EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 November 2017
EMEA/CVMP/EWP/133/1999-Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on conduct of pharmacokinetic studies in target animal species

Draft

Initial guideline adopted by CVMP	8 March 2000
Date of coming into effect	8 September 2000
Draft revision agreed by Efficacy Working Party (EWP-V)	13 September 2017
Adopted by CVMP for release for consultation	9 November 2017
Start of public consultation	20 November 2017
End of consultation (deadline for comments)	31 May 2018

The proposed guideline will replace the current CVMP guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL).

Comments should be provided using this template. The completed comments form should be sent to vet.guidelines@ema.europa.eu

Keywords	pharmacokinetics, target animal species, veterinary

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Guideline on the conduct of pharmacokinetic studies in target animal species

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Executive summary

The objectives of this guidance are to specify the pharmacokinetic factors to be investigated, acknowledging that this will depend on the active substance and its use, and to provide recommendations for the conduct of pharmacokinetic studies for the purpose of supporting the clinical part of the dossier for a veterinary pharmaceutical product. In addition, general guidance is given on pharmacokinetic-pharmacodynamic modelling and population pharmacokinetics, should applicants opt to pursue these approaches.

1. Introduction (background)

In general, pharmacokinetic studies can be carried out to support studies on clinical efficacy, tolerance in the treated animal, and safety for the consumer, the user and the environment. The principal objectives are to characterise the absorption, distribution, metabolism and excretion of the active substance(s) in the product for which authorisation is sought.

Pharmacokinetic studies, particularly in conjunction with pharmacodynamic data, are important to support effective and safe dosage regimens. Accordingly, a specific section on pharmacokinetic-pharmacodynamic modelling approaches has been added to this revised guideline. In addition, pharmacokinetic studies may be used to establish dosage regimens according to various population variables (e.g. age, breed, disease status). To address this, a section on the reporting of the results of population pharmacokinetic analyses has been included. Finally, pharmacokinetic studies can also highlight potential drug interactions, either between the active substance(s) and those in concomitantly administered products or between active substances intended for a fixed combination product.

2. Scope

This note is proposed to provide guidance and assistance to applicants in the design, execution and analysis of pharmacokinetic investigations of (a) a given systemically-acting active substance in a specific pharmaceutical form in the target species or (b) a locally-acting substance with potential unintended systemic effects, irrespective of the pharmacological class of the active substance or the animal species in which use of the product is intended. Guidance on studies to investigate consumer safety or studies to assess the pharmacokinetics of substances in biological products is outside the scope of this document. For more information on the pharmacokinetic and residue studies in target species required to address consumer safety, the reader is referred to VICH GL 46, GL 47 and GL 48 on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals.

This note for guidance only considers general principles and all the points mentioned do not necessarily apply to each active substance and all species. Therefore, each study should be planned and designed to take into account the properties and uses of the active substance and the anatomical, physiological and behavioural peculiarities of the species in which the active substance is investigated. For pharmacokinetic studies in fish, it is recommended that the Guideline on demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish (EMA/CVMP/EWP/459868/2008) is also consulted.

This note introduces guidance on the reporting of pharmacokinetic-pharmacodynamic modelling and population pharmacokinetic studies. However, guidance on physiologically-based pharmacokinetic modelling has been excluded, as the experience of employing this methodology for research in veterinary medicine is currently limited.

3. Legal basis

This document should be read in conjunction with Directive 2001/82/EC, as amended (Annex I, Part 4, Chapter I, section A.3). Applicants should also refer to other relevant European and VICH guidelines, including those listed under 'References'.

4. Pharmacokinetic factors to be investigated

Depending on the active substance and its use(s), all or some of the following items should be studied: absorption, distribution, metabolism and excretion.

4.1. Absorption

Both the rate and extent to which the active substance or active moiety are available systemically should be determined.

Generally, the rate and extent of absorption can be determined only from plasma/blood concentration-time curve data following extravascular administration.

4.1.1. Active substances intended to produce systemic effects

Whatever the route of administration (e.g. oral, intramuscular, subcutaneous, transdermal, inhalational) of the veterinary medicinal product, the rate of absorption of the active substance should be quantified.

