endpoint studies

(1) The analysis of these trials is described in the FDA Guidance for Industry #35, (see clause 6.3).

7 Demonstration of therapeutic equivalence via pharmaceutical equivalence

7.1 General considerations

(1) In general, *in vivo* bioequivalence studies are required to demonstrate that a similar test and reference product may be used interchangeably in a clinical setting, i.e., are therapeutically equivalent.

(2) However, for certain dosage forms, for which bioavailability of the API(s) is minimally formulation dependent, demonstration of pharmaceutical equivalence and provision of *in vitro* data and scientific argument may be sufficient to confirm that the test and reference products will be therapeutically equivalent. If equivalence can be successfully supported via this method, the requirement to undertake a bioequivalence study can be waived.

(3) Demonstration of therapeutic equivalence via pharmaceutical equivalence is not typically appropriate for highly formulation-dependant dosage forms such as:

a) pour-on formulations (e.g., ectoparasiticides)
b) suspensions
c) modified release dosage forms including intraruminal devices
d) products with a narrow therapeutic range (e.g., digoxin, theophylline).

(4) *In vivo* bioequivalence studies are generally unnecessary for *closely similar* test products that fulfil one or more of the following conditions:

a) The test product is a **reformulated generic** of the reference product produced by the original manufacturer that differs only in the use of dyes or colouring agents, flavours, preservatives, or other excipients that are recognised not to influence bioavailability. The products are otherwise identical.
b) The test product is a **simple aqueous solution** at the time of administration and contains the same quantity of the same active ingredient as the reference product. The buffers, preservatives, colouring or flavouring agents in the formulation must not be novel and should be the same or comparable to those in similar approved products. The products may be administered via the following routes: intravenous, intramuscular, subcutaneous, dermal, ophthalmic, aural, or oral.
c) The test product is an **aqueous solution** administered via the intravenous route and contains the same active ingredient(s) as the reference product.

   Note: if any excipients interact with the active ingredient (e.g., complex formation) or otherwise affect the disposition of the active ingredient, a bioequivalence study is required unless both products contain the same excipients in very similar quantities and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active ingredient.

d) The test product is a **solution** that is administered by intramuscular or subcutaneous injection or systemically acting topical administration. For these products *in vivo* bioequivalence studies are generally not required if the test and reference products are the same type of solution, contain the same concentration of the same active ingredient(s) and comparable excipients in similar amounts, if it can be scientifically justified that difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance. The physicochemical properties of the test solution should be the same as the reference product. The test product should not cause an injection site reaction that could potentially influence the rate and extent of absorption of the active ingredient. The maximum injection dose volume per injection site should be the same as for the reference product.

e) The test product is an **aqueous oral solution** or an aqueous oral solution when administered (e.g., soluble powder) and contains the same active ingredient in the same concentration as the nominated reference product which is an aqueous oral solution at time of administration. Excipients must not be novel for the formulation type and must not affect gastrointestinal transit (e.g., sorbitol, mannitol), absorption (e.g., polysorbate 80, polyethylene glycol, ethanol, surfactants or excipients that may affect transport proteins), solubility (e.g., co-solvents) or *in-vivo* stability of the active substance. Any differences in the amount of excipients should be justified by reference to other data.

f) The test product is a **medicated premix** containing a soluble active ingredient.

g) The test product is a **simple topical solution** (dermal, ophthalmic, otic, or nasal) intended for local therapeutic effects only.

h) The test product is as an **inhalant volatile anaesthetic** solution.

i) The test product is a **solution that does not contain pharmacologically active ingredients** (e.g., lubricants, irrigation or cleaning solutions).

j) The test product is an **orally administered dosage form not intended to be absorbed** systemically (e.g., as radio-opaque media and non-absorbed antacids).

k) The test product is an **intramammary product** which is pharmaceutically equivalent to the reference product, contains excipients that are qualitatively and quantitatively very similar, and has similar physicochemical properties (e.g., crystalline form, particle size distribution, viscosity, relative density, dissolution profile).

