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European Federation of Pharmaceutical Industries and Associations

EFPIA's Position on the Use & Acceptance of Real World Evidence by International Markets

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Introduction & Problem Statement

As medicinal product development is in essence global, EFPIA believes it is important to seek to build regulatory convergence among regulatory agencies, in particular on topics that help optimise Research & Development and accelerate patient access to innovative medicines. Real world Data (RWD) has recently emerged as one of the topics where alignment may enable this optimization and acceleration. To enable this, we need to drive a better understanding of the value of RWD worldwide amongst regulators and other authorities. Therefore, the focus of this paper is on the use and acceptance of Real World Evidence (RWE) to support benefit/risk decision-making.

The concept of RWD and the processes used to analyse RWD to generate RWE are not new. Increasing interest and excitement in the potential of RWD for decision making within the healthcare community in recent years has been triggered by a number of developments including: the greater availability and quality of electronic healthcare information, the emergence of tools for advanced analysis of large data volumes (greater computing power, data handling and analysis techniques), the ability to link data from multiple sources and broader awareness of the limitations of traditional clinical trials to answer all stakeholders' questions. A number of ongoing initiatives focus on the development of RWD/RWE standards and frameworks to facilitate generation of high-quality evidence to underpin healthcare decision-making (e.g., EMA Regulatory Science Strategy to 2025; FDA's RWE Programme; Health Canada-CADTH-INESS RWE framework; NMPA RWE project, Japan's Medical Information Database Network (MID-NET). As a result, researchers and healthcare decision-makers are using evidence and insights from RWD in a variety of ways, for example to:

- Understand disease epidemiology, progression and treatment patterns and the impact on patients and public health;
- Monitor new treatments for safety including effectiveness of Risk Minimization measures (RMMs) and effectiveness, including tolerability, adherence and coverage;
- Quantify better and more rapidly assess emerging safety signals;
- Support formal assessments by Regulatory and Health Technology Assessment (HTA) bodies;
- Provide insights for life science research (e.g. patient phenotypes with greatest unmet need; novel outcome measures);
- Increase the sustainability and effectiveness of healthcare systems including optimal use of medicinal products over their lifecycle.

There is potential to use RWD more effectively to support medicinal product development and utilisation. Further benefits could be derived by linkage and use of the data collected by the healthcare system, including "omics", or from the use of data collected directly from patients or via digital devices. However, the appropriateness of using evidence and insights from RWD depends greatly on the purpose and the nature of the decision being made, and the specifics of the disease area and medicinal product in question as well as the data source and study design that inform the decision. As pipelines are evolving, innovative medicinal products will bring new challenges for regulators and payers that RWD/RWE may help address, e.g., long term follow-up to confirm life-changing benefits and risk reduction; identification and confirmation of opportunities for precision medicine; providing context and control groups for assessment in rare diseases.

However, there are many challenges to address in a data landscape that is rapidly evolving. These include questions around relevance, depth and quality of RW source data; data privacy and access issues; and agreement on appropriate analytical methods. There are a range of multi-stakeholder

initiatives (e.g., the RWE Transparency Initiative[1], the GetReal Institute[2]) that are currently addressing these fundamental challenges.

In addition to these efforts, EFPIA also believes that local incentives (such as guidance documents or frameworks) need to be in place, and best practices disseminated to further support the collection of high quality RWD and analysis via robust scientific and analytical methods. Finally, the subsequent review, endorsement, and communication of research results conducted using such data sources in a transparent manner will be an important enabler for their acceptance as trustworthy sources of evidence available for use in decision-making.

EFPIA recommendations for the use & acceptance of Real World Evidence by International Markets

Regulators face significant challenges as treatments become more innovative and drug developments become more tailored. Recently, regulators through ICMRA have decided to strengthen global collaboration on COVID-19 RWE[3] and observational studies to discuss priority areas for cooperation on COVID-19-related observational research. The ICMRA action underscores that aligned and science-driven global regulatory standards provide assurance of quality, safety, and efficacy and can foster the generation of sufficient RWE to support timely access to innovative and effective medicinal products. Equally important are efficient regulatory pathways that enable good decision-making and optimal use of agency and industry resources. As regulators are developing frameworks and guidance documents on the use of RWE across the product lifecycle for regulatory decision-making, there are already recognised situations more amenable to regulatory acceptance, e.g., to contextualise a product safety profile or where standard randomised clinical trials (RCT) cannot be performed (e.g., for rare diseases, paediatric and/or oncology drug development). RWE can supplement RCTs, serve as a bridge to local data, and, as part of the totality of evidence support regulatory decision-making and allow new medicinal products to be made available to patients and for public health.

