Recent Trends in Drug Safety: The Growing and Evolving Role of Real-World Evidence

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Introduction

Historically, major drug safety issues have contributed to an evolution of the regulatory framework for drug safety, particularly in the post-approval period. Scientific developments and technological innovations have enhanced traditional passive pharmacovigilance activities with active surveillance and pharmacoepidemiological studies to bolster the precision and granularity of drug safety information.

In recent years, real-world evidence (RWE), derived from real-world data (RWD), has been playing an increasingly fundamental role in the post-authorisation supervision of medicines. In this new era, changes are not only driven by emerging drug safety issues, but rather by a wider regulatory context on evidence needs throughout the development and lifecycle management of drugs.


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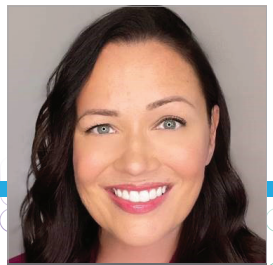
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The focus on use of RWE to inform drug safety in the United States (U.S.) and the European Union (EU) continues to grow for several reasons, such as:

- Greater availability and diversity of health-related data, such as digitized and patient-generated health care data (e.g., via apps, wearables, online tools)
- Increased acceptability of data sharing and applicability of safety surveillance in the interest of public health in the era of COVID-19
- Accelerated approvals of some drugs resulting in the need for more post-marketing RWE to inform patient safety and medication effectiveness in diverse populations
- Refinements in pharmacoepidemiological methods and conduct of RWE investigations

Against this backdrop, we explore the recent regulatory guidelines issued by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) from the perspective of post-marketing safety evaluation of drugs and biologicals (referred below as "drugs") to bring a clearer global picture of:

- Shifts in the regulatory environment
- Evolving approaches with RWD sources
- Consequences in terms of needs related to RWE for post-authorisation research

Shifts in Regulatory Environment

1970-2000: The Birth of Drug Safety

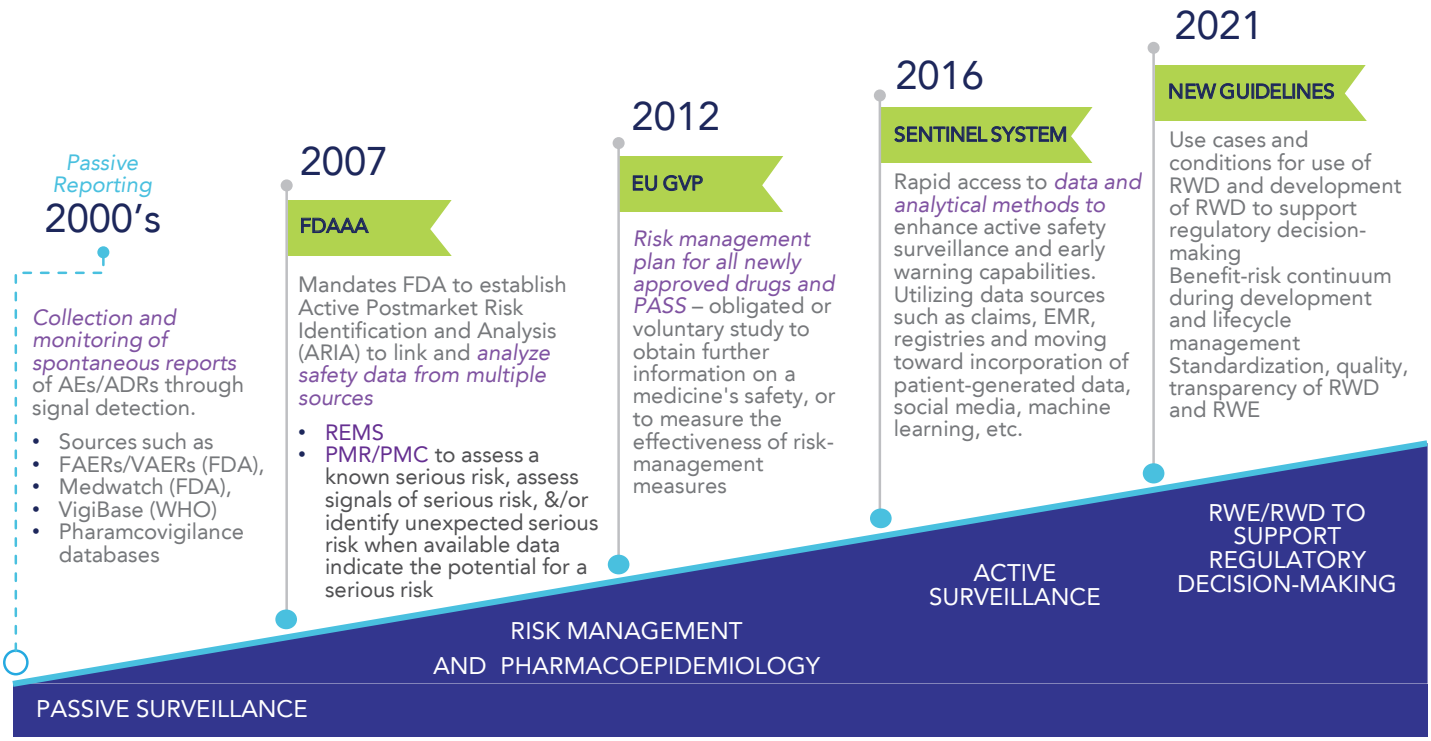
Over the previous two decades, the focus around post-marketing/authorisation drug safety in the U.S. and the EU has moved through the different steps represented in Figure 1.

