Swissmedic position paper on the use of real world evidence for veterinary medicinal products

Inhalt

1 Abbreviations

GCP	Good Clinical Practice
RCT	Randomised Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

2 Objective

With this position paper Swissmedic intends to provide guidance on the regulatory principles and data requirements for marketing authorisation applications containing Real World Evidence (RWE).

3 Definition of RWD and RWE

Swissmedic considers real world data (RWD) for veterinary medicines as data collected outside the framework defined as clinical trial per VICH GCP[1], as well as data from post-marketing surveillance and fertility or productivity data collected on livestock.

[1] VICH GL 9, Good Clinical Practice, June 2000

For the time being Swissmedic considers RWD in veterinary medicine as data collected from a variety of sources relating to the health and productivity of animals, the delivery of veterinary care, or the management of livestock/animals for food.

RWE is considered as the information derived from analyses of RWD.

4 Background

The drug landscape evolved rapidly during the last decades and the principles for generating evidence for drugs of the 20th century may not always be applicable to medicines of the 21st century. In the past, the majority of drugs were intended for a large group of treated animals with the same pharmacologic target of drug action, with the ultimate goal of achieving the minimally required market penetration of a veterinary medicinal product. The evidence in support of a marketing authorisation application resulted from randomized controlled trials (RCT) and the findings could be extrapolated across subpopulations such as low-risk or high-risk groups.

In contrast, recent applications for the treatment of companion animal (and more rarely food producing animals) point at the need to treat specific diseases in subgroups for which large numbers of animals are difficult to find and regroup in RCTs (e.g. localized parasitic diseases, hormonal dysregulations). With the focus on such specific diseases or conditions, the sample size of the potential target population decreases. Consequently, adequately powered RCTs are challenging, yet they remain the gold standard for regulatory decision-making and should be conducted whenever feasible.

Low disease incidences make the use of Real World Data (RWD)/RWE an interesting option when the conduct of adequately powered RCT is not feasible or unethical. Similarly, the use of RWE could enable therapeutic insights into the use of medical products among underrepresented subgroups.

In addition, RWD/RWE proved to be useful to support regulatory decision-making in settings with rare events as well as for the optimisation of approved therapy regimens (e.g. antimicrobial treatments), resistance monitoring and for the interpretation of safety signals.

However, a number of challenges associated with the use of RWD to produce RWE remain to be addressed on a scientific and regulatory level. These include the problem of obtaining complete source data and the risk of selection bias. Endpoints used in clinical trials may not always be available or assessed in a comparable manner in the real world. Statistical methods to adjust for e.g. unbalanced baseline characteristics often rely on subjective assumptions with respect to the relevant factors. Unknown confounding factors may compromise the interpretability of RWE. In addition, there is a risk of unintentional manipulation of the outcome by repeatedly analysing (partially) the same RWD.

5 Legal framework

As far as Swissmedic is aware, there is currently no legal basis for the inclusion of RWE in the authorization process for therapeutic products, either in Switzerland or abroad. The applicable law in Switzerland requires marketing authorization documentation to include, in particular, the results of the clinical trials (Art. 11 para. 2 let. a no. 2 of the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices; SR 812.21). For the authorization of veterinary medicinal products, requirements about target animal species and animal welfare are specifically defined in Art. 11 para. 2 let. b of the Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22). There is currently no national law or ordinance on clinical trials in animals; the legal requirements are set at cantonal level.

According to established Swissmedic practice, clinical trials for veterinary medicinal products must have been conducted in accordance with the recognised rules of Good Clinical Practice (VICH GL9 (GCP)). In addition, Swissmedic considers the principles defined in the EMA guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010-Rev.1, 28.01.2022) and in its references as essential for clinical trials on animals.

The use of algorithmic systems for RWE poses new challenges to the drug approval process, including detectability and traceability, discrimination, manipulation, liability, privacy/data security and consent. RWE documentations must meet the requirements of medicinal product and data protection laws, even though standards for quality measurements or a coherent regulatory framework for research with RWE have not yet been established in current law. The use of RWE involves data protection risks (rights of data subjects, unauthorized access, proportionality, etc.). The comprehensible, complete demonstration of compliance with the relevant aspects of data protection affected by RWE, including the current case law, is required.

The new data protection law has been in force in Switzerland since September 1, 2023. The data protection challenges remain high. In this context, self-determination on personal information is potentially affected if conclusions about the holder or owner or any other person in the respective context of RWD/veterinary medicinal product can be drawn. Therefore, the relevant data protection regulations must be observed.
Irrespective of the idea of data protection of individuals, the provisions of data protection - if consistently observed – strongly support data integrity and, as a consequence, data quality. Hence data protection regulations make a decisive contribution to ensure data integrity and preventing the corruption of data as far as possible.

Future experience will show whether and, if so, which new standards are required from a regulatory point of view and suitable for the harmonized establishment of RWE in the drug approval process.

6 Regulatory considerations

6.1 General considerations

Based on the legal framework under previous chapter, Swissmedic accepts the submission of RWE as supportive evidence in addition to data from clinical trials conducted according to VICH GLP.

