COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON THE CONDUCT OF BIOEQUIVALENCE STUDIES FOR VETERINARY MEDICINAL PRODUCTS

DRAFT AGREED BY EFFICACY WORKING PARTY       February 2009
DRAFT AGREED BY QUALITY WORKING PARTY         February 2009
DRAFT AGREED BY SAFETY WORKING PARTY          February 2009
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION 11 March 2009
FOCUS GROUP MEETING WITH INTERESTED PARTIES - see EMEA website “meetings and events” 6 May 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS) 30 September 2009

This guideline replaces the current “Guideline on the conduct of bioequivalence studies for veterinary medicinal products” (EMEA/CVMP/016/00-corr)

Comments should be provided using this template to vet-guidelines@emea.europa.eu or Fax +44 20 7418 8447

KEYWORDS Bioequivalence, biowaiver, generics, veterinary medicines
1. INTRODUCTION (BACKGROUND) ........................................................................................................ 4
2. SCOPE .................................................................................................................................................. 4
3. LEGAL BASIS ......................................................................................................................................... 4
4. SITUATIONS WHEN BIOEQUIVALENCE MAY BE APPLICABLE .................................................... 4
   4.1 PRODUCT DEVELOPMENT PRIOR TO FIRST AUTHORISATION OF A VETERINARY MEDICINAL
       PRODUCT CONTAINING A NCE OR A KNOWN ACTIVE SUBSTANCE .................................... 4
   4.2 EXTENSIONS AND VARIATIONS ................................................................................................. 5
   4.3 PRODUCT CONTAINING A KNOWN SUBSTANCE INTENDED TO BE A GENERIC ACCORDING TO
       DIRECTIVE 2001/82/EC, ARTICLE 13 ......................................................................................... 5
5. THE CONDUCT OF BIOEQUIVALENCE STUDIES ............................................................................. 5
   5.1 STUDY DESIGN IN GENERAL ...................................................................................................... 5
   5.2 SPECIAL CONSIDERATION FOR GENERIC MODIFIED RELEASE FORMULATIONS ................. 6
   5.3 SPECIAL CONSIDERATIONS FOR GENERIC PRODUCTS FOR USE IN MEDICATED FEEDING STUFF
       OR DRINKING WATER OR MILK/MILK REPLACER .............................................................. 6
   5.4 PARAMETERS ............................................................................................................................. 6
   5.5 REFERENCE AND TEST PRODUCT ............................................................................................ 7
   5.6 ANIMALS ...................................................................................................................................... 7
   5.7 SPECIES TO BE STUDIED ............................................................................................................ 7
   5.8 ROUTE OF ADMINISTRATION .................................................................................................... 8
   5.9 STRENGTH TO BE TESTED ......................................................................................................... 8
   5.10 DOSE TO BE TESTED ............................................................................................................... 8
   5.11 ANALYTES TO BE MEASURED ................................................................................................. 8
   5.12 BIOEQUIVALENCE IN CASE OF FORMULATIONS WITH DIFFERENT BIOAVAILABILITY .......... 9
   5.13 SAMPLING TIME CONSIDERATIONS ....................................................................................... 9
   5.14 CHEMICAL ANALYSIS .............................................................................................................. 9
   5.15 EVALUATION ............................................................................................................................ 10
      5.15.1 Statistical analysis .............................................................................................................. 10
      5.15.2 Acceptance limits .............................................................................................................. 11
      5.15.3 Two-stage design .............................................................................................................. 11
      5.15.4 Data to be included in analysis ......................................................................................... 11
      5.15.5 Presentation of data ........................................................................................................... 12
6. EXEMPTIONS FROM BIOEQUIVALENCE STUDY REQUIREMENTS FOR
IMMEDIATE RELEASE FORMULATIONS ....................................................................................... 12
   6.1 COMPARISONS BETWEEN FORMULATIONS ......................................................................... 12
   6.2 COMPARISONS BETWEEN STRENGTHS ............................................................................... 13
7. DISSOLUTION TESTING ..................................................................................................................... 13
8. DEFINITIONS ......................................................................................................................................... 16
9. REFERENCES (SCIENTIFIC AND / OR LEGAL) ............................................................................... 17
10. ANNEX – BCS-BASED BIOWAIVERS .......................................................................................... 18
11. 1. INTRODUCTION .......................................................................................................................... 18
12. 2. GENERAL CONSIDERATIONS ................................................................................................. 18
   2.1 CLASS I: HIGH SOLUBILITY, HIGH PERMEABILITY .............................................................. 18
   2.2 CLASS II: LOW SOLUBILITY, HIGH PERMEABILITY ............................................................... 18
   2.3 CLASS III: HIGH SOLUBILITY, LOW PERMEABILITY ............................................................. 18

TABLE OF CONTENTS
2.4 CLASS IV: LOW SOLUBILITY, LOW PERMEABILITY

3. SUMMARY REQUIREMENTS

4. ACTIVE SUBSTANCE

4.1 SOLUBILITY

4.2 ABSORPTION

5. VETERINARY MEDICINAL PRODUCT

5.1 IN-VITRO DISSOLUTION

5.1.1 General aspects

5.1.2 Evaluation of in-vitro dissolution results

5.2 EXCIPIENTS

6. FIXED DOSE COMBINATIONS

7. BIOWAIVERS FOR DOSAGE FORMS FOR USE IN-FEED OR DRINKING WATER

7.1 BIOWAIVER FOR DOSAGE FORMS FOR USE IN-FEED

7.2 BIOWAIVER FOR SOLUBLE DOSAGE FORMS FOR USE IN DRINKING WATER
EXECUTIVE SUMMARY

It is the objective of this guidance to define when bioequivalence studies could be used to demonstrate that two products will show similar systemic safety and efficacy in a certain target animal species and to formulate recommendations for the design, the conduct, and the evaluation of such studies. In addition, guidance is given on how to design, conduct and evaluate in-vitro equivalence studies.

