Introduction
Regulatory agencies are faced with the issue of making decisions based upon necessary limited data with inherent uncertainties on the aspect of real-world effectiveness. Consequently, in order to cope with such uncertainties and make new drugs available, the Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA) requires the implementation of registries with the aim to collect real world data (RWD) and apply performance-based risk sharing arrangements (PBRSA).

RWD is defined as an umbrella term regarding the effects of health interventions that are not collected in the context of conventional randomised controlled trials (RCTs). Registries are one of the many sources of RWD; electronic medical records, observational studies, administrative data, claims databases, health surveys and patient reported outcomes (PROs) are alternative tools.

AIFA Registries
The Italian National Health System, in its efforts to guarantee health insurance for italian citizens on a universal basis, is more and more engaged with the challenges of new pharmaceuticals, which can bring high prices along with innovation. To the extent possible, the system balances costs, treatment effectiveness and economic sustainability for every new marketing authorization (MA).

In fact, the early phases of marketing represent the most delicate period of the new drugs’ lifecycles. This is especially true for innovative drugs, due to incomplete information related to product efficacy, safety and applicability when used in normal clinical practice.

AIFA - founded on July 2004 - is the national authority responsible for pharmaceutical regulation and Health Technology Assessment (HTA) in Italy. AIFA’s institutional commitment is oriented towards the entire life cycle of a pharmaceutical product: from pre-authorization to registration, post-marketing surveillance and pharmacovigilance activity, inspection and certification, economic strategy and pharmaceutical policy, including pricing and reimbursement of ethical medicines through a negotiation process, monitoring and governance of public pharmaceutical expenditure, post marketing assessment and HTA.

The drug-product Registries, established by the AIFA in 2005, represent the example of a national application of a computerized workflow handling the personalized drug distribution in hospitals and local public pharmaceutical services, with the intent of improving the efficacy/efficiency of both regulatory and reimbursement related activities, including RW outcome analyses.
The AIFA drug-product Registries are national web tools placed in the early phases after MA, in some cases for the ‘authorized’ off label use with the clear purpose to measure RW safety and effectiveness and apply the Managed Entry Agreements’ (MEAs) procedures.

The eForms of an AIFA Registry are as follow:

- Demographic patient form, DPF
- Eligibility & clinical data form, ECDF
- Prescription drug form, PDF
- Dispensing drug form, DDF
- Re-evaluation form, ReVF
- End of treatment form, EoTF
- Pregnancy form, PF
- Adverse drug reaction form, ADRF (incoming)

Currently, 76 medicines are monitored through the system, for their use more than 55 different diseases; individual treatments recorded are more than 515,000, for a population of about 505,000 patients. Various categories of regulatory, clinical and administrative actors are involved with different profiles of access to data system: AIFA, 21 Regions, more than 1,000 connected hospitals, over 25,000 clinicians, over 1,500 pharmacists, and 32 pharmaceutical companies. The web monitoring is available from: https://www.agenziafarmaco.gov.it/registri/

**Data collection**

Each AIFA Registry is an Electronic Drug-Therapeutic Indication Record (EDTIR) system designed to integrate all the disparate functions of hospital or health local unit (physician or pharmacist) into one unified paperless system. EDTIR are optimized for single therapeutic indications and are accessible from multiple hospitals, pharmacies and different departments.

AIFA web platform of Registries are characterized by a cross-architecture, modular and flexible, enabling improved quality of data recording and enhanced data analysis performances. Further improvements and development of the system, also resulting from consultations with Regions, local health departments, scientific societies and pharmaceutical companies, are in the planning stage.

The Multi user access has the following characteristics:

- Data-centric approach
- Intuitive user interface requiring minimal training for non technical users
- A hierarchical accreditation system for access to Registries designed on two levels: a users’ accreditation level, in which top regional representatives grant access to health managers and the latter enable physicians and pharmacists; and a Registries’ accreditation level, in which regional representatives select health departments and centres to be granted access
- Data entry validation at the time of input
• Comprehensive record searching
• Look up fields, drug treatments and indications classification entries
• Traceability of all transactions and storing data
• Unique patient demographic form and consistency checks of the tax code. Secured confidential access to patient treatment’s record
• Data protection approved methodologies to ensure identification of the patient at point of contact but de-identification (anonymisation) of data for all aggregation and sharing analysis purpose
• Multiple electronic and technical manuals for the use of the system
• Automated backup, business continuity
• Identify and flag records with missing critical fields
• Links to relevant institution websites: EMA, AIFA
• Standardized data collection
• Consistency and quality data automatic check (e.g. on eligibility criteria and clinical data for continuing treatment, at re-evaluation and follow-up)
• Daily and total treatment dosages automatically calculated and dynamically checked (automatic e/o dynamic for each indication e/o drug)
• Possibility to partition the packages (solid and liquid pharmaceutical form when possible)
• Possibility to interrupt the therapy in case of dose adjustment (first and second level of dose reducing)
• Automated drug interaction notification
• Patients’ Re - evaluations inserted with automatic controls based on the number of cycles and time controls
• Enhanced real time analysis by SAS visual reporting
• Pre defined automated reports graphs and export data files (.xls) for users with preapproved access

Tables and browsers allow real time data entry from multiple remote sources. This not only saves enormous time and money but also provides immediate feedback to the clinician and pharmacist in the event that data entered is abnormal. This abnormality can be flagged as an error or warning requiring immediate intervention (service desk).

