RWD and RWE in Brazil: Perspective of the Brazilian Health Regulatory Agency (Anvisa)

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This article is an overview of the use of real world data (RWD) and real world evidence (RWE) for regulatory decision-making in Brazil, focusing on decisions regarding the registration process and post-approval changes of drugs at the Brazilian Health Regulatory Agency (Anvisa).

Since Anvisa hasn't issued a formal Guidance, there are no official definitions for RWD and RWE. Based on regulatory discussions in Brazil, the concept of those terms do not differ from what has already been documented by other international regulatory agencies:

> *Real world data (RWD) is data related to the patient's health or clinical condition, routinely collected from a variety of sources, such as electronic health records, medical procedure financing data, patient-generated data.*
>
> *Real world evidence (RWE) is clinical evidence about the use or potential risks/benefits of a drug based on the analysis of real world data.*

It is important to highlight that RWD and RWE, even without these specific designations, have always been included in documentation submitted for Anvisa assessment and in technical discussions with the pharmaceutical industry. Some examples are: information on national incidence and prevalence of diseases in target populations, comparison between routine standard of care and clinical trials, evaluation of therapeutic options (when they are available), and assessment of a drug's performance in clinical practice before a formal and planned assessment of its effectiveness.

However, there seems to be a trend towards increased use of RWD as supportive evidence of efficacy and safety of drugs in applications (including post-approval commitments associated with NDAs) and in post-approval changes related to efficacy and safety; in particular for drugs indicated for the treatment of rare diseases or serious and debilitating conditions, since conducting properly controlled clinical trials in these situations can be difficult or even not feasible.

The role assumed by RWE in recent years is viewed with great caution by the Agency's reviewers for the following reasons:

- It is necessary to improve the quality of data and sources that generate Brazilian RWD in order to provide adequate evidence that meets regulatory expectations.
- It is challenging to ensure representativeness of the Brazilian population to obtain external validity, given the vast size of Brazil, its cultural and

socioeconomic diversity, and the uneven access to technology and health resources.

- Limitations on the use of RWD and RWE to support efficacy claims for drugs.
- Confounding factors and biases arising from non-randomized evidence may present challenges for statistical evaluation due to uncertainties and limitations for assessment and interpretation of causal inferences.
- In cases in which the use of RWD and RWE has been previously agreed on with other regulatory agencies, it is common for applicants to submit the same documentation containing RWE and RWD, even though Anvisa does not have specific guidelines for this type of evidence.
- In the majority of cases, RWE and RWD are generated from international databases to meet the regulatory requirements of other countries, which makes the interpretation of results in the Brazilian context more complex. This situation is not completely new, because there are cases where data from clinical trials conducted exclusively in other countries to prove the efficacy and safety of drugs is accepted by Anvisa for review. However, in those cases, the Agency has a Guideline for reviewers that provides general considerations for extrapolation of foreign data.

Anvisa's Regulatory Initiatives on the Use of RWE Generated by RWD

In order to reduce those uncertainties and to increase confidence in RWE in regulatory decision-making, Anvisa has been seeking to increase its knowledge of these topics. Anvisa, together with the association of the Brazilian pharmaceutical industries (Sindusfarma), promoted technical discussions in two workshops in 2019: *Real World Data – An overview of the current status, trends, challenges and opportunities* and *Real World Evidence*. These events were attended by several different stakeholders, such as academic institutions, pharmaceutical industry representatives, and regulators. At these meetings, the discussions covered potential options for collection, quality control, validation, and acceptability of RWD; information on initiatives from other regulatory agencies on this topic; case studies of pharmaceutical companies and use of RWE at different stages of clinical drug development; data analysis driven by artificial intelligence in healthcare settings; opportunities and challenges of RWE studies; and perspectives of medical professionals and industry in relation to RWE. In addition to these events, workshops, and seminars focused on critical assessment of oncological drugs and drugs for rare diseases have also addressed, in recent years, the use of RWD and RWE in these specific contexts.

Within the scope of international cooperation and regulatory convergence, 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).

With the aforementioned initiatives, both national and international, Anvisa has begun its internal process of building understanding for the critical assessment of RWD and RWE. Since Brazil does not yet have a national regulation related to RWE/RWD, communication between the Agency and applicants is highly recommended to discuss the relevance of evidence to be submitted. This communication can be established through the following existing channels: pre-submission meetings for scientific advice (available for the drug registration process, post-approval changes, and clinical research for regulatory purposes); discussions of queries issued by Anvisa (for ongoing reviews); and ombudsman systems (which can be used not only by the pharmaceutical industry, but also by citizens and other government departments that are interested in seeking clarity from the Agency).

Several key aspects (among possible others) should be discussed with Anvisa prior to submission if there is an intent to use RWD and RWE to support claims of efficacy and safety (especially for drugs aimed at treating rare diseases and serious and debilitating conditions): pertinence of using primary or secondary sources of RWD; use of national or international data sources; uncertainties related to outcomes, follow up, sample size, comparators, and target population; design of studies that include RWD; and others.

RWD Sources in Brazil

As a country of more than 211 million, Brazil generates a huge diversity of health data, from both health research and healthcare: health database systems, population surveys, demographic censuses, and clinical/observational studies.

Most of the information generated in the country through health research, both in government and in the private sector, offers epidemiological and observational perspectives and promotes real world information that primarily guides decision-making in the healthcare sector. Although most surveys do not have a regulatory purpose, they can support expansion of knowledge about diseases, social determinants of health, and therapeutic approaches adopted on the Brazilian territory.

Regarding the information produced for patient assistance and coverage of health services, databases were built independently and aren't sensitive enough to detail the health history of individuals; the compilation of data generated by each database is not capable of addressing the health status of the population in all regions of the country in detail.

A recent strategy will contribute to the improvement of this current model of generating information, focusing on the subject/patient. This initiative is called Digital Health Strategy, which will include the National Health Data Network (RNDS), a component of the national health database, which will seek integration and interoperability of health information not only between public and private health institutions, but also among health management departments of federal entities, to ensure access to health information that is required for the continuity of subject/patient care. RNDS information may be valuable for epidemiological, statistical, research, and regulatory purposes, among others.

The computerized system will store data from the individual's medical history within a single electronic form, capturing exams, diagnostic tests, medication/vaccination, medical care, and hospitalization data that can be filled out by health professionals responsible for each service provided. Therefore, it is expected that in the coming years this unique computerized platform, given its promise, will become a national reference for the collection of data from users of healthcare services. It will still be necessary to overcome challenges to define the criteria for data use and adequacy ("fit for purpose") so that the information generated can guide Anvisa's regulatory decision-making.

Next Steps

We understand that there is still a long way to go to increasing the confidence in and the credibility of these sources of information. For these goals to be met, we will need to interact with stakeholders to share knowledge and define the best use of RWD in regulatory assessments; develop specific guidelines regarding the use of RWD, following the steps of good regulatory practices; update internal regulations and procedures in the different areas of the Agency that assess clinical evidence; interact with several national stakeholders to build the interoperability of databases; and to qualify existing ones, in order to improve the quality of data collected to ensure a better regulatory decision-making process.

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References available upon request.