EFPIA believes the Regulatory Reliance[4] principles as emphasised by WHO[5] and IFPMA[6] should also apply to medicinal products which have been developed using Real World Evidence. Indeed, when a regulatory agency is considering a medicinal product that has already been approved by another agency, addresses a medical need and for which approval was based on the use of RWE, the following should always be considered in order to expedite the approval and speed up the availability of this new medicine to local patients globally:

- Rely on the reference agency's overall assessment and perform an abbreviated review focussing on the applicability of the results to the local population and healthcare system, with consideration of ethnic factors where appropriate; this recommendation aligns with the 2021 WHO Good Reliance Practice document[7] and the ICH E5(R1) Ethnic factors guideline[8,9];
- Use RWD to evaluate the ethnic differences between regions, for example to support the concept of a pooled region or subpopulations, in order to optimise the implementation of the ICHE 17 Multi-Regional Clinical Trial Guideline[10].

For those agencies willing to establish a regulatory framework to foster uses of RWD while respecting data privacy concerns and providing accountability to patients, EFPIA has the following recommendations:

- Establish appropriate tools and methods for fit-for-purpose data generation (see Annex for additional details), and the incentives as appropriate to region, needed to ensure comprehensive and high quality data collection;
- Provide early engagement opportunity during medicinal product development and review to discuss specific local requirements, if appropriate;

[1]https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative
[2]https://www.getreal-institute.org/
[3]https://www.ema.europa.eu/en/partners-networks/international-activities/multilateral-organisations-initiatives/international-coalition-medicines-regulatory-authorities-icmra
[4]WHO defines **Reliance** as the act whereby the National Regulatory Authority (NRA) in one jurisdiction may take into account and give significant weight to – i.e., totally or partially rely upon – evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.
https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf
[5]https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliance_Practices.pdf?ua=1
[6]https://www.ifpma.org/resource-centre/ifpma-position-paper-assessment-reports-as-a-tool-for-regulatory-reliance/
[7]https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf
[8]https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf
[9]https://database.ich.org/sites/default/files/E5_Q%26As__R1_Q%26As.pdf
[10]https://database.ich.org/sites/default/files/E17EWG_Step4_2017_1116.pdf

- Ensure appropriate resources, capacity and expertise for communication and support during product development and review;
- Increase multi-stakeholders' awareness and capabilities related to the use of RWE through educational training and knowledge sharing;
- Consider establishing a RWE pilot program through which the agency and sponsors could gather insights and publicly share lessons learned.

For agencies which are already developing their own RWE regulatory framework and guidelines, EFPIA would welcome them to seek to align national requirements with existing recommendations and/or regulatory pathways available globally (see Annex for additional details).

Finally, EFPIA encourage regulators to share progress and experience through existing platforms such as ICMRA or DIA, as they continue to develop their frameworks and guidelines, and move as expeditiously as possible to align approaches through future ICH guidelines.

Annex

➢ Some definitions

While the following definitions are those included in the glossary of the IMI GetReal project, it is acknowledged that other definitions are in use, e.g. by the FDA[11] or HealthCanada[12].

Real World Data (RWD): an umbrella term for data regarding the effects of disease (patient characteristics, clinical and economic outcomes; health related quality of life) and health interventions (e.g. safety, effectiveness, resource use) that have not been collected through highly-controlled randomized controlled trials (RCTs). Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. RWD therefore, refers to the source of raw information. Both paper and electronic records are sources of RWD: including clinical notes, electronic health records (EHR) and medical records (EMR), insurance claims, patient registries, records of patient reported outcomes / experiences, and continuous patient monitoring data (e.g., from apps and wearables). It is possible to collect RWD in a study or trial following an initial intervention when the design is pragmatic.

Real World Evidence (RWE): evidence created by addressing specific research questions through the scientific analysis of RWD rather than from conventional highly controlled RCTs.