Passive surveillance and signal detection based on continuous monitoring of spontaneous reports of adverse drug reactions sent by physicians and compiled by biopharma companies and regulatory authorities.[1] Although signal detection approaches have been refined with adoption of metrics such as disproportionality measures,[2,3] this approach remains reactive, subject to limitations in voluntary reporting, and hypothesis-generating.

Risk management planning and evaluation was originally applied beginning in the late 1980s to specific drugs and evolved toward the current Risk Evaluation and Mitigation Strategies (REMS) in the U.S. and the Good Pharmacovigilance Practice (GVP) in Europe and was formalized by the ICH-E2E guideline.[4] Risk management planning led to post-authorisation safety studies, required by regulatory authorities or voluntary, to detect and/or monitor risks associated with newly approved drugs and evaluate the effectiveness of risk minimization measures.

Active surveillance became possible with the wider availability of RWD sources and methodological innovation. It can be complemented with subsequent investigation to further define the magnitude of any new or known risk and characteristics of patients that might alter the benefit-risk equation. A major example is the Sentinel System[5] launched by the FDA to develop a systematic approach to leverage electronic healthcare databases to enable active post-marketing safety surveillance. Another example is the EU-ADR project, a large European initiative based on a public-private partnership to enable analyses across different European electronic medical records (EMR) data sources to improve signal detection.[6]

Figure 1: An Overview of the Regulatory Focus around Safety Surveillance and Evaluation over Time



2000-2018: An Expanding Scope

Expanding the reach of drug safety via RWE

Since 2000, post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES) in Europe, and post-marketing requirements (PMR) or commitments (PMC) in the U.S., have become common requirements for medicinal products at the time they come to the market.

The European good pharmacovigilance practices (GVP) acknowledged RWE approaches for PASS (for both primary or secondary data).[7,8] Most PASS are observational studies,[9] and their designs have increasingly relied on RWD over the years.

In the U.S., the use of RWE for regulatory decision-making was acknowledged and defined in the 21st Century Cures Act (Cures Act) of December 2016.[10] The FDA integrated RWE as an important part of the activity in the Center of Drug Evaluation and Research (CDER) Drug Safety Priorities 2017 report and stated an expectation that RWE will begin to play a greater role in regulatory decisions.[10,11] This is already the case with the use of Sentinel data via the Active post-market Risk Identification and Analysis (ARIA) system[5] that is now used in the FDA regulatory context.

