swissmedic

Guideline

Swissmedic position paper on the use of real world evidence

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Contents

1 Abbreviations

GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
RCT	Randomised Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)

2 Objective

With this position paper, Swissmedic intends to provide guidance regarding the legal basis, 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) as all data other than those collected through a clinical trial conducted as per ICH GCP. This may include – but is not limited to – registries, observational studies, electronic healthcare records, medical claims, billing data, and patient-generated data (e.g. using mobile devices/wearables). Real world evidence (RWE) is defined as 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 in the 20th century may not always be applicable to 21st century medicines. In the past, the majority of drugs (e.g. statins) were intended for a large group of patients with the same pharmacologic target of drug action. The evidence in support of a marketing authorisation application resulted from large randomised controlled trials (RCT) and the findings could be extrapolated across subpopulations such as low-risk or high-risk groups.

In contrast, recent developments point to an increase in the heterogeneity of the target population, with mutation-specific targets. In this situation, extrapolation of efficacy information from one subpopulation to another is challenging, because the subpopulations may differ substantially.

With the focus on more personalised medicine and rare diseases, the sample size of the potential target population is decreasing. Consequently, adequately powered RCTs are challenging, yet they remain the gold standard for regulatory decision-making and should be conducted whenever feasible.

Nonetheless, the increasing "orphanisation" of some medical areas with correspondingly low disease incidences means that the use of RWD/RWE may be of interest when the conduct of adequately powered RCT is infeasible or unethical. Similarly, the use of RWE could provide therapeutic insights into the use of medical products among underrepresented and vulnerable populations.

In addition, RWD/RWE has proved useful in supporting regulatory decision-making in settings with rare events (e.g. vaccine trials), for the optimisation of approved therapy regimens (e.g. use of large registries in diabetes), for the extension of indications 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 authorisation process for therapeutic products, either in Switzerland or abroad. The applicable law in Switzerland requires marketing authorisation documentation to include, in particular, the results of the clinical trials (Art. 11 para. 2 let. a no. 2 TPA). Swissmedic describes these documents in more detail (Art. 11 para. 4 TPA).

According to Art. 5 para. 1 of the Ordinance on the Licensing Requirements for Therapeutic Products (TPLRO), the documentation on clinical trials must prove that the investigations in humans have been carried out according to the recognised rules of good clinical practice (ICH GCP).

The use of RWD, including algorithmic systems, for RWE poses new challenges for the drug approval process, including detectability and traceability, discrimination, manipulation, liability, privacy/data security and consent. RWE documentation must meet the requirements of medicinal product, human research 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 (quality of personal data in the case of anonymisation/pseudonymisation, rights of data subjects, unauthorised access, proportionality, etc.). Comprehensible and complete demonstration of compliance with provisions on human research and data protection affected by RWE, including the current case law, is required.

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

6 Regulatory considerations

6.1 General considerations

Based on the current legal framework, Swissmedic accepts RWE as supportive evidence in addition to data from clinical trials conducted according to ICH GCP.

Submissions must 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 possible. Given the uncertainties inherent in the use of RWE and the current law regarding acceptable clinical documentation, and due also to the highly dynamic development environment, the appropriate use of RWE should be discussed with Swissmedic in a pre-submission meeting prior to submission of an application.

6.2 Applications

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

Electronic health data records and registry data may be used as an additional source for signal detection and for the evaluation of risk minimisation measures. Accordingly, signal detection and validation as well as standard safety reports may also include RWE.

In addition to the above-mentioned sources, social media and patient health application data can be used in the pharmacovigilance setting. Although the data are easily accessible, the nature of social media presents several challenges for the extraction of signals related to risk minimisation measures. Nevertheless, current developments in the field of mobile/wearable devices may enable market authorisation holders to extract valid data for pharmacovigilance purposes. The challenge with this data is applying statistical methods that help to avoid misinterpretation and wrong conclusions with regard to therapeutic measures.

Furthermore, records may be influenced by prescribing decisions that are focused on comorbidity, insurance, etc. Such factors must be considered when using these data for pharmacovigilance purposes. Under these circumstances, further studies/information may be needed to implement suggestions in the safety context.

6.3 Requirements concerning the quality of RWE

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, detailed descriptions and explanations of the methodology and statistics, predefined in a study protocol, are of particular importance. The following general aspects need to be addressed when planning RWE:

- Definition of the research question(s) and objective(s), including rationale and appropriateness of outcome measures and preferably using the estimand framework (ICH E9(R1))
- Description and justification of the research/study design including a discussion of strengths and weaknesses
- Detailed information on the pertinent RWD sources including data standards applied, coding systems, traceability, quality check procedures and whether the data were collected prospectively or retrospectively
- Definition of the study population using inclusion/exclusion criteria, including a discussion on generalisability
- 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 with national and international law and regulations, ICH guidelines, ethical, legal and regulatory standards needs to be ensured.

Appropriate consents and data anonymisation/de-identification techniques are required to ensure compliance with data privacy requirements and must be confirmed to Swissmedic in writing.

7 Conclusions

Submissions exclusively based on RWE are currently not endorsed for new marketing authorisation or, as a general rule, for 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 where there is a high unmet medical need.

The relevance of the RWE depends in large measure on the data quality and the medical context. RWE is acceptable as supportive evidence when data are of adequate quality and detailed documentation on data collection and study conduct is presented.

For market surveillance purposes, Swissmedic accepts RWE for the implementation of or changes to risk minimisation measures.

For such applications or applications that modify the therapeutic use of a medicinal product, the marketing authorisation and variation applications may be based solely on RWE, provided that the data quality is appropriate.

Swissmedic follows international developments regarding the regulation and use of RWD/RWE actively and closely (e.g. FDA Sentinel System, DARWIN EU) and is in a continuous dialogue with Access partners and other regulatory agencies to further evaluate the potential use of RWD/RWE for regulatory decision-making.

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

Annex: Other relevant guidelines

When assessing the application documentation within the framework of this guideline, Swissmedic primarily refers to the guidelines and publications of the ICH, the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Access Consortium and ICMRA as a reflection of the current state of science and technology. Federal law may refer to specific versions of international guidelines.
The following list gives an overview of relevant international guidelines and publications. This list is not exhaustive and will be updated regularly.

ICH

Implemented (Step 5)

- E6 Good Clinical Practice
- E8 General Considerations for Clinical Studies
- E9 Statistical Principles for Clinical Trials
- E9(R1) Addendum: Statistical Principles for Clinical Trials
- E10 Choice of Control Group and Related Issues in Clinical Trials
- E19 A selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials

Drafts

- M14 General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines
- Reflection Paper on “Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines”

EMA

- Scientific guidance on post-authorisation efficacy studies (June 2017)
- Guideline on registry-based studies (October 2021)
- Data quality framework for EU medicines regulation (October 2023)
- Metadata list describing real-world data sources and studies (February 2024)
- Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation (Draft, April 2023)
- Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence (Draft, April 2024)

FDA

- Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products (August 2023)
- Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products (December 2023)
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products (July 2024)

- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (Draft, February 2023)
- Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics (Draft, March 2023)
- Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products (Draft, March 2024)

Other RWE guidance from the FDA

Change history

Version	Change	sig
3.0	Incorporation of annex: List of guidelines considered to constitute the current state of science and technology.	dts
2.0	New layout, no content adjustments to the previous version	dts
1.0	First version	dts