➢ Existing guidance and initiatives

Some Regulatory Authorities have already established regulatory pathways to optimise drug development with the use of RWE and are increasingly supporting the use of various data sources to generated RWD. The acceptability of RWE is important to provide additional evidence or supplement RCTs to secure optimized totality-of-evidence required for regulatory decision making and allow new medicines to be available as treatment options for patients in great needs. There has been and there will be significant interactions between Industry, regulators and other stakeholders on guidelines, recommendations and best practices for the appropriate use of RWE.

ICH

- June 2017 – ICH reflection paper on GCP renovation.
- June 2019 - ICH endorsed the Reflection paper on "Strategic Approach to International Harmonization of Technical Scientific Requirements for Pharmacoepidemiologic Studies Submitted to Regulatory Agencies to Advance More Effective Utilization of Real-World Data", and established a discussion group.

EMA, in Europe

- EMA Regulatory Science Strategy[13] to 2025.
- EMA-HMA Big Data Task Force Report[14] (2019).
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology.
- Aug. 2016: EMA Guidance[15] for companies considering the adaptive pathways approach (EMA/527726/2016).
- IMI ADAPT SMART project[16], which assessed the use of RWD to complement RCT data and provide sufficient evidence to either expand an existing indication to other patient subgroups, or support the addition of a new indication.
- IMI EHDEN project[17].
- IMI GetReal and GetReal Initiative projects (2013-2021)[18]: IMI is a public-private partnership between the European Union and the European pharmaceutical industry (EFPIA) that collaborates on a range of initiatives aimed to advance and accelerate patient access to medicines, particularly where there is unmet need. The GetReal projects discussed, proposed, and created tools to support new robust methods of RWE synthesis for use throughout the drug lifecycle, including regulatory decision-making. Of note, launched on 28 April 2021, the GetReal Institute[19] will build on the successes of the IMI GetReal project, to facilitate the adoption and implementation of RWE in health care decision-making in Europe.
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[11] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
[12] https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html
[13] https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy
[14] https://www.hma.eu/fileadmin/dateien/HMA_joint/00-_About_HMA/03- Working_Groups/Big_Data/2019_02_HMAEMA Joint_Big_DataTaskforce_summary_report.pdf
[15] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-companies-considering-adaptive-pathways-approach_en.pdf
[16] https://www.adaptsmart.eu
[17] https://www.ehden.eu/
[18] https://www.imi-getreal.eu/
[19] https://www.getreal-institute.org/

FDA, in the United States

- May 2019: FDA Draft guidance[20] - Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics.
- March 2019: FDA Draft guidance[21] - Rare Diseases: Natural History Studies for Drug Development.
- Dec. 2018: framework for FDA's RWE program[22] established under the 21st Century Cures Act and Prescription Drug User Fee Act (PDUFA) program
- August 2017: FDA guidance[23] - Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.
- May 2013: release of an FDA guidance[24]: Best practices for conducting and reporting pharmacoepidemiologic studies using electronic Healthcare data.

Health Canada, Canada

- Use of RWE in Single Drug Assessments Environmental Scan[25]
- Elements of RWD/RWE Quality throughout the Prescription Drug Product Life Cycle[26].
- RWE for Drugs Project[27].
- Strengthening the use of RWE for Drugs[28].

Of note, in Canada, the RWE framework is still work in progress for HealthCanada.

PMDA, Japan

- March 2021: MHLW published two guidelines
  - Basic Principles on Utilization of Registry for Applications: https://www.pmda.go.jp/files/000240806.pdf
  - Points to consider for Ensuring the Reliability in Utilization of Registry Data for Applications: https://www.pmda.go.jp/files/000240807.pdf
- Mar. 2020: PMDA "Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products".
- March 2019: PMDA "Procedures for Developing Post-marketing Study Plan" (originally published as "Procedures for Developing Post-marketing Study Plan" by PMDA in January 2018): https://www.pmda.go.jp/files/000226080.pdf
- Feb. 2018: PMDA "Points to consider for ensuring the reliability of post-marketing database study for drugs".
- June 2017: PMDA "Basic principles on the utilization of health information database for Post-Marketing Surveillance of Medical Products".
- Oct. 2017: MHLW "Amendment of Ministerial Ordinance on Good Post-marketing Study Practice for Drugs".
- March 2014: PMDA "Guidelines for the Conduct of Pharmacoepidemiologic Studies in Drug Safety Assessment with Medical Information Databases" https://www.pmda.go.jp/files/000240951.pdf
- To encourage RWD utilization, the ministerial ordinance (Good Post-Marketing Study Practice, or GPSP) was amended in October 2017 and implemented on April 1, 2018. MID-NET (Medical Information Database Network) was also formally launched on April 1, 2018, allowing certain stakeholders to utilize this database. The next five years will be an important period for considering and expanding the use of RWD to support regulatory processes.
- Establishment of MID-NET[29] (Medical Information Database Network) as a reliable and valuable database for drug safety assessments in Japan.
- MIHARI (Medical Information for Risk Assessment) project[30]: for reinforcement and enhancement of the system for safety information collection and evaluation of medical products in the PMDA 2nd midterm plan (2009-13); the project on the use of electronic medical records, etc. for safety measures was launched.