1. INTRODUCTION (background)

For two products, pharmacokinetic equivalence (i.e. bioequivalence) is established if the rate and extent of absorption of the active substance investigated under identical and appropriate experimental conditions only differ within acceptable predefined limits. Rate and extent of absorption are typically measured by $C_{\text{max}}$ (peak concentration) and $AUC$ (total exposure over time), respectively, in plasma or serum to ensure that plasma/serum versus time profiles are similar. Bioequivalence studies are often part of applications for generic veterinary medicinal products as a means to preclude the need for studies on systemic tolerance and efficacy, but may also be part of an application for a New Chemical Entity (NCE) e.g. when comparing different formulations during product development.

Bioequivalence studies may also support applications for alternative dosage forms, new routes of administration, significant manufacturing changes or changes in composition which may affect the rate and/or extent of drug absorption.

In case of hybrid applications (according to Directive 2001/82/EC as amended, article 13, paragraph 3) and occasionally in case of product development there might be situations e.g. in case of locally active substances, where pharmacokinetic endpoints cannot be used. This is however beyond the concept of bioequivalence and this guideline does not cover these aspects.

2. SCOPE

The aim of this guideline is to provide guidance regarding study design, conduct and evaluation including statistical considerations and acceptance limits for bioequivalence studies and in-vitro dissolution tests. In addition, recommendations are given on when in-vivo studies are mandatory and when in-vitro data are likely to be sufficient. Aspects related to both generic applications and product development are covered. If bioequivalence cannot be demonstrated using pharmacokinetic endpoints, pharmacodynamic or clinical endpoints may be used, in exceptional circumstances, to demonstrate similar efficacy and safety. However, this situation is outside the scope of this guideline and the reader is referred to therapeutic area specific guidelines where available.

3. LEGAL BASIS

This document is intended to provide guidance on the conduct of bioequivalence studies for veterinary medicinal products. It should be read in conjunction with Directive 2001/82/EC as amended. Applicants should also refer to other relevant European and VICH guidelines, including those listed under “References”.

4. SITUATIONS WHEN BIOEQUIVALENCE MAY BE APPLICABLE

Bioequivalence data may be pivotal in a number of different situations. In the following text the level of detail differs according to the anticipated need for guidance and some parts, as indicated in the text, are applicable for generic products only.

4.1 Product development prior to first authorisation of a veterinary medicinal product containing a NCE or a known active substance

During development of a product containing a NCE or a known active substance, comparative pharmacokinetic studies may be used as bridging studies between different formulations e.g. between pivotal and early clinical trial formulations.

Such studies may be exempted if the absence of differences in the in-vivo performance can be justified...
by satisfactory in-vitro data.

Bioequivalence within the acceptance limits as defined in this document might not be needed in all cases and other study designs than those presented in this document might be found appropriate e.g. in case a tolerance study (as regards to systemic tolerance to the active substance) is performed with a different formulation, it will be sufficient to show that the rate and extent of absorption from this formulation is at least as high as that for the formulation intended to be marketed.

4.2 Extensions and variations

Approvals of extensions and variations such as alternative dosage forms, new dosage strengths, new routes of administration or significant changes to manufacturing or composition which may affect active substance bioavailability often need support of bioequivalence studies. Exemptions from bioequivalence studies should always be justified.

4.3 Product containing a known substance intended to be a generic according to Directive 2001/82/EC, Article 13

In case of systemically active substances when reference is made to an approved product in terms of efficacy and/or safety, bioequivalence to this product should be demonstrated. It should be noted that there are several aspects such as palatability, animal owner’s compliance, local tolerance and residue concentrations at the injection site that might differ between products and that are not covered by bioequivalence data. The need to document such aspects might differ between applications and is beyond the scope of this guideline. It should be noted that bioequivalence cannot be used for extrapolation of withdrawal periods between injectable products for intramuscular and/or subcutaneous injection in food producing animals.

5. THE CONDUCT OF BIOEQUIVALENCE STUDIES

In the following sections, requirements for the design and conduct of bioequivalence studies are formulated. It is assumed that the applicant is familiar with pharmacokinetic principles underlying bioequivalence studies. The design should be based on a reasonable knowledge of the pharmacokinetics of the active substance in question. Specific guidance is given for modified release products as there are specific issues to be addressed for these products.

5.1 Study design in general

Bioequivalence studies should be conducted under Good Laboratory Practice (GLP) and/or Good Clinical Practice (GCP), as appropriate.

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is usually considered to be the design of choice. The study periods should be separated by a sufficiently long wash-out period to ensure that there is no remaining exposure or remaining physiological effects such as metabolic enzyme induction from the first period. The allocation of test animals to the treatment sequences should be randomised.

A crossover design is preferable whenever possible. If other designs are used, this should be justified and in case the choice of design is of concern, it is recommended to ask for scientific advice. In cases where the length of the wash-out period is not compatible with a crossover design (e.g. substances with very long half-life or studies performed with growing animals), a parallel group design could be considered.

In case of substances with highly variable disposition where it is difficult to show bioequivalence due to high intra individual variability, different alternative designs have been suggested in literature. It is recommended to ask for scientific advice in case it is estimated that a traditional crossover design would not be feasible without the inclusion of a very high number of animals.
Regarding single dose versus multiple dose studies, single dose studies are preferred as the potential to detect a difference in rate of absorption is lower if the active substance is accumulated. Multiple dose designs should be justified and could be considered if e.g. problems of sensitivity of analytical method preclude sufficiently precise plasma concentration measurements after single dose administration.