Submissions have to be in accordance with the latest state of science and technology. Therefore, Swissmedic supports new scientific approaches and technologies in the therapeutic products sector as best as possible. Given the uncertainties inherent to the use of RWE and the current law regarding the acceptable clinical documentation, and the highly dynamic development, the appropriate use of RWE should be discussed with Swissmedic in a pre-submission advice meeting prior to submission.

6.2 Applications

If an application contains RWE, the rationale of using RWE must be summarised in the cover letter and specified in detail in the dossier. RWE should be critically discussed in the context of all available evidence. Studies or analyses based on RWD should be listed and the sources of RWD used to generate RWE should be described in detail and referenced to the relevant sections.

For new *marketing authorisations* and *variation applications* that broaden the therapeutic scope of a medicinal product, Swissmedic accepts RWE as a complement to clinical trial data – for example, the thorough use of adequate RWD control groups in terms of quality,

size and time period to contextualise and support the clinical trial evidence regarding the efficacy and safety of a specific drug. New marketing authorisation applications solely based on RWE are currently not acceptable as the legal, scientific and regulatory frameworks are yet to be established. At present, data from adequate clinical trials remain a minimum requirement, allowing the application of the new therapeutic principle in a controlled VICH-GCP setting even in the absence of a control study arm. As a general rule, this also applies to variation applications that broaden the therapeutic scope; exceptions must be discussed with Swissmedic before regulatory submission.

In the *post-marketing surveillance* setting, Swissmedic accepts RWE for the implementation of or changes to risk minimisation measures. Thus, for the inclusion of new safety or effectiveness information in the *Information for healthcare professionals* or for other post-marketing changes to such Information that modify the therapeutic use of a medicinal product, the marketing authorisation application may be based solely on RWE. In this setting RWE can also be used for the surveillance of resistance to antimicrobials (or antiparasitics) used in companion and food-producing animals together with prescription data. Such data may also be submitted as supportive evidence for initial marketing authorization applications.

6.3 Requirements concerning the quality and sources of RWE

6.3.1 General Aspects

When using RWD to generate RWE, the quality of the data sources and an adequate methodological approach are crucial for attaining appropriate evidence levels to support marketing authorisation.

Due to the various uncertainties associated with the use of RWD/RWE, the detailed description and explanation of the methodology and statistics, predefined in a study protocol, is of particular importance. The following general aspects need to be considered, when planning RWE:

- Definition of the research question(s) and objective(s) including rationale.
- Description and justification of the chosen research/study design
- Detailed information of the pertinent RWD sources including used data standards, coding systems, traceability, applied quality check procedures and whether collected prospectively or retrospectively
- Definition of the study population using inclusion/exclusion criteria including a discussion of generalizability
- Statistical Analysis Plan including sample size considerations, detailed description of primary and secondary outcome measures, statistical methods, planned sensitivity and subgroup analyses.
- Milestones/timelines such as approval/waiver by ethics committees, data capture (start/end date), data cut off(s), database lock, planned reporting (interim/final)
- Discussion of anticipated limitations, challenges and potential biases
- Reporting of amendments and protocol deviations

In addition to the critical points listed above, compliance to cantonal, national and international law and regulations, VICH guidelines when applicable, ethical (incl. animal welfare), legal and regulatory standards need to be ensured.

Appropriate consents and data anonymization techniques are required to ensure data privacy obligation requirements are met.

6.3.2 Real world data sources

RWD sources are generally not developed for the purposes of regulatory decision-making and often, such data are not collected for the purposes of analysis at group/population level.

Lack of standardized terminology and/or completeness of records, concerns regarding data sharing/privacy, and difficulties with the interoperability of systems are some of the most important challenges posed by RWD.

Within animal health records in particular, there is currently a lack of standardization in how data are entered, how conditions are characterized, and how outcomes are documented. Animal health records can vary by veterinary practice or even among individual veterinarians within a practice, producer and type/species of animal. Outside RCTs, completeness of case histories may also be a challenge as owners may not report the outcome of treatment or may seek care at more than one veterinary clinic, and practices have limited time and resources for follow-up.

The following non-exhaustive list provides examples of RWD applicable to veterinary medicinal products:

- Data derived from animal health records of veterinary practices, farms, or any form of livestock management (including precision livestock farming[2])
- Data from product and disease registries or any form of registries related to companion or livestock animals
- Data collected by mobile sensors, remote sensing (health) devices worn by animals[3]
- Data collected by animal owners (e.g. quality of life of companion animals)[4]
- Data from laboratories, slaughterhouse records
- Data from various surveillance programs (including disease surveillance), run by either private organizations or state
- Data from use of a specific class of products (e.g. antimicrobials, antiparasitics) in populations to optimize dosing recommendations (currently only investigated in human medicine)
- Compilation of such data in a central database
- Data from post-marketing surveillance such as pharmacovigilance data or data resistance monitoring programs

When considering using RWD to generate RWE the quality of the data sources is crucial. For this reason, Swissmedic can accept the following sources:

1. observational studies
2. electronic records
3. farm records on fertility or productivity (as supplemental information e.g. for safety)
4. Disease surveillance data from private or state organizations
5. Data from post-marketing surveillance programs (pharmacovigilance, monitoring of antimicrobial resistances) from private or state organisations

The use of any other data sources must be discussed with Swissmedic before an application is submitted.