l) The formulations are **identical** (identical active ingredients and excipients, and identical physicochemical properties [e.g., identical API concentration, dissolution profile, crystalline form, pharmaceutical form and particle size distribution] with an identical manufacturing process).

m) The test product is a **solid or semi-solid oral immediate-release dosage form** which exerts systemic action. For these test products a case for therapeutic equivalence may be able to be based on the principles of the Biopharmaceutics Classification System. The test and reference products generally fulfil the following criteria:

   i) The active ingredient(s) have high solubility and permeability (BCS class I) or the active ingredient(s) have high solubility and low permeability (BCS class III).
   ii) The products are very rapidly dissolving (>85% in 15 minutes).
   iii) Excipients that may affect bioavailability are quantitatively and qualitatively the same.

n) The application is for test products that are **solid oral immediate-release dosage forms with multiple dosage strengths** where efficacy and safety has been confirmed via clinical data (innovator) or *in vivo* bioequivalence (generic) for one, generally the highest, dosage strength. In this case, *in vitro* equivalence data may be sufficient for the additional dosage strengths if all of the following conditions are met:

   i) The products are manufactured using the same processes.
   ii) The compositions of all formulations are qualitatively identical.
   iii) The ratio between concentrations of active ingredient(s) and excipients among the different strengths is identical (proportional formulations). Coating components, capsule shell, colour agents and flavours are exempt from this requirement.
   An alternative to proportional composition may be considered if:

      1) the amount of the active substance(s) is less than 5 % of the tablet core weight, or of the weight of the capsule content; and either:

         (a) the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed; or
         (b) the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths.

iv) The dissolution profiles between the additional strengths and the currently registered strength (biobatch) used in the bioequivalence study are considered similar as defined in the appendix.

7.2 Information requirements

(1) Test and reference products must be pharmaceutical equivalents, i.e., they must contain the same active ingredient(s) in the same strength or concentration manufactured to comparable compendial specifications and must be of the same dosage form and administered via the same route. Test and reference products will also fit the definition of being 'closely similar'.

(2) Supply *in vitro* data and/or scientific argument to confirm that the test and reference products will also be therapeutically equivalent when administered according to the product label directions.

(3) To support therapeutic equivalence via pharmaceutical equivalence, supply the following information as applicable for the product type:

a) documentation to support similarity of the dosage form, administration route, active ingredients, active ingredient strength or concentration and label clams for the test and reference product;
b) a side-by-side comparison of the test and reference formulations, both quantitative and qualitative, if this information is available for the reference product;
c) comparative physicochemical testing of a minimum of two batches of test product and New Zealand reference product using the proposed release specifications and test methods developed for the test product;
d) comparative impurity profiles for a minimum of two batches of test active ingredient, test product, and reference product using a methodology with adequate specificity;
e) active ingredient aqueous solubility;
f) additional testing for solutions could include comparative pH, viscosity, specific gravity determinations, or any test that may be relevant to compare the physicochemical characteristics test and reference product;
g) for intramammary products refer to Annex in EMA/CVMP/344: Guideline on the conduct of efficacy studies for intramammary products for use in cattle.
Guideline on the conduct of efficacy studies for intramammary products for use in cattle (europa.eu)
h) for soluble powders, medicated premixes, and immediate-release solid oral dosage forms equivalence should be addressed with reference to the following guidelines:

i) Soluble powders and medicated premixes
Guidance for Industry #171, Waivers of *In Vivo* Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles, Food and Drug Administration, Center for Veterinary Medicine (CVM).
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-171-demonstrating-bioequivalence-soluble-powder-oral-dosage-form-products-and-type-medicated
https://www.fda.gov/regulatory-information/search-fda-guidance-documents

ii) Immediate release solid oral dosage forms meeting BCSI and BCSIII criteria
Appendix I: Guideline on the conduct of bioequivalence studies for veterinary medicinal products, European Medicines Agency, Committee for Medicinal Products for Veterinary Use (CVMP).
Guideline on the conduct of bioequivalence studies for veterinary medicinal products (europa.eu)

iii) Immediate release solid oral dosage forms with multiple dosage strengths where *in vivo* bioequivalence has been demonstrated for one dosage strength