Whenever possible, comparison with an equivalent intravenous dose should be made, as only intravenous (bolus or infusion) data permit the evaluation of the absolute bioavailability.

Preferably, a precise pharmacokinetic analysis of the entire plasma concentration profile should be made. This refers particularly to special formulations, for which a delayed release of the active substance or a prolonged duration of action is claimed. Deviations from this should be justified. As a minimum, the following parameters should be determined for the active substance(s) and/or relevant metabolite(s): concentration at peak (C_{max}), time to reach peak concentration (T_{max}), and area under the concentration/time curve (AUC_{∞} and AUC_t).

The pharmacokinetic study should be conducted in accordance with the intended use of the product. In particular, for orally administered products, it may be necessary to evaluate the impact of the feeding state (e.g. fed versus fasted) on the rate and extent of absorption of the active substance by means of bioavailability studies.

4.1.2. Active substances not intended to produce systemic effects

Confirming that systemic exposure to the active substance(s) is not of a magnitude at which systemic effects could be elicited may be sufficient to waive further pharmacokinetic investigations. However, a

low bioavailability does not necessarily infer an absence of systemic effects since plasma concentrations may still be sufficiently high to produce such effects (e.g. if the administered dose is high). Furthermore, some active substances can produce systemic effects at very low plasma concentrations (e.g. corticosteroids, antimicrobial agents, ectoparasiticides) or when presented in a particular pharmaceutical dosage form (e.g. intrauterine, intramammary formulations). In relation to this, the lower limit of quantification for the analytical method should be justified.

As an alternative to *in vivo* studies, the use of suitably validated *in vitro* models to demonstrate non-absorption of the active substance(s) may be considered. Models must be relevant to the species for which the product is intended. Usually, such models will have been described in recognised peer-reviewed literature and will have been shown to be repeatable across different laboratories.

4.2. Distribution

Unless otherwise justified, the distribution of the active substance and/or relevant metabolites should be investigated. Distribution of an active substance (and/or its metabolite(s)) in relevant body fluids (e.g. cerebrospinal fluid, synovial fluid, mucus, milk) and tissues may provide supportive information for the clinical efficacy of active substances. Determination of the distribution of active substances (and/or their metabolite(s)) could also highlight potential safety concerns (e.g. significant distribution of an active substance to renal tissue may highlight potential dose-limiting nephrotoxicity).

Protein binding can significantly affect the pharmacokinetic profile and pharmacodynamic action of an active substance (and/or its metabolite(s)). Therefore, the extent of binding of the active substance to proteins should be studied over the anticipated range of drug concentrations in plasma or other relevant biological matrices obtained after administration of the proposed dose(s).

The volume of distribution (V_d) is a measure of the extent of distribution, determined by the ratio of the amount of drug in the body (i.e. dose) to the plasma drug concentration, and should be reported. The larger the V_d, the more likely that the substance is found in the tissues of the body, while small V_d values indicate that a substance is restricted to plasma or interstitial fluid. However, the value obtained does not often correspond to a real volume. For example, tissular binding can result in volumes of distribution exceeding the total body volume many times. The V_d can be used (together with bioavailability) to calculate the dose corresponding to a desired plasma (unbound)concentration, i.e. a loading dose.

4.3. Metabolism

Unless otherwise justified, the formation of metabolites should be investigated. This should comprise not only identification of the metabolites themselves, but also the determination of the pathways involved in the metabolism of the active substance, in order to establish potential drug interactions. *In vitro* methods (e.g. hepatic microsome assays) may be considered as an option to generate such data.

If there is an indication that pharmacologically or toxicologically active metabolites are formed, and if there is reason to suspect that they contribute to the therapeutic activity and/or adverse effects, then the rate of their formation, distribution and excretion should be investigated in the target species.

4.4. Excretion

The relative contribution of the different routes of excretion of the total substance [active substance + metabolite(s)] should be quantified (e.g. expressed as a percentage of the administered dose). For

example, it is useful to know the fraction of the dose subjected to renal and/or hepatic clearance in order to predict the influence of renal and/or hepatic disease on the excretion of the active substance from plasma.

