

Guidance document

Authorisation of veterinary medicinal product with known API

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1 Definitions, terms and abbreviations

1.1 Definitions and abbreviations

1.1.1 Veterinary medicines with known active pharmaceutical ingredients (known APIs)

Veterinary medicines with known APIs are those containing an active pharmaceutical ingredient that is or was contained in a veterinary medicine authorised by Swissmedic (Art. 12, para. 1, VAZV). The possibility of referring to complete, approved documentation on a reference product that is in the possession of Swissmedic constitutes justification for the simplified authorisation of veterinary medicines with known APIs.

Veterinary medicines that have been authorised abroad for a considerable time (over 10 years, i.e. APIs with "well-established use") but that have never been authorised by Swissmedic are therefore not considered to be known APIs.

1.1.2 Reference product for a product with a known API

A reference product for a product with a known API is a medicinal product authorised by Swissmedic on the basis of complete, specific documentation (Parts I-IV) containing the same active pharmaceutical ingredient as that in the product for which authorisation is sought. The reference product is used as a reference in the authorisation documentation submitted for a product with a known API with regard to the preclinical and clinical characteristics (efficacy and safety).

An applicant may base documentation on test results provided for other reference products if the application for its product with a known API concerns an indication, a pharmaceutical form, a target species, a dosage strength, a dosage recommendation and / or a route of administration that has / have not been authorised for the primary reference product. In this case, the innovative aspects with regard to the additional product used as a reference must have been authorised on the basis of complete documentation.

1.1.3 Requirements relating to the comparator product

The following alternatives are available in order to prove that the test results from a trial can be applied by analogy:

- a) The reference product authorised in Switzerland is compared directly to the product with the known API concerned by the authorisation application, or
- b) A foreign comparator product is used, whose quality-relevant properties are then compared with the Swiss reference product (pharmaceutical bridging).

1.1.4 Comparability of a foreign comparator product with the Swiss reference product (pharmaceutical bridging)

If a medicinal product obtained abroad is used, the data on the foreign comparator product must be submitted in Part 1 of the documentation and mentioned in the cover letter. Reference must be made to all of the comparison criteria between the foreign comparator product and the Swiss reference product listed below and must be presented in a tabulated summary and assessed.

A comparator product obtained abroad may be used as such as long as it fulfils all of the following criteria for proving comparability with the Swiss reference product:

- 1st The medicinal product is authorised in a country with comparable medicinal product control in accordance with Art. 13, TPA. A current list of these countries is published on the Swissmedic website.
- 2nd Name and address of the authorisation holder of the foreign medicinal product used, name of the medicinal product, country where authorised, source country, source supplier (address of wholesaler or pharmacy), authorisation number, batch number, expiry date and analysis certificates for the foreign medicinal product) must be provided.
- 3rd If the foreign comparator product is used in a bioequivalence trial, proof must also be provided that the qualitative and quantitative composition of the active pharmaceutical ingredient is comparable and that the qualitative composition of the excipients is comparable. If the data available reveals differences or if such differences are proved to exist, it must be demonstrated that they have no influence on efficacy, safety and tolerability. Reference may be made to scientific literature in this connection.
- 4th For solid pharmaceutical forms used in a bioequivalence trial, any differences with regard to the pharmaceutical form used (tablets, film-coated tablets, capsules, etc.) must be evaluated. The dimension and weight must be determined and – for pharmaceutical form with modified release – the release principle must be defined.
- 5th In order to determine the similarity, in vitro active substance release profiles must be carried out under various pH conditions in accordance with the *Guideline on the Conduct of Bioequivalence Studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4*.

1.1.5 Test product

The test product is

- the medicinal product used in the comparative analysis to compare it with the reference product
- or the active pharmaceutical ingredient used within the framework of the preclinical analysis

The medicinal product for which authorisation is sought and the test product have the same composition and specifications, and are manufactured using the same procedures. Any differences between the test product and the product for which authorisation is sought must be described and evaluated.

1.1.6 Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent if they have the same molar mass of the same active pharmaceutical ingredient, are in the same pharmaceutical form, and are administered under the same conditions via the same route of administration. Pharmaceutical equivalence does not necessarily imply bioequivalence, since differences in the composition of the excipients and / or in the manufacturing process or additional variables may have an impact.