6.3.3 Quality checks before submitting RWE

Companies submitting RWD should consider the following factors to determine if such data are suitable for regulatory use (as appropriate on case by case basis):

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[2] D. Berckmans, Animal Frontiers, 2017. https://doi.org/10.2527/af.2017.0102

[3] Griffies et al., BMC Vet Res 14 : 124, 2018 ; Benjamin and Yik, Animals (Basel), 9(4), 2019.

[4] Belshaw et al., The Veterinary Journal, 2015. https://doi.org/10.1016/j.tvjl.2015.07.016

a. **Are the following background information about the data source available?**
   - Standardized methods of disease diagnosis
   - Procedures for prescribing or procuring veterinary drugs for therapeutic and/or production uses, including for approved indications, formulations, and doses
   - Preferred treatments for the disease or indication of interest
   - Standard methods to measure production variables, as appropriate
   - Degree to which such information is collected in the proposed data source.

   Background information may also include prior documented (e.g., peer reviewed publications or practice guidelines) use of the RWD source.
b. **Are the animals in the RWD source representative of the intended target animal/class?**
   It is important to identify whether the data sources cover all populations relevant to the study if those sources are to be used to examine the study hypothesis.
c. **Do RWD contain sufficient detail and completeness to capture the critical data elements?**
   Critical elements relate to exposures, key covariates, the outcomes of interest in the appropriate target animal population, and any other important parameters (e.g., inclusion/exclusion criteria, timing of exposure, timing of outcome, etc.) that are relevant to the study question (hypothesis) and design. As part of this factor, companies should evaluate whether the RWD source contains necessary elements to capture specific drug formulation information (e.g. proprietary name, manufacturer, lot and/or batch numbers, etc.). In addition, if animal health records are used as a source of RWD, companies should consider the continuity of care: whether an animal receives all or only a portion of care at a particular practice (i.e., use of multiple primary care practices, or referral or emergency practice). If animal health records from a veterinary referral or emergency practice are used without linkage to records from the animal's primary veterinarian, the amount of preventative care, comorbidity, and concomitant medication data available in the RWD source may be limited. Use of over-the-counter (OTC) drugs and supplements should also be considered when using animal health records as a source of RWD. Moreover, drugs might be acquired through different channels (eg. importation) and not recorded. Animal health records or protocol should capture the use of OTC drugs or supplements if these exposures are relevant to the study question. Protocol should describe how a potential information gap will be addressed.
   Other aspects to consider include whether the RWD source adequately captures animal health history and preexisting conditions, as well as follow-up information needed to evaluate the question being addressed.
   The RWD source should also be evaluated to determine if sufficient data elements are collected to adjust for any confounding factors that may impact the exposure or outcomes of interest. These include factors that are well-captured in the proposed data source (measured confounders) and those that are not well captured (unmeasured or imperfectly measured confounders). Examples of confounders that are unmeasured or imperfectly measured in many animal health record data sources include management factors (e.g., diet or physical activity), certain physical measurements (e.g., body condition), diagnostic laboratory test results, concurrent drug administration by animal owners such as OTC drugs and supplements.
d. **Does the data source contain an adequate number of animals that represent the target animal/class?**
   Is the length of follow-up adequate to ascertain outcomes of interest based on the biologically plausible timeframe when the outcome might be expected to occur?
   Information should be provided about the distribution of length of follow-up for

animals within the data sources, because the length of follow-up may dictate whether the selected data sources are appropriate or whether additional supportive data are needed to evaluate outcomes that require long follow-up periods.

e. **Are supplemental data sources available if needed?**
When critical information in a data source is absent, the data source may not be sufficient to achieve the study objectives. In this case, using alternative data sources, linking multiple data sources, or prospectively collecting additional information may be necessary. The linking of RWD sources should be scientifically appropriate and account for differences in coding and reporting across sources

7 Conclusions

Submissions exclusively based on RWE are currently not endorsed for new marketing authorisation and, as a general rule, changes to marketing authorisation that extend the therapeutic use of a medicinal product. RWE is regarded as a supplemental tool to support marketing authorisation, especially in rare disease settings with a high medical need. The relevance of the RWE highly depends on the data quality and the medical context. RWE is acceptable as supportive evidence when high quality data are provided and a detailed documentation of data collection and study conduct is presented.

For market surveillance purposes, Swissmedic accepts RWE for the implementation or changes of risk minimization measures. For such applications or applications that modify the therapeutic use of a medicinal product, the marketing authorisation and variation applications may be solely based on RWE, provided that the data quality is appropriate.

RWE can also be used for the surveillance of resistance to antimicrobials or antiparasitics used in companion and food-producing animals together with prescription data.

Swissmedic follows international developments regarding the regulatory use of RWD/RWE actively and closely (e.g. FDA, EMA).

For *new marketing authorisations* and *variations* broadening the therapeutic use, a pre-submission meeting is recommended prior to the submission of applications containing RWE.