

Use of Real-World Data and Real-World Evidence for regulatory decision-making

Position Paper

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Objective: With the present paper, EuropaBio would like to support the generation of EMA/HMA guidance(s) on RWD/RWE aligned with international regulatory requirements already used by other Regulatory Authorities.

Executive Summary

Health data which are generated in clinical practice and are increasingly in day-to-day life by novel technologies provide a large data pool that should be more broadly utilized to support regulatory decision-making.

Fit-for-purpose Real-World Data (RWD) and subsequent Real-World Evidence (RWE) should become more broadly acceptable for regulatory decision-making beyond the already established use of reactive post-approval safety changes based on real-world market surveillance data. EuropaBio members, who develop treatments for the recognised unmet needs relying on evolving science for biotherapeutics, call for the development of guidance on RWE to pave the way for its use in support of regulatory decisions for sponsor-desired post-approval changes, as well as of initial filings where Randomized Controlled Trials are not appropriate.

In particular, EuropaBio, asks the EU regulators to foster collaborations between relevant stakeholders including HTA bodies and develop a RWE framework and guidelines in alignment with international stakeholders, establish real-world data standard and a common data model, as well as for facilitation of RWE pilots. EuropaBio will advocate use of high-quality and fit-for-purpose RWD and RWE in the decision-making process in the context of new approvals, where clinical trials are not feasible, or post-marketing authorisation labelling changes. We will also proactively

involve in guideline commenting and multi-stakeholder activities related to RWD/RWE for regulatory purpose.

Introduction

RWD collected in clinical practice and the RWE generated thereof is today accepted as standard for regulatory decision-making related to regulator required post-approval safety monitoring and updates of the product information (reactive use of RWE). There is a high interest to improve the acceptability of RWD/RWE for sponsor-desired label revisions regarding effectiveness and safety and initial registrations. Approaches are being critically assessed (proactive use of RWE by sponsor). On a case-by-case basis, RWD/RWE may already be accepted by regulatory authorities in areas of high unmet medical need, or when there is an evidence gap in the clinical practice and depending on the quality of the data and generated evidence. Natural history external control arms in support of single-arm clinical studies in some rare diseases have already been successfully submitted for approval. Due to feasibility issues with, and limitations of, Randomized Controlled Trials (RCTs), some companies have submitted RWE as supplementary evidence to support safety and efficacy of some innovative medicines. RWD and RWE can also be used throughout a product lifecycle, for example, to gain an understanding of unmet medical needs and current standard of care, identify prognostic and/or predictive markers, inform trial design (including dose definition) and help trial recruitment, assess adherence pattern, etc. This position paper focuses on acceptance of RWD/RWE for initial registration purpose, as well as for sponsor-desired post-approval label changes. To create synergies, requirements for RWD/RWE by regulatory authorities should be aligned with requirements by HTA bodies.

Current status of regulatory discussions

In Europe, broadening of the use of RWE for regulatory decision-making is under discussion. Initiatives like IMI Get REAL, the Patient Registry Initiative and the Joint Big Data Task Force have generated documentation and tools to this respect. The EMA Regulatory Science Strategy to 2025, the summary report of the Joint Big Data Task Force, as well as the published ten priority actions for the EU regulatory network, signal the intent to evolve the EU regulatory ecosystem capabilities to gather, analyse and

utilise different data sources, to build up capability and capacity in the area of RWD/RWE and big data. This is also being echoed by recent publications by EMA representatives (Cave et al, 2019, Olmo et al, 2019, McGettigan et al, 2019, Pacurariu et al, 2018).

Definition of quality standards for RWD sources as well as data standards and a common data model are under discussion. The priority recommendations include: building an EU platform to access and analyse healthcare data from across the European Union (Data Analysis and Real-World Interrogation Network - DARWIN) by 2023; establishing guidelines for an EU RWE framework to capture high quality and representative data; developing skills and infrastructure to process Big Data; launching a 'Big Data Learnings Initiative' to collect data that can be used to develop guidelines is viewed as highly valuable; and the need for establishing an EU Big Data 'stakeholder implementation forum'; delivery of expert advice; as well as collaboration with international initiatives on Big Data are addressed.