1.1.7 Bioequivalence

Two medicinal products with the same active pharmaceutical ingredient(s) are considered as equivalent after administration of the same molar doses to the same target animal species if the rate of absorption (C_{max} and t_{max}) and the extent of the systemic availability (AUC) are comparable. The individual conditions applicable with regard to trial design, measurement parameters, statistical methods, threshold values, etc., see *Guideline on the conduct of Bioequivalence Studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4* and *VICH GL 52: Bioequivalence: blood level bioequivalence study*.

1.1.8 Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) classifies pharmaceutical substances on the basis of their solubility in aqueous solutions and their intestinal permeability. Together with the *in vitro* release of the active pharmaceutical ingredient from the pharmaceutical product, the BCS takes three main factors into account, which define the rate and extent of the absorption of oral forms. For details, see *WHO Prequalification Technical Report Series 937 – Annexes 7 and 8* and the *Guideline on the conduct of Bioequivalence Studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4 Appendix I*.

1.1.9 Biowaiver

Subject to certain requirements that must be fulfilled, Swissmedic may state that there is no need for a bioequivalence trial in animals. In such cases evidence for equivalence is not provided by *in vivo* bioequivalence trials by other investigations or evidence (e.g. *in vitro* trials)

1.2 Abbreviations

AUC	Area under the Curve
BCS	Biopharmaceutical Classification System
CVMP	Committee for Veterinary Medicinal Products
C_{maX}	Peak plasma level
EMA	European Medicines Agency
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Known API	Medicine with known active pharmaceutical ingredient
t_{max}	Time of occurrence of peak plasma level
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Licensing of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance, TPO) (SR 812.212.21)
VICH	International Conference on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation

2 Introduction and objective

This guidance document describes the requirements pertaining to the documentation that must be submitted with an application for the authorisation of a veterinary medicine with a known active pharmaceutical ingredient or a veterinary medicine with a combination of known active pharmaceutical ingredients. When Swissmedic evaluates application documentation, it also takes into consideration the latest valid edition of the Pharmacopoeia, the relevant guidelines from the European Committee for Veterinary Medicinal Products (CVMP) and from the International Conference on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

3 Scope

This guidance document is valid for applications for the simplified authorisation of a veterinary medicine with a known active pharmaceutical ingredient or a combination of known active pharmaceutical ingredients in accordance with Art. 14, para. 1 a TPA.

4 Legal basis

The simplified procedure for the authorisation of veterinary medicines with known active pharmaceutical ingredients is based primarily on the following legal foundations (provisions of laws and ordinances):

TPA:

- Art. 10 Conditions for granting a marketing authorisation
- Art. 12 Authorisation of essentially identical medicinal products
- Art. 13 Medicinal products and procedures authorised in foreign countries
- Art. 14 Simplified procedures for marketing authorisation, medicinal products with known active pharmaceutical ingredients (para. 1 a)

TPO

- Art. 30 Period of protection for original preparations (Art. 12 TPA)

TPLRO

- Art. 7 Documentation on the analytical, chemical and pharmaceutical tests
- Art. 8 Documentation on innocuousness
- Art. 9 Additional documentation on innocuousness and residues, for tests on livestock
- Art. 10 Admissibility of pharmacologically active substance and proposed withdrawal times
- Art. 11 Documentation on the preclinical and clinical tests
- Art. 12 Veterinary medicine information (see Annex 6)

TPLO

- Art. 12 Basic principle
- Art. 13 Documentation on the pharmacological and toxicology tests
- Art. 14 Proof of safety and therapeutic efficacy

5 General requirements

A product containing a known API may have a new or additional indication compared to the reference product. New or additional pharmaceutical forms, dosage strengths, dosage recommendations, target species or routes of administration are also possible.

For new aspects not previously authorised in Switzerland, the documents in accordance with the guidance document *Authorisation of veterinary medicinal products HMV4* are required in principle. For the known aspects, reference can be made to the reference product that has already been authorised if the comparability of the preclinical and clinical efficacy and safety is demonstrated.

The product information for a veterinary medicine with a known API must be to a large extent identical to that for the reference product. Passages that differ from those concerning the reference products must be noted as such. Art. 28 TPO should be taken into consideration: it states that it is the duty of the authorisation holder to keep the product information updated in line with the current status of science and technology and to adjust it to reflect new findings and evaluations. These modifications must be submitted to Swissmedic as variations requiring approval.

6 Requirements relating to the dosage strengths to be examined

The dosage strength(s) and single doses to be examined and any cumulative requirements to be fulfilled for biowaivers are described in detail in the *Guideline on the conduct of bioequivalence studies for veterinary medicinal products* EMA/CVMP/016/00-Rev.4.