5. Methodology and conditions of study

All pharmacokinetic studies should be performed according to validated and internationally accepted methods. Studies conducted following Good Laboratory Practice (GLP) are preferred. Preferably, the final formulation intended for marketing should be used for such studies. Failing this, a justification for extrapolation of the data to the final formulation must be provided.

5.1. Animals

Studies should be performed in the target species under well-defined and controlled conditions. The breed, group size, age (adult, young, neonate), physiological status (e.g. pregnancy) and gender should be specified and justified.

Basic pharmacokinetic studies should be carried out under laboratory conditions in a number of clinically healthy animals. The number of animals used should be justified. However, if it is known or suspected, e.g. through peer-reviewed literature, that the pharmacokinetics of the active substance (and/or its metabolites) are likely to be significantly altered by the treated disease or by a common concomitant condition, consideration should be given to further investigating the pharmacokinetics in animals enrolled in clinical efficacy studies or in field studies (see also section 6.2).

If a PK/PD modelling approach, as outlined in section 6.1, has been chosen as a means to select the dosage regimen, the pharmacokinetic data obtained from this(ese) study(ies) (generally conducted in experimental disease models) may be sufficient to satisfy the requirements for pharmacokinetic data.

5.2. Administration

Special attention should be given to the route and method of administration of the veterinary medicinal product, as this may affect the absorption of the active substance.

For administration of the active substance to individual animals, the dose should be expressed on a body weight (mg/kg bw) basis; if the dose is intended to be on a body surface area basis, it should be expressed both on a body weight and body surface area basis. The procedure used to estimate body surface area should be described.

In case of a solid formulation, e.g. tablet or bolus, which cannot be administered precisely on a mg/kg body weight basis, the actual dose of active substance administered to animals should be calculated based on their individual body weights.

When the product is administered via the feed or drinking water, the daily dose of the active substance in mg/kg bw should be calculated, preferably on an individual animal basis. If the exact dose per animal cannot be measured, the dose should be estimated based on the following parameters: number of animals per group, average bodyweight, concentration of active substance in the feed or drinking water, and average feed or drinking water intake. Since the concentration-time profile for an active substance can be affected by the method of administration, administration of such products by oral gavage will only be accepted if suitable for the purpose of the study, e.g. determination of basic pharmacokinetic parameters.

5.3. Fixed combinations

In combining substances into a fixed combination product, unintended pharmacokinetic interactions might occur, leading to a lack of activity and/or adverse effects. Alternatively, an interaction may be the intention of combining substances, e.g. combination with a metabolism inhibitor. In order to evaluate possible pharmacokinetic interactions, the concentration-time profile should be determined for each individual active substance when administered as a mono-substance product, and compared to the concentration-time profile of the active substances when administered as the combination product, unless otherwise justified.

The study should be designed based on the expected behaviour of the substances in combination, and be suitably powered to enable a difference between pharmacokinetic parameters to be detected, if a difference truly exists. When an absence of interaction is to be claimed, it is recommended to use equivalence testing. Superiority testing is not adequate to conclude on an absence of interaction as a non-significant outcome may relate to a low statistical power. The acceptance limit for the 90% confidence intervals around the ratios (substance in combination/mono-substance) for the main pharmacokinetic parameters (generally C_{max} and AUC) should be justified.

For certain topical or local treatments, such data may not be required; in these cases, the omission of data should be justified.

5.4. Dosing

The pharmacokinetics of the active substance(s) should be determined at the recommended dosage regimen in the target species. In addition, investigation of dose proportionality is important to facilitate prediction of the effects of dose adjustments. Preferably dose proportionality should be investigated during the early phases of drug development. However, kinetic data obtained from target animal safety studies or dose determination studies may also be accepted as a means to determine dose proportionality.

For an active substance that has not previously been used in a veterinary medicinal product in the target species, kinetic studies using at least three different dose levels should be performed. The choice of dose levels should be justified. Appropriate statistical tests should be carried out to determine dose proportionality. The omission of data should be justified.

For established active substances where a range of therapeutic doses is recommended and dose proportionality is documented in the target species, single dose studies, corresponding to the highest intended therapeutic dose, are generally sufficient. Where there is no dose proportionality or a very steep dose/effect curve, studies using three different dose levels, encompassing the dose range, may be necessary.