An increasing number of public-private initiatives have contributed to greater consideration of the generation and use of RWE. The Sentinel System has provided opportunities for partnerships between the FDA and data providers as well as healthcare centers. For example, the Innovation in Medical Evidence Development and Surveillance (IMEDS) collaboration allows public and private partners to access Sentinel data while ensuring data security and integrity.[10,11] In Europe, the Innovative Medicines Initiative (IMI) is the biggest public-private partnership on drug development. Recently, IMI issued a call for proposals on several topics, including medicine safety in pregnancy and breastfeeding and the prediction of drug safety early in development. These projects will be funded jointly by the EU's Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Currently, public-private partnerships govern most of the innovative projects with the aim of pooling data sources and/or delivering standardized methods.

Focusing on specific populations

Understanding the safety of drugs in populations that are usually excluded from clinical trials (e.g., pregnant and lactating women and children) is an important concern of regulators and biopharmaceutical companies.

Regarding pregnancy and breastfeeding, the FDA issued guidance for industry in 2002 to establish pregnancy exposure registries[12] and another guidance in 2005 to introduce clinical lactation studies.[13] The European Medicines Agency (EMA) introduced the need for post-authorisation data in 2005[14] and the FDA was granted the authority to require post-marketing pregnancy registries and lactation studies based on the Food and Drug Administration Amendments Act (FDAAA) in 2007.[15] The Pregnancy and Lactation Labeling Rule (PLLR) issued by the FDA in 2015 brought more emphasis on evidence supporting the label and benefit-risk evaluation in pregnancy, including the existence of a pregnancy registry, and the impact of the underlying disease.[16] Finally, in 2019, the FDA released additional guidance on approaches including pharmacovigilance, pregnancy registries, and complementary data sources in the post-market setting to evaluate the safety of products during pregnancy.[17] Subsequently, the percentage of FDA-approved products with at least one pregnancy-related PMR/PMC nearly doubled.[18] Most requirements have come in the form of establishing either a prospective pregnancy registry or a worldwide surveillance program (depending on likelihood of exposure during pregnancy), but a growing number are requiring both a pregnancy registry and a complementary data study.[18] It is anticipated that this trend will only increase in the future.

There is an increased acknowledgement of the specific challenges of assessing drug safety in children (e.g., long-term outcomes such as impact on growth and development), especially in chronic and rare diseases. The Cures Act acknowledges these challenges by promoting pediatric research, supporting, amongst others, the implementation of the 2013 National Pediatric Research Network Act.[10]

Increased development of therapies for rare diseases, often under special regulatory requirements, has also contributed to a need for active surveillance. The FDA has announced an Orphan Drug Designation Modernization Plan and established an Orphan Products Council. The European Union and other countries have followed.[19] The Cures Act has also brought focus on regenerative advanced therapies and pathways for early approval.[10] As the need for continuous safety data generation is high for these drugs, and their use is limited to small patient populations, rare disease/orphan drug registries provide a good solution for long-term safety studies.

2018-2022: Entering a New Era

The increased focus on use of RWD to support regulatory decision-making, both in the pre- and post-marketing space, has led to recent advances.

Accelerated regulatory processes (e.g., adaptive pathways, conditional market approval) and early access programs have allowed patients with no other therapeutic options or who are ineligible for clinical trials to access new drugs more rapidly. Through these programs/pathways, regulatory decision-making is based on less clinical evidence than usually required. In some cases, preliminary clinical data could be supported by RWE, for example in the case of trials using external control arms. In return, the market authorisation holder (MAH) is expected to continue

generating evidence on the marketed product or from patients in the early access program. Safety data are particularly sought after to clarify the benefit-risk ratio over time, due to the limited number of patients exposed during clinical trials and due to the limited duration of exposure / follow-up.[20,21]

The most recent regulatory guidelines from the EMA and the FDA were released in late 2021.