Authority	RWE discussion status
ANVISA	RWE workshop in December 2019. ANVISA is open for discussions on this topic.
NMPA China	<p>The Chinese NMPA has already published a detailed guideline on Using Real-World Evidence including examples of use to support registration with the following objectives:</p> <ul style="list-style-type: none"> • clarity on NMPA's definition, • guide the collection and suitability assessment of data, • specify the status and applicable scope of RWE in drug regulatory decision-making, and • explore the principles for the evaluation of RWE in using RWE to support drug regulatory decision-making. <p>Companies are encouraged to seek early interactions with the Centre of Drug Evaluation (CDE) regarding the use of RWE during planning and prior to start of real-world (RW) studies, and before registering applications when including RWE. However, the Chinese</p>

	<p>health authority still highlight that RCTs are considered as the “gold standard” for medicine approvals.</p>
<p>FDA</p>	<p>US FDA's framework for its Real-World Evidence Program (published in December 2018) promotes a multifaceted approach to RWE, which advocates:</p> <ul style="list-style-type: none"> • demonstration projects, • stakeholder engagement, • internal processes to bring senior leadership input into the evaluation of RWE, • shared learning processes, and • systematic application of the framework. <p>Technical guidance documents to assist industry sponsors interested in using RWD are expected to be published by end 2021. In May 2019, FDA published draft administrative guidance entitled "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics", reflecting their expectations on the use of standards on how to document the submission of RWE as part of a filing for FDA internal tracking purpose.</p>
<p>Health Canada</p>	<p>Health Canada has started working on how to use RWE for regulatory decisions under the 'Strengthening the Use of Real World Evidence for Drugs' project. A document “Elements of Real-World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle” was issued in March 2019 and a respective workshop was held in December 2019. Health Canada encourages the following RWE submissions:</p> <ul style="list-style-type: none"> • to expand evidence-based indications for populations often excluded from clinical trials (children, seniors, and pregnant women); • diseases where clinical trials are not feasible such as it may be the case with rare diseases; • where clinical trials are unethical.

MFDS	MFDS Issued booklet about utilization of RWE/RWD in EU/US and has voiced interest in the development of international guidance.
PMDA	<p>PMDA seeks to expand promote the use of RWD, such as electronic medical records (EMRs) and data of patient registries for drug safety assessment by pharmaceutical industries; respective guidelines were published in 2017 and 2018. In order to encourage the use of RWD, an amendment to the ministerial ordinance (Good Post-Marketing Study Practice) was implemented in April 2018. The MID-NET (Medical Information Database Network) was formally launched on 1 April 2018. It collects electronic medical records, claim data, laboratory test values, etc. for evaluation of post-approval ADR frequency and epidemiology studies; the information is available to certain stakeholders.</p> <p>In 2019, a pilot-based consultation service on the use of registries in regulatory submissions for drugs, medical devices, and regenerative medicine-based products was introduced; two new guidance documents regarding registries are expected in 2020.</p>
Swissmedic	Integrated in Swissmedic Strategic Objectives 2019 – 2022.

Real-World Data

No globally agreed definition of RWD is available and discussions are ongoing whether such definition is needed. In general terms, RWD are all clinical and ancillary (such as images, digital feeds) data collected in a routine setting and outside a clinical trial. Relating to patient health status and/or the delivery of health care, RWD are collected from a variety of sources; examples of RWD sources include the following (not exhaustive):

- Data derived from electronic medical records (EMRs);
- Medical claims and billing data;
- Data from product or disease registries;
- Ancillary data derived from patient care/patient reported outcomes, including digital feeds, images, PDFs, digital lab feeds;
- Omics, genomics data;

- Social media data;
- Data collected via wearables, etc.; and
- Patient-generated data, including in-home use and/or other decentralized settings.