For established active substances, single dose studies may be sufficient where a single dose level is recommended. The ability to dose accurately should be considered when designing such studies, particularly in cases where there is a solid formulation e.g. tablet.

If the posology requires repeated (including long-term) treatment or if therapeutic use of the active substance relies on steady-state conditions, repeated dose studies should be performed. In the case of products intended for long-term (or lifelong) use, the duration of such studies should exceed the time required to reach steady-state, thereby clearly demonstrating the time at which steady-state is attained.

Repeated dose studies should be conducted using the recommended dosage regimen (dose, dosing interval, number of administrations); such studies should give insight into questions such as accumulation kinetics, steady-state levels and induced effects (e.g. altered metabolism rate and altered disposition). Comparison of plasma concentration profiles after administration of the first and last dose is highly desirable.

Repeated dosing followed by an examination of the washout period may elucidate the existence of a slow elimination phase which might not be detected following a single dose.

Derivation of data relating to repeated dosing from target animal safety studies may be acceptable.

5.5. Sampling

Suitable biological fluids (blood, plasma, serum, urine, etc.) and tissues, if appropriate, should be selected for pharmacokinetic investigation. Plasma is generally considered to be the most useful biological fluid for such studies.

5.5.1. Blood sampling

Attention should be given to the site of blood collection, sampling procedure, the material used for sampling, blood collecting tubes, anticoagulant and conditions of centrifugation to obtain plasma. The stability of the substance during sampling and under conditions of storage pending analysis should be assessed.

The number of blood samples and the timing of sampling should be appropriate to allow adequate determination of absorption, distribution and excretion. With regard to absorption, there should be a sufficient number of samples taken around the anticipated T_{max} to ensure a reliable estimate of peak exposure (C_{max}). In addition, unless otherwise justified, AUC_t should equate to at least 80% of AUC_∞ to achieve a reliable estimate for the extent of exposure.

To investigate the distribution and excretion phases, blood samples in the post-absorption phase should be obtained over as long a period as is necessary for the purpose of the investigation. At least three samples are needed during the terminal log-linear phase in order to reliably estimate the elimination rate constant and obtain accurate estimation of AUC_∞.

5.5.2. Other biological fluids and tissues

In some cases, the collection of other biological fluids and/or tissues may be considered appropriate for the determination of pharmacokinetic parameters (e.g. if analytical constraints limit the usefulness of blood samples, urine samples may be used to determine the terminal disposition slope if this is the main route of excretion) or parameters of particular interest (e.g. local distribution to support a claim). The choice of biological fluid and/or tissue should be justified.

Collection of some of these fluids requires special attention (e.g. immediate pH measurement of urine, conditions of storage).

According to Directive 2010/63/EU, ‘special attention should be paid to ascertain the absence of pain and discomfort when using a biopsy method’; therefore, repeated biopsies using local anaesthesia are only acceptable in those cases where no other sampling techniques are possible.

5.6. Analytical procedure

Active substance (and its metabolite(s)) concentrations should be determined using appropriate analytical methods. When relevant, the pharmacokinetics of isomers of the active substance should be considered (see guideline, Investigation of chiral active substances, EMEA/CVMP/128/95). The omission of pharmacokinetic data for inactive enantiomers is acceptable, provided that their lack of pharmacological and toxicological activity is sufficiently justified.

The use of a chemical assay method is preferred (e.g. HPLC methods). The method and its validation should be accurately described using an internationally accepted format. For validation of the method, other guidelines might provide useful information, for example, the CHMP guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009-Rev.1).

5.7. Pharmacokinetic calculations and interpretation

Appropriate mathematical methods should be used to generate basic parameters (compartmental and/or non-compartmental analysis). With regard to compartmental analysis, the relevance of compartments should be discussed, if necessary (e.g. presence of a 'deep' compartment in relation to antimicrobial resistance).

Appropriate pharmacokinetic computer programs should be used under specified conditions (regression methods, weighting factor, etc.).

Pharmacokinetic parameters should be calculated using time-concentration data from individual animals, and descriptive statistics should be presented. The individual animal data should be provided.