In 2012 AIFA Registries officially became part of the SSN Information Technology (IT) system, in order to ensure the appropriateness of drugs use and allow MEAs' application and monitoring of their financial effects (Law n. 135/2012). For those medicines for which AIFA established to have a registry, data collection is mandatory under the national legislation. This adds an administrative burden to physicians and pharmacist but must be seen as a mean to ensure the drug availability. The data collected through Registries is owned by AIFA and the maintenance costs are shared with the MAHs.

The Registry becomes a virtual EDTIR system highly optimized around the target therapeutic indication (or disease) at national level and the information obtained are considered an acquisition of drug knowledge.

**Managed Entry Agreements**

In the last decade, MEAs - with a taxonomy based both on financial schemes, coverage with evidence development (CED) and PBRSAs - have been widely implemented in Italy, in order to foster access to new medicines with a high level of uncertainty at launch.
A MEA is an arrangement between a manufacturer and payer/provider that enables access to (coverage/ reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact. PBRSAs are payment schemes—they involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the level of reimbursement is based on the health and costs outcomes achieved.

MEAs can be based on different models of conditioned reimbursement:
- Cost sharing (CS) - provides a discount on price of first courses of therapy for all patients eligible for treatment, as identified by the Summary of Product Characteristics
- Risk sharing (RS) - compared to the previous, the discount applies only to non-responders
- Payment by result (PbR) - extends the terms of the RS, providing for full refund from the pharmaceutical company on all "non-responders" (100% of treatment failures).

The Italian Management

At present, the overall percentage of Registries aimed at allowing the application of MEAs is 46%. Unlike CS (20%) agreements, which is less often used, PbR agreements are the most frequently used schemes (around 30%), especially for medicinal products whose risk-benefit ratio presents a greater degree of uncertainty.

RWD collected by Registries together with pharmacovigilance and economic information allow the re-assessing of pharmaceuticals’ value and related decisions. In its HTA pathway, AIFA performs the re-evaluation of cost-effectiveness profile, by resorting data from Registries. After a pre-specified period, usually 24-36 months, the pricing and reimbursement agreement is reassessed, also comparing results, in terms of efficacy and safety, expected at the moment of the decision, with real practice outcomes (effectiveness). This activity eventually determines a reconsideration of the original reimbursement and pricing decision and a new negotiation with the MAH is conducted.

Outcome measurement
Drug-product Registries that systematically collect data on all eligible patients are a tremendous resource for capturing important information on safety. Patients treated in real life and tracked by Registries differs, on average from those enrolled in RCTs with regards to
complexity of their underlying disease, comorbidities, and concomitant medications. Drug-product Registries, by definition, focus on patients treated with a particular medical product.

Each drug-product Registry records specific information on patient baseline characteristics including prior treatments and comorbidities, and gives the longitudinal view of each patient treatment including route of administration, dose, duration of use and reason for treatment discontinuation/interruption.

By using standardized eligibility criteria within treatments with different drugs for the same therapeutic indication AIFA Registries allow not only to analyse the real life outcome for a given drug, but also to compare the different treatment options (e.g. with the use of match paired analysis). Furthermore it is also possible to describe the various treatment pathways used in clinic practice for specific therapeutic indication and measure their respective outcome.

By collecting events in the broad population with conditions of interest, AIFA Registries make a meaningful contribution to understanding adverse event rates in real life.

AIFA Registries, rather than specific drug-product Registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing legitimate comparisons, to the extent possible, across types and generations of drugs. Consideration should be given during the Registry design phase to inclusion/exclusion criteria, appropriate comparator groups, definitions of the exposure and relevant risk window(s), and analysis planning.

The Registries involving products new to the market may be affected by selection bias, channelling bias, and unmeasured confounding by indication. Channelling bias occurs when patients prescribed the new product are not comparable to the general disease population. For example, channelling bias occurs when sicker patients receive new treatments because they are nonresponsive to existing treatments; conversely, patients who are doing well on existing treatments are unlikely to be switched to new treatments.

In Italy, sometimes cost constraints imposed by reimbursement status means that new therapies are restricted to narrower populations than indicated by the approved indication. In some settings, AIFA Registries are used to collect specific adverse events or events of interest. The implementation of routine follow up is a key feature to ensure that analyses of the occurrence of adverse events among the Registry population are not biased by extensive missing data. Indeed, the possibility that, patients ‘lost to follow up’ may differ from those with repeat visits, with regard to risk of adverse events, cannot be excluded.