For the oral route, special attention must be paid to the different factors that are known to affect absorption of the active substance, such as feeding. Feeding may interfere with drug absorption, depending upon the characteristics of the active substance and the formulation and may also increase the inter- and intra-individual variability in the rate and extent of drug absorption. The rationale for conducting each bioequivalence study under fasting or fed conditions should be provided in the protocol. The protocol should describe the diet and feeding regimen that will be used in the study. If the reference product is limited to administration either in the fed or fasted state, then the bioequivalence study should be conducted accordingly.

The number of test animals must be appropriate for statistical analyses and should be carefully estimated and justified in the protocol.

5.2 Special consideration for generic modified release formulations

Generic versions of formulations designed to modify rate or site of absorption need special consideration. In veterinary medicine there are numerous different types of modified release formulations. These could be for oral use such as prolonged release tablets for companion animals (similar to formulations for human use), pastes for horses or intraruminal boluses for cattle. Many modified release formulations are parenteral such as spot-ons and pour-ons, which are absorbed through the skin, or prolonged release injectables. In most cases such products are intended for single use and no accumulation between doses is expected. If so, single dose bioequivalence data is normally sufficient to demonstrate similarity between products. For prolonged release formulations intended for repeated dosing, i.e. the aim of the modification is to reduce fluctuations during steady state therapy or to reduce the frequency of administration, where there is accumulation between doses, demonstration of bioequivalence should be based on multiple dose studies. For such products $C_{\text{min}}$ is an important parameter to consider, in addition to $C_{\text{max}}$ and AUC.

For orally administered modified release formulations to non ruminants, bioequivalence normally need to be established under both fed and fasting conditions.

5.3 Special considerations for generic products for use in medicated feeding stuffs or drinking water or milk/milk replacer

Most veterinary medicinal products, excluding suspensions and emulsions, for use in drinking water are likely to be exempted from the demand of in-vivo bioequivalence data on the basis of the product being an aqueous oral solution at time of administration (see section 6.1 and Annex). For products to be administered in milk/milk replacer, special consideration should be applied.

Premixes and other dosage forms for use in-feed can only be eligible for a biowaiver if they belong to BCS (Biopharmaceutics Classification System)-class I or III (see Annex). In all other cases, bioequivalence should be studied in-vivo and it is recommended to ask for scientific advice regarding the appropriate study design under such circumstances. This applies in particular for poorly soluble compounds or cases where differences in qualitative composition between products might be of concern.

5.4 Parameters

In single dose studies $\text{AUC}_t$, $\text{AUC}_{\infty}$, $C_{\text{max}}$ and $t_{\text{max}}$ should be determined and bioequivalence should be based on $\text{AUC}_t$ and $C_{\text{max}}$.

In steady state studies $\text{AUC}_{\tau}$, $C_{\text{max,ss}}$, $C_{\text{min,ss}}$, and $t_{\text{max,ss}}$ should be determined and bioequivalence should be based on $\text{AUC}_{\tau}$, $C_{\text{max,ss}}$ and $C_{\text{min,ss}}$. 
Additional parameters that may be relevant to report include the terminal rate constant, $\lambda_z$, t$_{1/2}$ and t$_{lag}$.

Parameters should normally not be dose normalised (for exemptions, see section 5.9).

Additional parameters may be presented. The methods of estimating parameters should be specified. The use of compartmental methods for the estimation of parameters is not acceptable.

5.5 Reference and test product

The sponsor should carefully consider his choice of reference product. For generic applications, the reference product must be a veterinary medicinal product authorised in a Member State or the Community on the basis of a complete dossier in accordance with the provisions in Directive 2001/82/EC, as amended. Bioequivalence testing must be conducted with a reference product approved for the same target animal species as intended for the generic product.

Test products in an application for a generic product are normally compared with the corresponding pharmaceutical form of a reference product.

In an application for extension to a new formulation of a concerned veterinary medicinal product and when there are several dosage forms of this product on the market, the formulation used for the initial approval of the concerned product (and which was used in clinical efficacy and safety studies) should be used as comparative product, unless otherwise justified.

When variations to a generic product are made or extensions are made to include a new food producing target animal species, the comparative veterinary medicinal product for the bioequivalence study should be the reference product.

Batch control results of the test and reference products should be reported. The assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test procedure proposed for routine quality testing of the test product. In order to demonstrate that a representative batch of the reference product with regards to dissolution and assay content has been selected, the applicant should present dissolution profiles and content analysis of at least 3 batches of the reference product, unless otherwise justified.

The test product used in the study should be representative of the product to be marketed and this should be justified by the applicant. The production of pilot batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale.

5.6 Animals

Animals used in bioequivalence studies should be clinically healthy representatives of the target population, and preferably from a homogeneous group (age, breed, gender, weight, hormonal and nutritional status, level of production, etc.). However, when it is difficult to achieve homogeneity of all animals within a study it is acceptable to use a non-homogenous stock, provided that the study is of a crossover design as each animal would act as its own control in such studies.

In parallel design studies, the treatment groups should be homogeneous and comparable in all known prognostic variables that affect the pharmacokinetics of the active substance e.g. age, weight, gender etc. (if relevant). This is an essential pre-requisite to give validity to the study results.

5.7 Species to be studied

The included animals should be of the target species. In case a product is intended for more than one species, bioequivalence studies should normally be performed in each species. Exemptions should be clearly justified.
5.8 Route of administration

In case of generic applications, the route of administration should always be the same for test and reference products. When the generic product is intended for more than one route of administration (e.g. both intramuscular and subcutaneous administration), all different routes should be tested.