6. Special approaches

Special approaches (e.g. simultaneous modelling of pharmacokinetics and pharmacodynamics, population kinetics) are encouraged, where applicable.

6.1. Pharmacokinetic-pharmacodynamic (PK/PD)modelling

Selection of dose level and dosing interval by means of a PK/PD modelling approach may be considered, though the duration of treatment would have to be demonstrated by other means. Such data may replace standard dose determination studies provided that the selected dose level and dosing interval are supported by standard dose confirmation studies. Furthermore, all aspects of the PK/PD methodology should be justified. These include, but are not limited to, the following:

- The number of animals used for the PK/PD study, taking into account expected variability in PK and PD parameters.
- Samples: Samples should be collected from the most relevant biological matrix. In most cases, this will be plasma or whole blood but, in some instances, drug concentration in other biological fluids or tissues might be more relevant to the observed pharmacological effect. However, with regard to tissue samples, in particular, it should be noted that whole tissue (homogenate) drug concentrations are largely uninformative with regard to the drug concentration at the target site. Therefore, where possible, drug concentrations in the relevant tissue compartment should be determined.

Ideally, pharmacokinetic and pharmacodynamic data should be collected from the same animals. However, where this is not possible (e.g. if the PD parameter is altered by the sampling procedure), a further group of animals that is matched for demographic data and methodology may be used. The inclusion of a vehicle-treated control group should also be considered for establishing the PD baseline, e.g. if the formulation vehicle is suspected to have a pharmacological effect or if the PD parameter exhibits circadian variation.

- Sample numbers and time-points: The frequency of time-points should allow a detailed description of (a) the rise and decay of drug concentrations, and (b) the onset, duration and cessation of the PD response. To obtain reliable parameter estimates (e.g. E_{max} (maximum effect), EC_{50} (drug concentration that elicits 50% of E_{max})), a study comprising multiple dose levels (including negative control) may be required. In addition, it should be possible to determine if hysteresis (i.e. a temporal delay between drug exposure and PD response) has occurred and, furthermore, if the delay is PK (e.g. slow rate of drug distribution from the plasma to the site of action) or PD (e.g. a cascade of cellular events occurs before the response is observed) in origin, in order to inform construction of the PK/PD model (e.g. effect compartment model versus indirect response model).

- Pharmacodynamic parameter selection: The selected PD parameter should be relevant, sensitive and reproducible. In cases where direct measurement of the clinical endpoint is difficult, the use of biomarkers/surrogate end-points may be considered. However, the choice of biomarker/surrogate end-point should be justified (e.g. through studies from peer-reviewed scientific literature).

- Model selection: The selected PK/PD model, including assumptions and rationale for model components (e.g. temporal changes in baseline, presence/absence of an effect compartment, presence/absence of moderator functions to account for tolerance or drug-induced induction/inhibition of PK processes) should be fully described. The method used for fitting a model to the data, the ability of the model to predict the observed data, and the treatment of outliers and/or missing data should also be provided.

- Interpretation: In addition to discussing the results, the variability observed in the PK and PD parameters should be discussed with regard to the impact on data quality, selection of the PK/PD model and interpretation of the results.

Further guidance on the PK/PD relationship for specific therapeutic drug classes can be found in the following documents:

- Guideline for the demonstration of efficacy of veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).

- Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (EMA/CVMP/EWP/1061/2001).

6.2. Population Pharmacokinetics (PopPK)

Within a population, the effect of a drug can vary markedly from one individual to another, and therefore between animals used in laboratory-based dose determination studies and those encountered in field trials. Sources of this variability may be pharmacokinetic and/or pharmacodynamic in origin, and factors that have been reported to influence pharmacological effect include age, gender, body weight, disease status and genetics. The aforementioned factors may not only alter the mean value of a parameter but also its variance, thereby increasing inter-individual

variability. Meanwhile, intra-individual variability may arise through cellular mechanisms such as those related to the development of tolerance or up-regulation of metabolic processes. Further unpredictable variability may occur, e.g. as a result of methodological errors.