- **EMA guidance on registry-based studies[22]:** In this guideline the EMA defined registry-based studies and advised that these studies can be used for several purposes, including to meet post-authorisation commitments (PASS, PAES) and to complement clinical development data for certain therapies (e.g., investigational cell and gene therapy and medicinal products with orphan designations) for which single-arm trials are often the only option. The EMA also communicated that registry-based studies can be classified as either interventional, low interventional or non-interventional studies.
- **FDA draft guidances[23-27]:** The FDA issued a series of five draft guidelines, which as of spring 2022 were open for public review. Through these, the FDA has provided an expanded framework and considerations for the use of RWD in support of regulatory decision-making. This is the first step toward the implementation of the 2018 Framework for FDA's Real-World Evidence Program[28] and supports the use of RWD for new indications and post-approval study requirements. The earliest guideline in the series addresses the use of electronic health records (EHR) and medical claims data, the second explores utility of registry data and linking of registry data to other data sources, and the third explores the potential use of RWD to support Investigational New Drug Applications, identify potential trial participants, and as a comparator arm in externally controlled trials, including historically controlled trials. The remaining two draft guidances clarify the requirements for RWD standards and submission, thereby setting the framework for future use of RWD in the pre- and post-marketing space.

Evolving Approaches to Real-world Data

EMR and Claims Databases

Epidemiology and pharmacoepidemiology investigations for drug safety have been evolving with the greater availability and expanded content of existing data sources such as EMR databases and claims databases. The FDA has reviewed the methodological characteristics of these databases regarding the specific needs of RWD to support regulatory decision-making[23] and has placed an emphasis on the following methodological aspects:

- Review and relevance of the different data sources, including most recent ones (e.g., distributed data networks, possibilities of linkage)
- Definition, ascertainment, and validation of exposure
- Definition, ascertainment, and validation of outcomes
- Data quality and data management

Although these methodological recommendations are part of usual good practices, their inscription in regulatory draft guidances and the requirements for specific data standards create a new paradigm, since EMR and claims data are not initially collected for research purposes. This is an evolving topic and is expected to lead to further discussions and evolution in data collection and curation practices and the responsibilities between study sponsors and data providers.

In Europe, this trend also translates into the creation of data networks across countries such as the EMA initiative called Data Analysis and Real World Interrogation Network (DARWIN EU). DARWIN EU is a federated network of data, expertise and services that should facilitate RWE generation (including safety studies) with the primary aim of supporting regulatory decision-making.[29]

Registries

Registries are often used to generate safety data for rare diseases, orphan drugs, or drug exposures during pregnancy. They can be exhaustive (including all the patients treated with a given drug; registry is a condition for prescription) or not (e.g., pregnancy registry with or without a non-exposed arm; inclusion on a voluntary basis). It is estimated that between 2005 and 2013, a registry was required in almost 10 percent of newly approved drugs to provide additional data on safety. Most of these drugs were approved under exceptional circumstances or orphan designation.[30]

Registries often have long follow-up and require strong operational organization to ensure adequate recruitment and retention. These now can be supported by new advancements in technologies. For example, recruitment for pregnancy registries has been augmented by leveraging social networks and other communication platforms, enabling more rapid recruitment and improved patient diversity.[31]

Patient registries are increasingly recognized as an important source of RWD due to the current focus on rare diseases, the increased number of patient registry initiatives, and the acknowledged value of data from these studies. For some time, the EMA has been encouraging the use of registry data, with the initial aim of optimizing research on rare diseases and personalized medicine.[32,33] This resulted in the EMA issuing a guideline on registry-based studies in October 2021.[22] This guideline defines registry-based studies and focuses on aspects relevant to

the European regulatory context, such as details of ethics and data privacy, application of GVP guidance on PASS/PAES, ENCePP methodological guidelines, and adverse event reporting. PASS and PAES have been the first type of studies where this guideline was applied, both by sponsors and the Product Risk Assessment Committee (PRAC) when it was already in draft state from September 2020.

In parallel, in November 2021, the FDA issued a draft guidance for industry[23] specifically presenting patient registries and how they can be used to support regulatory decision-making, as part of its abovementioned overall RWD/RWE framework,[28] which has been implemented as a result of the Cures Act.[10] The focus of the FDA draft guidance is methodological challenges related to this data source, recommendations for registry setup, and possible use cases of registry data. See Table 1 for a comparison of the EMA and FDA registry guidance.