5.9 Strength to be tested

If a new application concerns several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable (see section 6.2). In case the strength of the test product differs from the reference product’s and this precludes equal doses in the two treatment groups, it is recommended to use different doses and then dose normalise (i.e. to divide AUC and \( C_{\text{max}} \) with the amount administered) the pharmacokinetic parameters. Care should be taken to ensure that solid oral dosage forms are not manipulated in a way that could bias the bioequivalence study. In general, all sorts of manipulation such as grinding or filing in order to achieve equal doses should be avoided. If the dosage form nevertheless is manipulated, a justification must be given. Tablets intended to be divided may be divided along their score lines but not into smaller pieces.

The same strength should be administered to all animals in a study independent of their bodyweight unless the animals differ substantially in body size (see section 5.10).

5.10 Dose to be tested

The general rule is that bioequivalence studies should be performed with an approved dose. However, it is acknowledged that for some animal species e.g. the dog it could be difficult to find subjects suitable for investigation of high strength solid dosage forms. In this case overdose studies might be considered if tolerated.

Most products have a single approved dose adjusted for body size which is expressed as e.g. mg/kg bodyweight. Thus, exact dosing can only be achieved in case of dosage forms that allow an indefinite number of dose levels (such as an oral suspension). For all solid dosage forms the amount to be administered will depend on the different strengths available and the exact dose per kg bodyweight might therefore vary somewhat. To limit the amount of bias introduced due to difficulties regarding dose accuracy the following should be considered:

a) If there are no tolerance concerns, administration of higher or lower doses than the approved dose may be acceptable acknowledging the fact that there might not be suitable strengths available to allow the approved weight-adjusted dose to be administered to all animals included in the study.

b) The amount administered should be the same in each individual in all periods regardless of changes in body weights between study periods unless the change in body weight is considerable.

c) An attempt should be made to restrict the weight of the test animals to a narrow range in order to maintain the same dose across study animals.

d) When a solid oral dosage form is compared to a dosage form that allows an indefinite number of dose levels, the amount administered should (for both formulations) depend on the options available with the solid form.

5.11 Analytes to be measured

In most cases evaluation of bioequivalence will be based upon the measured concentrations of the parent compound. In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound, e.g. if the concentration of the parent compound is too low to be accurately measured (e.g. major difficulty in analytical method, the product is unstable in the biological matrix or if the half-life of the parent compound too short). Bioequivalence determinations based on metabolites should be justified in each case bearing in mind that the aim of a bioequivalence study is to compare the in-vivo performance of test and reference products.
If adequately justified, the use of urine data may be acceptable in exceptional cases.

Regarding enantiomeric active substances, the use of achiral bio-analytical methods is possible when it is demonstrated that both enantiomers show at least one of the following characteristics:

- the same pharmacokinetics,
- the same pharmacodynamics, or
- the concentration ratio of enantiomers is not modified by a change in the rate of absorption.

If none of these characteristics is fulfilled or can be asserted with confidence, enantiomeric bio-analytical methods are required. If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer. If both enantiomers contribute significantly to activity, bioequivalence should be demonstrated for both enantiomers.

The use of achiral bio-analytical methods is also possible when both products contain the same single enantiomer and there is no inter-conversion in-vivo.

### 5.12 Bioequivalence in case of formulations with different bioavailability

If suprabioavailability is found, i.e. if the test product displays an extent of absorption appreciably larger than the reference product, the bioequivalence concept could be a useful tool to demonstrate that similar AUC and C\text{max} is achieved following administration of a lower dose of the test product as compared to the reference. If equivalent in terms of rate and amount of absorption, it may be expected that the two products have similar systemic efficacy and safety although administered at different doses. It should be noted that suprabioavailable products cannot be generics.

### 5.13 Sampling Time Considerations

A sufficient number of samples to adequately describe the complete plasma concentration / time profile should be collected. The sampling schedule should include frequent sampling around C\text{max} to provide a reliable estimate of peak exposure. The sampling schedule should be planned to avoid C\text{max} being the first point of a concentration time curve. The sampling schedule should also cover the plasma concentration / time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if AUC\text{t} is at least 80% of AUC\text{c}. At least three to four samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of AUC\text{c}).

For active substances with a long half-life, relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of the absorption process i.e. the absorption should be complete.

In case of multiple dose studies, sampling should be performed to show that steady state conditions are reached (i.e. trough concentrations during the loading period should be sampled until C\text{min} is stable) in addition to sampling after the last dose administered.

To maximise sampling time efficiency, it may be necessary to run a pilot study to help identifying the shape of the concentration/time curve and the likely variability in the concentration values.

### 5.14 Chemical analysis

The bioanalytical part of bioequivalence trials should be conducted according to the principles of GLP. However, as such studies fall outside the formal scope of GLP, the sites conducting the studies are not required to be certified as part of the GLP compliance certification scheme.

The bioanalytical methods used must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to
demonstrate the reliability of a particular method for the quantitative determination of an analyte(s)
concentration in a specific biological matrix. The main characteristics of a bioanalytical method
essential to ensure the acceptability of the performance and the reliability of analytical results are:
(1) stability of the stock solutions and of the analyte(s) in the biological matrix under processing
conditions and during the entire period of storage; (2) specificity; (3) accuracy; (4) precision (5) limit
of quantification and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase
in which compliance of the assay with the characteristics listed above is verified and (2) the study
phase itself in which the validated bioanalytical method is applied to the actual analysis of samples
from the bioequivalence study in order to confirm the validity of the determinations.