Population pharmacokinetics may be considered as a means to refine dose level and dosing interval using PK data from individuals, which are more closely representative of the target population (e.g. if the animals used in laboratory studies have markedly different demographics and/or disease status to those that will be treated in the field) or to support dosing recommendations for specific sub-populations (e.g. with regard to age, breed). In most cases, PopPK data will be generated as part of a field trial, though it must be ensured that assessment of efficacy and/or safety endpoints is not compromised. Should such an approach be undertaken, the following general guidance on reporting of the analysis is applicable:

- A description of the data used for the analysis (e.g. sample matrix, the number of animals, the number of samples per animal, sampling time-points, covariates measured) should be provided. The sampling protocol used (e.g. single/multiple-trough sampling design versus full pharmacokinetic screen) should be justified, including an explanation of any limitations and their potential impact on the study results.
- All raw data should be presented appropriately (e.g. linear and/or log-linear plots for PK data; summary statistics and histograms for continuous covariates; frequencies for categorical covariates). If applicable, the accuracy and precision with which covariates were measured should be stated.
- The modelling approach should be described and justified. This should include discussion of assumptions made during analysis, and the criteria used for model selection and covariate inclusion. With regard to the latter, both statistical and clinical relevance should be considered, as should correlation between covariates. All stages of model construction should be presented, including diagnostic plots, and the software and version used stated. Model validation procedures should be described and justified.
- The approach used to handle missing data and outliers, if any, should be addressed.
- Results should comprise PopPK parameter estimates (with standard errors/confidence intervals), estimates of random effect parameters (inter- and intra-individual variability), the effects of covariates on PK parameters and inter-individual variability, and results of model validation.
- The discussion should contain the following elements: outcome of model validation, the influence of covariates on PopPK parameters, and how well the results correlate with data obtained from laboratory-based studies. The consequences of the results (e.g. requirement for dosage regimen adjustment or dosing recommendations for specific sub-populations) should be discussed.

Definitions

Accumulation: The increase in drug concentration that occurs with each additional dose.

Area under the curve (AUC): Area under the drug concentration versus time curve, which serves as a measure of drug exposure. It includes several different types of AUC estimates:

- AUC_t: AUC to the last sampling time associated with quantifiable drug concentrations. The last quantifiable concentration (the lower limit of quantification, LLOQ) is determined by the sensitivity of the analytical method. The last quantifiable drug concentration may occur prior to the last sampling time.
- AUC_∞: AUC_t with the addition of the extrapolated area from the last quantifiable drug concentration to time infinity.

C_{max}: The maximum (or peak) concentration of the active substance or its metabolite(s) in the matrix of interest during a dosing interval.

Covariate: Secondary explanatory variable to the measured clinical variable that likely influences the observed result.

Dose: Amount of active substance(s) to be given to an animal; it is usually expressed in mg/kg bodyweight.

Dose proportionality: For a linear pharmacokinetic system, measures of exposure (e.g. AUC, C_{max}) are proportional to the dose.

Enantiomers: Active substances with a chiral structure, i.e. two forms exist which are non-superimposable mirror images of each other. Enantiomers may exhibit different pharmacological and/or toxicological activities.

Fixed combination: A combination of active substances within a single pharmaceutical form.

Racemic mixture: Mixture composed of equal amounts of left-handed and right-handed enantiomers.

Steady-state: The situation when the amount of drug administered in a given time period is equal to the amount of drug eliminated in that same period.

T_{max}: Time to the C_{max}.

Volume of distribution: Ratio of the amount of drug in the body at a given time to the plasma (blood) concentration at that time.

References

CHMP Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009-Rev.1)

CVMP Guideline on the conduct of efficacy studies for non-steroidal anti-inflammatory drugs (NSAIDs) (CVMP/EWP/1061/2001)

CVMP Guideline on the demonstration of efficacy of veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)

CVMP Guideline on the demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish (CVMP/EWP/459868/2008)

CVMP Guideline on the investigation of chiral active substances (EMEA/CVMP/128/95)

Directive 2010/63/EU of 22 September 2010 of the European Parliament and of the Council on the protection of animals used for scientific purposes

VICH GL46 – Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues (MRK)

VICH GL47 - Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: comparative metabolism studies in laboratory animals

VICH GL48 - Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker-residue-depletion studies to establish product withdrawal periods