The current focus of regulatory agencies on registries, the increased interest of pharmaceutical companies on rare diseases, and the need to generate pre- and post-marketing RWD are leading to the development of new types of registries called "Dynamic Cohorts." These are patient registries that are initiated early enough during the development process to serve multiple purposes and fulfill different needs, both for regulatory and payers/HTA bodies, along the product lifecycle. Typically, these registries initially include patients diagnosed with a specific disease and then continue to include patients routinely treated with the drug of interest.

Table 1. Comparison of EMA and FDA Registry Guidance

	EMA Guideline	FDA Draft Guidance
Registry Definition	Patient registry (synonym: registry): Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition, or exposure. The term "patient"' highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature.	A registry is defined as an organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure.
Approach to Registries	EMA is introducing patient registries as a data source to generate registry-based studies. Registry-based studies are defined by EMA as investigations of a research question using the data collection infrastructure or patient population of one or several patient registries EMA is introducing patient registries as a data source to generate registry-based studies. Registry-based studies are defined by EMA as investigations of a research question using the data collection infrastructure or patient population of one or several patient registries and can be used for several purposes, including: • Supporting clinical trial optimisation • Post-authorisation commitment (PASS, PAES)[7] Registry-based studies can be classified as interventional, low interventional or non-interventional.	FDA's guidance on registries is part of an overall framework regarding the use of RWD to generate RWE in support of regulatory decision-making, including: • Review of other RWD sources (e.g., EHR and claims databases). • Practical aspects and acceptability of RWE for regulatory purposes, e.g., data standardization, submission process. Registries have the potential to support medical product development, and registry data can ultimately be used, when appropriate, to inform the design and support the conduct of either interventional studies (clinical trials) or non-interventional (observational) studies.
Use Cases of Registry Data	Complement the evidence generated in the pre-authorisation phase (e.g., contextualise the results of uncontrolled trials). Provide evidence in the post-authorisation phase (PASS, PAES)[7]. Evaluate the effects of medicinal products used during pregnancy and breast feeding.	Characterize the natural history of a disease. Provide information to help determine sample size, selection criteria, and study endpoints when planning an interventional study. Select suitable study participants for an interventional study (e.g., randomized trial) to assess a drug's safety or effectiveness. Identify biomarkers or clinical characteristics associated with important clinical outcomes of relevance for planned interventional and non-interventional studies. Support, in appropriate clinical circumstances, inferences about safety and effectiveness in the context of: • A non-interventional study evaluating a drug received during routine medical practice and captured by the registry. • An externally controlled trial including registry data as an external control arm.

The Particular Case of Pregnancy Registries

Pregnancy registries are a specific type of registry that has been a focus of the FDA for several years. In its 2019 pregnancy safety study guidance, the FDA recommended the development of multiproduct pregnancy studies to potentially reduce the burden on patients and healthcare providers, reduce costs, and improve efficiency.[17] In such cases, the same participants may serve in the control arm for the investigation of multiple products. A variation of this trend is when sponsors cooperatively agree to pool control data for studies of products with the same indication. There are distinct advantages to this approach as it helps reach sample size goals more rapidly, while reducing costs.

The 2019 guidance also outlined the FDA's current requirements for evaluating the safety of pharmaceuticals and biologics in pregnancy. For products that are expected to be commonly used among females of childbearing potential, the FDA now requires two studies examining largely the same outcomes: a prospective pregnancy registry coupled with a complementary study using a different design, such as a case-control study or retrospective cohort study using EHR or claims data.[17] The prospective studies can capture a greater level of detail and may be less prone to biases, while the retrospective data can boost overall sample size and potentially capture a segment of the population that is not enrolled in prospective studies during the same timeframe. It should be noted that certain outcomes that can be collected in a prospective study, such as elective terminations of pregnancy, cannot be reliably captured through claims data due to the way they are coded.