Pre-study phase
As validation involves documenting that the performance of characteristics of the method are suitable
and reliable for the intended analytical application, commercial kits need to be re-validated for their
use in bioequivalence studies. Similarly, demonstration of stability based on literature data only is not
acceptable. The applicant should discuss the ability of the analytical method to distinguish between the
analyte and other related substances (e.g. metabolites or co-medication during study phase) that may
be formed after product administration but that are not present in the spiked samples employed in the
pre-study phase of the validation. The risk of back-conversion of a metabolite into the analyte during
the successive steps of the analysis should also be addressed.

Study phase
A calibration curve should be generated in each analytical run and it should be used to calculate the
concentration of the analyte in the unknown samples in the run. A sufficient number of separately
prepared Quality Control samples should be analysed with processed test samples at intervals based on
the total number of samples. In addition, it is necessary to validate the method of processing and
handling the biological samples.

The applicant should discuss the number of samples (and percentage of total number of samples) that
have been re-analysed, the initial value, the reason for reanalysis, the values obtained in the
reanalyses, the finally accepted value and a justification for the acceptance. Any other deviation of the
analytical protocol should also be discussed. All procedures should be performed according to pre-
established Standard Operating Procedures (SOPs). All relevant procedures and formulae used to
validate the bioanalytical method should be submitted and discussed. Any modification of the
bioanalytical method before and during analysis of study specimens may require adequate
revalidation; all modifications should be reported and the scope of revalidation justified.

5.15 Evaluation

5.15.1 Statistical analysis
The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the
population geometric means (test/reference) for the parameters under consideration. This method is
equivalent to two one-sided tests with the null hypothesis of bio-inequivalence at the 5% significance
level.

The pharmacokinetic parameters under consideration should be analysed using ANOVA (or
equivalent parametric method). The data should be transformed prior to analysis using a logarithmic
transformation. A confidence interval for the difference between formulations on the log-transformed
scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain
the desired confidence interval for the ratio on the original scale. A non-parametric analysis is not
acceptable.

The precise model to be used for the analysis should be pre-specified in the protocol. The statistical
analysis should take into account sources of variation that can be reasonably assumed to have an effect
on the response variable. For example, if a two-period, two-sequence crossover design has been used,
the terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation. The presentation of the findings of a bioequivalence trial should include a 2x2-table that presents for each sequence (in rows) and each period (in columns) means, standard deviations and number of observations for the observations in the respective period of a sequence. In addition, tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment. A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test. The potential for carry-over of the analyte can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable). If there are any animals for which the pre-dose concentration is greater than 5 percent of the C max value for the animal in that period, the statistical analysis should be repeated with those animals excluded. Results from both analyses should be presented, but the analysis with the animals excluded should be considered as primary.

However, if the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using some form of baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment. The method for baseline correction should be pre-specified and justified in the study protocol. In this situation it cannot be directly assessed whether carry-over has occurred, so extra care should be taken to ensure that the washout period is of an adequate duration.

5.15.2 Acceptance limits

For immediate release formulations, a 90% confidence interval for the ratio of the two treatment means of AUC and C max, respectively, should be entirely contained within the limits 80% to 125%. This applies to data from both single dose studies and multiple dose studies and, where applicable, also to C min in addition to AUC and C max. However, it is acknowledged that there are certain compounds where it might be difficult to show bioequivalence within these limits due to large intraindividual variability. Normally, in such cases, the number of included animals should be increased to ensure sufficient statistical power. Exceptionally, a tighter acceptance interval could be needed in the case of substances with a narrow therapeutic window. The pharmacokinetic parameters to be tested and the procedure for testing should be set a priori in the protocol.

5.15.3 Two-stage design

It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of animals can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups can be combined in a final analysis. If this approach is taken appropriate steps must be taken to preserve the overall type I error of the experiment. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). The plan to use a two-stage approach must be prespecified in the protocol along with the adjusted significance levels to be used for each of the analyses.

5.15.4 Data to be included in analysis

All treated animals should be included in the statistical analysis, with the exception of animals in a crossover trial who do not complete at least one period receiving each of the test and reference products (or who fail to complete the single period in a parallel group trial).

Unbiased assessment of results from randomised studies requires that all animals are observed and treated according to the same rules which should be independent from treatment or outcome. In consequence, the decision to exclude an animal from the statistical analysis must be made before bioanalysis. Normally all treated animals should be included in the analysis provided that the necessary number of treatment periods has been completed. Exclusions can only be made based upon reasons that have been defined in the protocol. Exclusion of data can never be accepted on the basis of
statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects affecting the pharmacokinetics.

5.15.5 Presentation of data

All individual animal data should be provided. These presentations should include available data from animals that eventually dropped-out from the study. Drop-out and withdrawal of animals should be fully documented.

All individual plasma concentration data and pharmacokinetic parameters should be listed by formulation together with summary statistics such as geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration/time curves should be presented in linear/linear and log/linear scale.

For the pharmacokinetic parameters that were subject to statistical analysis, the point estimate and 90% confidence interval for the ratio of the test and reference products should be presented.

For single dose studies, the percentage of AUC$_\infty$ that is covered by AUC$_t$ should be reported for each animal in each period.

The report should be sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual times of blood sampling, active substance concentrations, values of the pharmacokinetic parameters for each animal in each period and the randomisation scheme should be provided.

The analytical report should include a detailed description of the bioanalytical method used, a detailed pre-study validation report and a detailed description of the in study validation results including the results for all standard and quality control samples. A representative number, of chromatograms or other raw data (e.g. for the first 5 animals) should be included covering the whole concentration range for all standard and quality control samples as well as the specimens analysed. Any manual integration of chromatograms should be justified and listed together with values from the automatic integration.