7 Biowaivers based on BCS and waiving of bioequivalence trials

Under certain conditions, the need for bioequivalence trials can be waived or an authorisation as a BCS-based biowaiver for rapid-release oral forms of administration may be requested. In this regard Swissmedic adheres to the detailed requirements of the *Guideline on the conduct of bioequivalence studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4 (Section 7 and Appendix I)*.

8 Documentation

Part I

The formal requirements regarding application documents in general, and the formal requirements for Part 1 and the cover letter, are laid down in the guidance document *Formal requirements HMV4* and in the associated list, *Table of documents to be submitted HMV4*.

Part II

Full Part II in accordance with Art. 7, TPLRO

Part III

- Summary of preclinical experimental and / bibliographical data on toxicology plus a risk assessment. The use of new or – with regard to the original product / test product – difference excipients or salts should, in particular, be the subject of a critical assessment concerning their possible relevance to safety. In addition, in comparison with the original product / test product, new impurities or those that do not comply with the specifications for toxicity should be qualified and if necessary, toxicological investigations should be conducted (e.g. on mutagenesis and cytotoxicity).
- User safety (e.g. on notification of a higher dosage strength compared to the reference product)
- The Environmental Risk Assessment (ERA) report is required if an ERA is required if an increased burden on the environment can be expected from placing the medicinal product on the market.
- Documentation to be submitted in line with the EMA directives, stating and describing the analysis methods and the test animals (type, species, age, weight etc.), the active pharmaceutical ingredient (name, safety of the residues, code no., batch no., quality, etc.), the trial conditions (e.g. feeding and environment for the test animals), and the results. The trials must be submitted in the form of dated, signed reports from the trial centres concerned. The specified highest concentrations for residues for the active pharmaceutical ingredient(s) contained in the medicinal product in foods of animal origin must be stated. The accuracy of the proposed withdrawal point must be justified.

Part IV

For known APIs, proof must be provided for all target species that the findings with regard to preclinical and clinical efficacy, safety and tolerability that led to the authorisation of the reference product are transferable to a sufficiently reliable extent to the medicinal product for which authorisation is sought.

The type, scope and scientific reliability of the necessary proof depend not only on the pharmaceutical form, the route of administration, and the type of active pharmaceutical ingredient (its physicochemical and pharmacological characteristics) but also on the indications and target species

for which authorisation is sought. The type of proof of transferability is chosen by the authorisation holder and summarised in the form of a critical stance, with scientific justification.

Basically, the following types of proof are possible and may also be combined within the framework of an application:

- Proof of pharmacokinetic comparability
- Proof of pharmacodynamic comparability
- Proof of therapeutic comparability in clinical efficacy / safety trials.
- Proof that based on the particular characteristics of the medicinal product and of the active pharmaceutical ingredient, *in vivo* proof of transferability is not required if conclusive *in vitro* data indicates that comparable bioavailability is likely (e.g. BCS based biowaivers). More detailed requirements can be found in the *Guideline on the conduct of bioequivalence studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4*.

Transferability can be assumed without further proof in certain situations, e.g. when the medicinal product for which authorisation is sought and the reference product are both aqueous solutions for injection of the same active pharmaceutical ingredient, in the same concentration and without additional excipients. Other examples where such proof is not required are provided in the *Guideline on the conduct of bioequivalence studies for veterinary medicinal products EMA/CVMP/016/00-Rev.4*. Depending on the veterinary medicine, other factors (such as palatability or owner compliance) must also be investigated.

9 Document protection

Document protection can be granted for innovative applications for the authorisation of medicinal products with known active pharmaceutical ingredients (known APIs with innovation). The corresponding requirements are described in the guidance document on *Document protection HMV4*. If the authorisation holder does not consent to any referencing to its protected documents, an application for authorisation of an essentially identical medicinal product based on the protected data may be submitted, at the earliest, two years before the protection period expires (Art. 12, para. 2 TPA). If a corresponding application is submitted sooner, Swissmedic will not consider the application (Art. 30, para. 6 TPO).

10 Time limits

The time limits are based on the guidance document *Time limits for authorisation applications HMV4*.

11 Fees

Fees are charged in accordance with the *Ordinance of 14 September 2018 on the Fees charged by the Swiss Agency for Therapeutic Products (FeeO-Swissmedic) (SR 812.214.5)*.

Change history

Version	Change	sig
1.2	Periodic revision New layout, no content adjustments to the previous version.	lac dei
1.1	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
1.0	Implementation of TPO4	lac, dts