AIFA Registries are also used to increase awareness of prescribers on safety concern and Risk Minimisation Measures in order to optimize the safe and effective use of drugs. Upon registry inception, clinicians and pharmacists who may encounter patients participating in the Registry are educated about what adverse events or other special events of interest should be noted, and how and within what parameters (e.g., time) they should report untoward events that may occur while they are participating in the Registry. They also are reminded about the need to follow up on events that may not obviously be of immediate interest and encourage to report adverse drug reactions by asking for the occurrence of AEs at each new prescription and providing a link to the National Network of Pharmacovigilance.

In conclusion the additional tasks of the new approach of the AIFA Registries are:
• Disease-centered approach (same indication means same data tracked)
• Broad collection of baseline characteristics
• Education on safety concerns and Risk Minimisation Measures.

This kind of (R)evolution should allow to AIFA to have more information about the effectiveness, safety and treatment pathways.

Example: thalidomide and lenalidomide

The introduction of novel agents, such as thalidomide and lenalidomide (usually in combination with dexamethasone) has led to a clear improvement in myeloma patients’ survival.

Due to thalidomide and lenalidomide, known human teratogen effects and their important clinical risks, a Risk Management Plan (RMP) has been implemented in agreement with EMA indication. This plan includes a Pregnancy Prevention Plan to avoid any thalidomide or lenalidomide exposure during pregnancy, monitoring of other clinically important risks associated with thalidomide such as peripheral neuropathy and thromboembolism and the provision of educational materials. The PPP’s goals are to:

• Prevent foetal exposures
• Educate about risks
• Provide procedures to reduce the risk of foetal exposure
• Identify at-risk behaviours by surveying patients and prescribers
• Provide a mechanism for intervention and remediation when at-risk behaviours are identified via the PPP
• Serve as the mechanism for controlled drug distribution.

Both programs (PPP thalidomide and PPP lenalidomide) include the following safety measures:

• Mandatory registration of all patients, prescribers and pharmacies
• Pregnancy testing in all females of childbearing potential
• Education for prescribers, pharmacists and patients
• No refills and a 28-day limit to prescriptions.

The RMP for lenalidomide and thalidomide is the result of ‘historic reminiscence’. Their approval was conditional on implementation of an RMP very closely supervised by the Thalidomide Victims Association in Europe. To prevent foetal exposure in Italy, these products are available only under the special restrictions of the AIFA Registry, a unique vehicle for the most advanced implementation of an RMP. The Registry gives the opportunity to know in real time the condition of the drug use, allows physicians to ‘certify’ the drug’s use and ensure patients and victims’ associations that the RMP is always applied. Currently are 4,752 treatments with lenalidomide and 2,827 with thalidomide and no pregnancy are reported.

In addition to minimizing the potential risk for foetal harm associated with thalidomide or lenalidomide therapy, the Registry may provide a model for future cases where a drug offers compelling benefits but poses profound risks unless its distribution is carefully controlled.

Perspectives

From an evolutionary perspective, AIFA Registries could be intended as common evidence generators in real life treatments, representing an opportunity and a starting point for new cooperation between patients, academia, regulators, HTAs, payers and industry, encouraging synergy and strategic interactions for allowing data collection and improving patient access to therapeutics.
Eichler et al., reported that ‘the flexibility of MEAs in addressing post initial licensing uncertainty and enabling access to expensive treatments provides an opportunity for synergies with regulatory initiatives’. AIFA anticipates a high number of post-authorization safety and/or efficacy Registries. ‘These could be prospectively planned and aligned with post-licensing evidence generation foreseen by payers under a MEAs/CED scheme’. The AIFA decisions showed that products approved under conditional marketing authorization (CMA), or with orphan designation were subsequently reimbursed with a MEA and consequently with a national web system monitoring.

The following further potentialities of monitoring registries are worth mentioning:
- Contribution in establishing integrated healthcare approaches and pathway management, based on standardized measurements of clinical outcomes;
- Development of creative approaches through the use of e-health tools for improving adherence, promoting self-management, and collecting patient-reported adverse events and outcomes.

It is acknowledged that as Garrison et al., said, 'care must be taken in analysing and interpreting the data due to the inherent limitations' of Registries. ‘There is no guarantee that patient groupings are comparable; therefore, registries may not be suitable to test hypothesis, but are useful to generate them’. Anyway, drug-product Registries constitute key instruments for real life evidence generation and the improvement of patient care and healthcare planning.

AIFA’s responsibility with regards to both regulatory and HTA, as well as pricing and reimbursement activities at national level, facilitates the alignment between regulatory and HTA decisions. In this context, the use of regulatory tools such as monitoring registries could contribute to responding to the need of ensuring safe and timely access to innovative therapies for patients.

**Bibliography**


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