6. **EXEMPTIONS FROM BIOEQUIVALENCE STUDY REQUIREMENTS FOR IMMEDIATE RELEASE FORMULATIONS**

6.1 Comparisons between formulations

The formulation and the characteristics of the active substance are factors which may affect the requirements regarding support of data from bioequivalence studies. When the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference product, bioequivalence should be demonstrated in appropriate bioavailability studies. However, when active substance in test and reference products are identical or contain comparable salts, in-vivo bioequivalence studies may, in some situations, not be required.

Studies to compare the rate and extent of absorption between two formulations or products containing identical active substances are generally not necessary if both products fulfil one or more of the following conditions:

a) The product is to be administered solely as an aqueous intravenous solution. The excipients should not interact with the active substance (e.g. complex formation).

b) In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the product is of the same type of solution (aqueous or oily), contains the same concentration of the active substance and the same excipients in similar amounts as the reference product, bioequivalence studies are not required.
c) If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. 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 either by reference to other data or by a bioequivalence study. The same requirements for similarity in excipients apply for oral solutions as for biowaivers according to the BCS criteria (see Annex, section 5.2).

d) The products are classified as biowaivers according to the BCS criteria (see Annex).

e) The product is intended to be a gas for inhalation at time of administration.

6.2 Comparisons between strengths

If a new application concerns several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable provided in-vitro equivalence data is presented for additional strengths. A pre-requisite is that all of the following conditions are fulfilled:

a) The dosage strengths are manufactured by the same manufacturer and process,

b) The composition of all formulations are qualitatively identical,

c) The ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar, and

d) The dissolution profiles under identical conditions are similar.

The criteria above apply also to the situation where there are several strengths of a generic immediate release product to be approved. If one of the strengths (appropriately selected, see sections 5.9 and 5.10) is found bioequivalent with the reference product, in-vitro data could be sufficient to document bioequivalence for the other strengths of the generic application. In this case, each strength of the test product should be compared to the corresponding strength of the reference product whenever feasible.

7. DISSOLUTION TESTING

During the development of a veterinary medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the active substance. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to demonstrate bioequivalence. Therefore, dissolution studies can serve several purposes:

a) Testing on product quality

• To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control.

• To be used as a tool in quality control to demonstrate consistency in manufacture.

• To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.

b) Bioequivalence surrogate inference

• To support the assumption of similarity between reference products from different Member States provided that the manufacturing process, composition and specifications are similar.

• To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic products).
To investigate batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the *in-vivo* study.

The test methodology should be in accordance with pharmacopoeial requirements unless those requirements are shown to be unsatisfactory and/or do not reflect the *in-vivo* dissolution (i.e. biorelevance). Alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product *in-vivo*.

The recommendations as briefly outlined in the following should be noted as being basic regarding the development of meaningful *in-vitro* dissolution methods. However, current state-of-the-art information must always be considered. If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration and the excipients are known not to affect the dissolution, stability and absorption processes. A bioequivalence study may in those situations be waived based on similarity of dissolution profiles which are based on discriminatory testing, provided that the other exemption criteria in the Annex are met. The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH 1.2, 4.5 and 7.5).

If an active substance is considered to have a low solubility, the rate limiting step for absorption may be dosage form dissolution. This is also the case when one or more of the excipients are controlling the release and subsequent dissolution step of the active substance. In those cases a variety of test conditions is recommended and adequate sampling should be performed until either 90% of the active substance is dissolved or an asymptote is reached. Knowledge of dissolution properties under different conditions e.g. pH, agitation, ionic strength, surfactants, viscosity, osmotic pressure is important since the behaviour of the solid system *in-vivo* may be critical for the active substance dissolution independent of the physico-chemical properties of the active substance. An appropriate experimental statistical design may be used to investigate the critical parameters and for the optimisation of such conditions.

Dissolution similarity should normally be based on a maximum 10% average difference between the test and reference dissolution profiles, unless fully justified.

The variance of the test and reference product data should also be similar, unless otherwise justified.

For immediate release dosage forms, comparison at 15 minutes is essential to know if complete dissolution is reached before gastric emptying.

In cases where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.

In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%.

In the case of gastro-resistant formulations, where the dissolution takes place in the intestine, similarity should be assessed during the immediate release phase of the dissolution profile. During this phase, frequent sampling (e.g. every 5 minutes) is required.

In general five to eight sampling times within a 0 to 60 minute interval are recommended to achieve meaningful dissolution profiles.
Dissolution similarity may be determined using the $f_2$ statistic as follows:

$$f_2 = 50 \log \frac{100}{\sqrt{\frac{\sum |R(t) - T(t)|^2}{n}}}$$

In this equation $f_2$ is the similarity factor, $n$ is the number of time points, $R(t)$ is the mean percent drug dissolved of e.g. a reference product, and $T(t)$ is the mean percent drug dissolved of e.g. a test product.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded).
- The time points should be the same for the two formulations.
- Twelve individual values for every time point for each formulation.
- Not more than one mean value of > 85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

An $f_2$ value between 50 and 100 suggests that the two dissolution profiles are similar.

When the $f_2$ statistic is not suitable, then the similarity may be compared using model-independent or model-dependent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods to the $f_2$ statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified. Evidence that the relevant mathematical software application has also been satisfactorily validated should also be provided. A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

Appropriate regulatory guidance is also published by the FDA “Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms.” Although this is not specifically intended for veterinary medicinal products the same principles apply.
DEFINITIONS

ANOVA model: Analysis of variance model

BCS: Biopharmaceutics Classification System, see Annex

Bioavailability: The proportion of an administered compound that is absorbed from a pharmaceutical form and becomes systemic available.