Current and Emerging Needs

Validated Systems and Methods

Safety studies require the use of efficient technologies and methods to optimize the internal and external validity of results by minimizing biases and ensuring transparency and reproducibility. Data collection platforms are frequently required to collect and combine data from physicians, patients, and caregivers. These platforms may need to integrate with central databases containing other data such as from EMRs or wearables.

In electronic databases, using validated algorithms to define inclusion criteria or outcomes/events of interest is highly recommended, as reiterated in the recent draft FDA guidance.[23] If validated algorithms are not available, a validation step must be planned.[34] A major example is the definition of pregnancy and pregnancy outcomes in electronic databases, which can be quite complex based on the database type. Algorithms have been developed separately for different databases, which is justified due to differences in data structure and type. However, there have also been attempts at creating standardized algorithms across databases to allow for comparability or pooling.[35]

These systems and methods deliver their full value only if reported in a transparent manner, with enough information to ensure reproducibility. This is part of the validity and credibility of a study.

Faster Turnaround Time

The need for rapid analyses to increase the speed of the public health response by regulatory authorities has been clearly highlighted by the EMA.[36] The FDA also used this argument when presenting and justifying its new initiatives toward active surveillance systems and common data models.[37] Furthermore, there are several examples of efficacy and safety studies that relied on RWD to provide timely evidence-based answers during the pandemic. The value in contextualizing possible risks and signals in real time has been recognized and may be expected to increase the acceptability of using digitized health data collected via apps or other types of online tools in the post-marketing/authorisation drug safety study space. Quickness should not reduce quality, and new analytical methodologies are expected to develop along with expansions in the diversity of RWD sources. Accuracy, transparency, and reproducibility are needed for credible drug safety studies.

Data Standards, Quality and Transparency

Although data quality and transparency have always been part of good practices and encouraged in several methodological guidances,[8,38] consideration of using RWD for regulatory decision-making beyond the post-marketing space requires a comparison of post-authorisation requirements with clinical trial requirements. RWD will not allow the same kind of control as clinical trial data, as 1) primary data collection implies minimal disruption of routine care for patients, therefore limiting or forbidding frequent visits or non-routine assessments, and 2) EMR or claims data are not initially collected for research purposes and are usually collected and managed by third-party data providers. However, it can be expected that the potential use of RWD for regulatory submissions will collectively increase the level of quality and transparency.

In addition, the FDA has explicitly mentioned the requirement of applying Clinical Data Interchange Standards Consortium (CDISC) standards to RWD.[26] Based on the FDA draft guidance, this requirement might evolve toward the application of standards more relevant to the structure and type of RWD. The EMA has not yet issued any recommendation in terms of standards, but this is pending given the expressed will to also consider RWE for regulatory decision-making. We also observe the trend to apply CDISC standards to European RWD. Therefore, the introduction of data standards and the need to include RWD in regulatory packages in the same way as clinical trials will certainly impact how data will be collected and managed in the future, including post-marketing safety data.

Conclusion

In the last 20 years, generation of safety data outside of clinical trials has developed from single-source, passive systems to holistic and proactive approaches that leverage a combination of data generation systems and a multitude of data sources and designs. Benefit-risk assessment of medicinal products is becoming a continuous process throughout development and lifecycle management. Within an evolving regulatory environment, RWE safety data has moved from supportive data to a key element in regulatory decisions.

As a result of the latest guidelines from the EMA and the FDA, it is expected that patient registries will become more frequently used as part of post-approval studies. In addition, it is expected that there will be increased requirement for strategic, well-justified and transparent approaches to study design, conduct and decision-making in post-marketing/authorisation safety studies. For instance, robust feasibility assessments can be expected more frequently prior to the full launch of long-term drug safety studies.

Therefore, it is anticipated that, with growing use of RWE expected in the pre-market/authorisation phase of drug development, there will continue to be an increase in the number of post-marketing/authorisation safety studies using RWE. Due to the expectation that post-marketing safety data will be fully part of regulatory decision-making and any standards applied to pre-marketing RWD will also apply to post-marketing RWD, we anticipate a new era for post-marketing safety studies.

For more information, please contact us.

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