Discussions are ongoing about the limitations of the different data sources and the data standards.

Real-World Evidence

In general terms, RWE is the clinical evidence about the use and potential benefits or risks of a medical product derived from analysis of RWD.

Efforts are ongoing to use robust study design and statistical methods to show concordance between results from randomized trials and RW studies and to derive general rules to build trust and confidence in the validity of results using RWD.

Regulatory acceptance

Randomized controlled trials are considered as the standard for regulatory decision-making. RWE is already accepted as supplementary information in some jurisdictions. In certain situations, RWD and RWE may be accepted by different Health Authorities as pivotal evidence to support safety and effectiveness related to label changes of already approved medicines or of a new medicine approval in case of high unmet medical need or as (part of a) post-marketing requirements to support a regulatory decision. Questions that will be considered during review are the quality, standard (where applicable), accuracy, and considerations regarding fit for purpose of the RWD, the appropriateness of the study design to generate RWE from RWD to address a particular regulatory question/uncertainty and if this study stands up to regulatory scrutiny. Development of a common data model and common minimal data set to increase interoperability are being discussed. Early Health Authority interaction during the process of planning the generation of RWE are considered key to a successful submission.

EuropaBio position regarding the use of RWD and RWE for sponsor-desired label changes and initial registrations

EuropaBio considers fit-for purpose RWD relevant and innovative data, especially in the age of digitalisation. We also consider the generated RWE appropriate to support regulatory decisions in a certain context that will fulfil patient need. In particular, the regulatory acceptability of RWD is considered of high relevance for bringing innovative biotechnology products, including ATMPs, which are frequently developed for small and targeted indications to patients.

EuropaBio endorses multi-stakeholder approaches to advance the acceptance of RWE as pivotal evidence for regulatory decisions regarding the effectiveness related to label changes of approved medicines, and subsequently also regarding the approval of new medicines. We will proactively engage into these activities. We will also proactively contribute to initiatives aiming to overcome challenges associated with expanding the use of RWE for regulatory decision-making, taking into consideration privacy rights.

In particular, EuropaBio advocates the regulatory acceptance of fit-for purpose RWE in the EU to complement the development of innovative medicines, for which only single-arm clinical studies are feasible to support registration (e.g. initial registration and extension of indication).

Consideration of data of new sources (e.g. digital) for regulatory decision-making is important for some highly innovative SMEs.

EuropaBio policy and action recommendations to the EMA/HMA on the regulatory use of RWD and RWE:

- Foster collaboration with stakeholder, including HTA bodies, at workshops sharing best practices on regulatory use of RWE for innovative medicines and ATMPs.
- Development of an European framework for the use of RWE in regulatory decision-making, in alignment with other regulatory authorities (e.g. FDA, China, Health Canada, Brazil, etc) and discussion through international platforms such as ICMRA, IPRP, ICH, etc.

- Alignment of emerging guideline with the requirements of HTA bodies, as scientifically feasible.
- Establishment of a data standard and a common data model, with extensions for images, digital feeds.
- Facilitation of RWE pilot programs by the EU network on appropriate use of RWE to generate a basis for regulatory guidelines.

EuropaBio commits to the following:

- Advocacy for the use of high-quality and fit-for-purpose RWD and RWE in the decision-making process in the context of new approvals where RCTs are not feasible or post-marketing authorisation labelling changes.
- Contribution to multi-stakeholder activities related to RWD for regulatory purpose.
- Proactive involvement in the development of European guidance in alignment with other regulatory authorities (e.g. FDA, China, etc), in order to facilitate worldwide acceptance of RWD and RWE.
- Advocacy of sustainable, appropriate industry access to RWD in line with EU privacy rights in the light of challenges with data access posed by the GDPR.

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