Bioequivalence: The similarity between two products that contain the same active substance(s) or the same therapeutic moiety and that show similar rate and amount/extent of absorption of the compound. In most cases the rate and amount/extent of absorption is expressed as $C_{\text{max}}$ and AUC. The aim is to show that two medicinal products are similar to such degree that their systemic effects, with respect to both efficacy and safety, will be essentially the same.

Biowaiver: The possibility of waiving in-vivo bioequivalence studies in favour of specific comparative in-vitro testing in order to conclude bioequivalence of oral immediate release products with systemic action.


Immediate release formulations: Formulations showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid dosage form, the dissolution profile of the active substance depends essentially on its intrinsic properties.

Modified release formulations: Formulations where the rate and/or place of release of the active substance(s) is different from that of a conventional-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified-release dosage forms include prolonged-release, delayed-release and pulsatile-release dosage forms.

NCE: New Chemical Entity

Therapeutic moiety: The molecule or ion, excluding those appended portions of the molecule that cause the active substance to be an ester, salt or other non-covalent derivative (e.g., hydrate, complex, chelate) of the molecule, responsible for the physiological or pharmacological action of the active substance.
REFERENCES (scientific and/or legal)

- Guideline on statistical principles for veterinary clinical trials (CVMP/816/00)
- Guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/EWP/133/99)
- Guideline on Fixed Combination Products (EMEA/CVMP/83804/2005)
- Guideline for investigations of chiral substances (EMEA/CVMP/128/95)
- Quality of Modified Release Dosage Forms for Veterinary Use (EMEA/CVMP/680/02)

References to scientific publications which also might be of use for the applicant include:

ANNEX – BCS-BASED BIOWAIVERS

1. INTRODUCTION

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the requirements for *in-vivo* bioequivalence studies, i.e. it may represent a surrogate for *in-vivo* bioequivalence. *In-vivo* bioequivalence studies may be exempted if the equivalence in the *in-vivo* performance can be justified by satisfactory *in-vitro* data. Provided certain prerequisites are fulfilled as outlined in this document comparative *in-vitro* dissolution could be even more discriminative than *in-vivo* studies.

Applying for a BCS-based biowaiver is restricted to highly soluble active substances with known absorption in target animals and which are considered non-critical in terms of efficacy and safety. The concept is applicable to pharmaceutically equivalent immediate release, solid pharmaceutical forms for oral administration and systemic action. However, it is not applicable for modified release formulations.

BCS-based biowaiver are intended only to address the question of bioequivalence between a test and a reference product. Hence, respective investigations may be useful to prove bioequivalence between early clinical trial formulations and final formulation to-be-marketed, generics and innovator products, and in the case of variations that require bioequivalence testing.

2. GENERAL CONSIDERATIONS

By knowing a compound’s solubility and intestinal permeability characteristics, active substances can be classified into one of four categories.

2.1 **Class I: high solubility, high permeability.**

These are generally very well absorbed. For those Class I compounds formulated as immediate release products, dissolution rate generally exceeds gastric emptying. Therefore, nearly 100% absorption can be expected if at least 85% of a product dissolves within 15 minutes of *in-vitro* dissolution testing across a range of physiological pH values.

2.2 **Class II: low solubility, high permeability.**

The bioavailability of products containing these compounds is likely to be dissolution-rate limited. For this reason, a correlation between *in-vivo* bioavailability and *in-vitro* dissolution rate may be observed.

2.3 **Class III: high solubility, low permeability.**

Absorption is permeability-rate limited but dissolution will most likely occur very rapidly (more than 85% within 15 minutes). For this reason, there has been some suggestion that as long as the test and reference formulations do not contain agents that can modify the active substance permeability or gastrointestinal transit time, waiver criteria similar to those associated with Class I compounds may be appropriate.

2.4 **Class IV: low solubility, low permeability.**

These show very poor oral bioavailability. These compounds are not only difficult to dissolve but once dissolved, exhibit limited permeability across the gastrointestinal mucosa.
3. SUMMARY REQUIREMENTS

BCS-based biowaiver are applicable for an immediate release formulation if:

- the active substance has been proven to exhibit high solubility and complete absorption (BCS-Class I; for details see Annex section 4), and
- very rapid (more than 85% within 15 minutes) in-vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements (see Annex section 5.1), and
- excipients which are not expected to have any relevant impact on bioavailability (see Annex section 5.2).

BCS-based biowaiver are also applicable for an immediate release formulation if:

- the active substance has been proven to exhibit high solubility and limited absorption (BCS-Class III; for details see Annex section 4), and
- very rapid (more than 85% within 15 minutes) in-vitro dissolution of the test product and the reference product has been demonstrated considering specific requirements (see Annex section 5.1), and
- excipients are qualitatively the same and quantitatively very similar (see section 5.2).

Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing BCS Class III than for BCS Class I active substances.

Since interspecies differences in diet and gastrointestinal physiology might result in differences in the absorption characteristics of various compounds, it should be noted that BCS classification will be species specific.

4. ACTIVE SUBSTANCE

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the characteristics of the active substance particularly required in this biowaiver concept.

Biowaiver may be applicable when the active substances in test and reference products are identical or belong both to the BCS-class I (high solubility and complete absorption; see Annex sections 4.1 and 4.2) in case of different salts. However, biowaiver may not be applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference product since these differences are likely to lead to different bioavailabilities not deducible by means of experiments used in the BCS based biowaiver concept.

The active substance should not belong to the group of ‘narrow therapeutic range’ medicinal products.