Guideline on the conduct of bioequivalence studies for veterinary medicinal products, European Medicines Agency, Committee for Medicinal Products for Veterinary Use (CVMP), Sections 7.2 and 8
Guideline on the conduct of bioequivalence studies for veterinary medicinal products (europa.eu)

i) scientific discussion should include the rate limiting steps in absorption of the active ingredient(s) for drugs with systemic action, or for the active ingredient achieving access to the site of effect if applicable;
j) provide relevant scientific argument to justify the case for equivalence based on pharmaceutical equivalence without *in vivo* studies and consider the clinical consequences of therapeutic inequivalence.

Appendix: Dissolution testing

Comparative dissolution profiles may be used to support a case for therapeutic equivalence without *in vivo* bioequivalence studies for some solid oral immediate release dosage forms as discussed in clause 7.1(4) m & n.

Dissolution studies may also be required to investigate batch to batch consistency of products (test and reference) to inform selection of appropriate batches for an *in-vivo* bioequivalence study. They may also be required to support the use of a non-New Zealand registered reference product in bioequivalence studies conducted in other jurisdictions.

General requirements

(1) The test methods used to determine disintegration and dissolution profiles should be those contained in the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur) or United States Pharmacopoeia (USP) and must be described. If another method is used, it should be that proposed for the generic test product and methodology must be justified in the application.

(2) Test and reference products must be tested using the same methodology and, if possible, tests should be conducted on the same day.

(3) Obtain dissolution profiles in three different dissolution media which span the gastrointestinal physiological pH range of the target species (e.g., pH 1.2, 4.5 and 7.5). At least 12 dosage units (e.g., tablets, capsules) of each product are tested individually and mean and individual results reported. The percentage of nominal active ingredient release is measured at a number of sampling time points (e.g., 10, 15, 20 and 30 minutes) to provide a profile for each product. Sampling number and frequency must be adequate to generate a meaningful profile. More frequent sampling may be required for rapidly dissolving products.

Assessment of dissolution similarity

(1) For test and reference products where ≥ 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as being similar based on a single time point.

(2) For test and reference products where less than 85% of the drug dissolved at 15 minutes and more than 85% is dissolved within 30 minutes, at least three time points are required:

a) the first time point before 15 minutes; and
b) the second time point at 15 minutes; and
c) the third time point when the release is close to 85%.

(3) For test and reference products where ≥ 85% of drug is not dissolved within 30 minutes, more than three time points, and a longer study duration may be required to elucidate the profile.

(4) For the last two cases, dissolution profiles obtained should be compared using the similarity factor ($f2$), which is a measurement of the similarity in the percent dissolution between the two curves as determined by the following mathematical formula:

$$f2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{t=1^{n}}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

$f2$ is the similarity factor, n is the number of time points, R(t) is the mean percent drug dissolved of the reference product, and T(t) is the mean percent substance dissolved of the test product.

(5) The two dissolution curves are considered similar if the $f2$ value is ≥50.

(6) When calculating a similarity factor the following conditions must be met:

a) sampling must occur at a minimum of three time points (zero excluded); and
b) the sampling time points should be the same for the test and reference products; and

c) twelve individual dosage units are to be tested for every time point for both products; and
d) not more than one mean value of > 85% dissolved for any of the formulations; and
e) in order to use mean values, the relative standard deviation or coefficient of variation should not be more than 20% at the first time point and not more than 10% at the other time points.

Additional guidance
Consultation of the following international standard is recommended before conducting dissolution studies to support registration applications:

Guideline on the conduct of bioequivalence studies for veterinary medicinal products, European Medicines Agency, Committee for Medicinal Products for Veterinary Use (CVMP). Refer section 8 Dissolution testing
Guideline on the conduct of bioequivalence studies for veterinary medicinal products (europa.eu)