NMPA, China

- The RWE project has been set up since 2018 to call the 3-party collaboration between regulator, Academia, and industry.
- April 2021, NMPA published "Guidelines for RWD used to generate RWE"
- Hainan Boao RWE pilot project established in 2020
- In May 2019, NMPA released its draft guidance on "Real-World Evidence to support drug development". See publication[31] on experience and lessons from China. This guideline was finalised in Jan. 2020 using the following title: Guidance for RWE supporting the drug development and evaluation.

[20] https://www.fda.gov/media/124795/download
[21] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development
[22] https://www.fda.gov/media/120060/download
[23] https://www.fda.gov/media/99447/download
[24] https://www.fda.gov/media/79922/download
[25] https://www.cadth.ca/use-real-world-evidence-single-drug-assessments-environmental-scan
[26] https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.htm
[27] https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/strengthening-use-real-world-evidence-drugs.html
[28] https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html
[29] https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4879
[30] https://www.pmda.go.jp/english/safety/surveillance-analysis/0001.html
[31] file:///C:/Users/kjrb672/Downloads/Real_world_evidence_Experience_and_lessons_from_Ch.pdf

- In Nov 2020, release of the Guidance for Using RWD in the clinical evaluation for Medical Device.
- Between Aug. and Oct 2020, the draft guideline on "Real-world data used to generate real-world evidence" was released for public consultation. This guideline is meant to supplement the above-mentioned "Guideline for Real-World Evidence to Support Drug Development and Evaluation" that was finalised in Jan 2020.
- In Aug 2020, CDE released the final Guideline "Use of Real-World Evidence to Support Research & Development and Review of Paediatric Drugs".

MFDS, South-Korea
- Mar 2020, MFDS issued comprehensive plan for drug safety management: use RWD/RWE in PV management.
- Feb. 2020: RWD topic proposed to ICH for an ICH M guideline.
- In June 2019 - casebook on usage of RWD and RWE for biological drugs in overseas.
- In October 2019 - further casebook for drug & biologics and vaccines.
- Dec. 2019, MFDS updated the Risk Management Plan(RMP) to accept TWE/RWD studies as the RMP.
- In June 2018 - "Considerations for medical treatment and efficacy comparative study in use of Real Word Data (RWD)" (which is ISPOR-ISPE TF guidance).

Taiwan FDA, Taiwan
- In May 2020, TFDA released draft guideline "Guidance for Use of Electronic Health Records in Clinical Trial/Study" for public consultation.
- August 2020 – RWE - Main Considerations for Pragmatic Clinical Trials (Draft).
- July 2020 - Basic Considerations for Using Real-World Evidence to Support Drug Research and development.
- In Sept. 2020, TFDA released draft guideline "Research design for real-world evidence- Main considerations for Pragmatic trial" for public consultation.

TGA, Australia
- TGA can accept RWE to fulfil PAC for provisional procedure approved products
- June 2021, TGA made consultation meeting among stakeholders to further understand the use of real world evidence in the regulatory context.

ANVISA, Brazil
- In addition to the organization of two workshops in 2019: Real World Data – An overview of the current status, trends, challenges and opportunities and Real World Evidence, Anvisa has been participating in recently created working groups that seek to harmonize international standards for assessing the use of RWD to generate RWE. The Agency has representatives in the Real-World Data and Real-World Evidence in Regulatory Decision Making" Working Group of The Council for International Organizations of Medical Sciences (CIOMS) and in the "Pharmacoepidemiology Discussion Group" of The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Saudi
- Pilot database using OHDSI common data model conducted in 2019.
- MDS-G31 Guidance on Post-Market Clinical Follow-Up Studies.