4.1 Solubility

The pH-solubility profile of the active substance should be determined and discussed. The active substance is considered highly soluble if the highest single amount administered as immediate release formulation(s) is completely dissolved in a volume of buffer corresponding to the gastric volume of the target species of buffers within the range of possible physiological pH values (1 - 7.5) at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 7.5) and in addition at the pKa, if it is within the specified pH range. A minimum of three replicate determinations at each pH condition is recommended (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active substance to a buffer.
Appropriate buffer volumes could be estimated as follows:

<table>
<thead>
<tr>
<th>Species</th>
<th>Gastric volume (to be used as volume of solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>200 litres (rumen)</td>
</tr>
<tr>
<td>Pre-ruminating calf</td>
<td>2 litres</td>
</tr>
<tr>
<td>Swine</td>
<td>8 litres</td>
</tr>
<tr>
<td>Horse</td>
<td>18 litres</td>
</tr>
<tr>
<td>Chicken</td>
<td>0.1 litres</td>
</tr>
<tr>
<td>Turkey</td>
<td>0.4 litres</td>
</tr>
</tbody>
</table>

### 4.2 Absorption

Complete absorption (i.e. extent of absorption at least 85%) in target animals is preferred for BCS-based biowaiver applications. Complete absorption is generally related to high permeability.

Complete absorption of the active substance should be justified based on reliable investigations in target animal species. Data from

- absolute bioavailability or
- mass-balance studies could be used to support this claim.

Data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound, Phase 1 oxidative, and Phase 2 conjugative metabolites account for at least 85% of the amount administered. It has also been demonstrated that high Phase 1 (oxidative) and Phase 2 (conjugative) metabolism would support the evaluation of complete absorption if the recovery in urine and faeces account for more than 85% of the amount administered.

In addition highly soluble active substances with incomplete absorption, i.e. BCS-class III compounds, could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and in-vitro dissolution (see also Annex section 5.2).

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed in-vitro permeability investigations including a reference standard may also be considered supportive to in-vivo data.
5. VETERINARY MEDICINAL PRODUCT

5.1. In-vitro Dissolution

5.1.1 General aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference product should have a similar in-vitro dissolution considering physiologically relevant experimental pH conditions. At least three different pH conditions should be employed, representative of the full physiological spectrum of the gastrointestinal tract of the target species, e.g. pH 1.2, 4.5, and 7.5. Additional investigations may be required at pH values in which the active substance has minimum solubility. The use of any surfactant is strictly discouraged.

Test and reference products should meet requirements as outlined in section 5.5 of the guideline. It is advisable to investigate more than one single batch of the test and reference products in order to ensure that respective results are representative.

The test methodology should be in accordance with pharmacopoeial requirements unless those requirements are shown to be unsatisfactory and/or do not reflect the in-vivo dissolution (i.e. biorelevance). Alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in-vivo.

Complete documentation of in-vitro dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

5.1.2 Evaluation of in-vitro dissolution results

Medicinal products are considered ‘very rapidly’ dissolving when more than 85% of the amount is dissolved within 15 minutes. In cases where this is demonstrated for the test and reference product in all requested media the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation. Discussion of dissolution profile differences in terms of their clinical/therapeutic relevance is considered inappropriate since the investigations do not reflect any in-vitro/in-vivo correlation.

5.2 Excipients

Although the impact of excipients in immediate release formulations on bioavailability of highly soluble and completely absorbable active substances (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I products it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

If a biowaiver is applied for a BCS-class III active substance excipients have to be qualitatively the same and quantitatively very similar to exclude different effects on membrane transporters.

As a general rule, for both BCS-class I and III active substances well-established excipients in usual amounts should be employed and possible interactions affecting the active substance’s bioavailability and/or solubility characteristics should be considered and discussed. A description on the function of the excipients is required with a justification whether the amount of each excipient is within the normal range.
So-called ‘active’ excipients should be identified as well as their possible impact on:
- gastrointestinal motility (e.g. sorbitol, mannitol),
- susceptibility of interactions with the drug substance (e.g. complexation with EDTA),
- drug permeability,
- interaction with membrane transporters.

In cases where critical excipients are relevant the same amount should be used in the test product as in the reference product.

6. FIXED DOSE COMBINATIONS

BCS-based biowaiver are applicable for immediate release Fixed Dose Combinations products if all active substances in the combination belong to BCS-class I or III considering specific formulation considerations (see Annex section 5.2). Otherwise in-vivo bioequivalence testing is required.

7. BIOWAIVERS FOR DOSAGE FORMS FOR USE IN-FEED OR DRINKING WATER

7.1 Biowaiver for dosage forms for use in-feed

These products may be treated as immediate release formulations and can be regarded as eligible for a biowaiver if they fulfil the BCS criteria.

Feed constituents may affect the bioavailability of the active substances administered in-feed. However, it is believed that this should not be a factor in considering a biowaiver request since the variability in-feed constituents between the test and reference product should not be greater than the natural variations that can occur in the final feed to which the animal will be exposed, whether that feed contains the test product or the reference product. Accordingly, a product for use in-feed which contains insoluble constituents as excipients could also be eligible for a biowaiver, provided the active substance fulfils the BSC criteria.

7.2 Biowaiver for Soluble Dosage Forms for Use in Drinking Water

The conceptual basis for granting biowaivers for these soluble dosage forms is that once a medicinal product is presented in a solution prior to administration, the product's formulation will usually not influence the bioavailability of the active substance.

This is because, from a mechanistic perspective, it is believed that the rate-limiting step in systemic drug absorption will be: a) the rate of gastric transit; and b) the permeability of the active substance across the gastrointestinal mucosal membranes. Both of these variables are here formulation-independent.

The only exceptions are when the formulation contains substances other than the active substance that could cause a direct pharmacologic effect (e.g., altered gastrointestinal transit time, membrane permeability, or drug metabolism), or when there is inactivation of the active substance by, for example, a chelating agent.