The Italian post-marketing registries

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The post-marketing registries, established by the Italian Medicines Agency in 2005, represent the example of a national application of an automated workflow handling the personalized drug distribution in hospital pharmacies and local public pharmaceutical services, with the intent of both improving the efficacy/efficiency of analysis and regulatory activities themselves, as well as closely monitoring the clinical activity. In fact, within the correct clinical practice the prescriber shall take into account the parameters, such as therapeutic drug indication, actual benefit the patient should gain in comparison to the trials, potential and actual risk of adverse reactions, drugs interactions, and cost of the therapy. On the track of the cancer registry's experience, the Italian Medicines Agency has extended the scope to the following areas: ophthalmology, rheumatology, dermatology, orphan drugs, cardiology, diabetology, respiratory, and neurological diseases. It involves more than 60 drugs (most of them with risk sharing schemes on a population of over 400 000 patients) and is available from http://monitoraggio-farmaci.agenziafarmaco.it.

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The Registries of Italian Medicines Agency

The aim of drugs monitoring is the computerized national management[1] of the whole process concerning the request of dispensation and analysis of consumption data of an innovative drug. The computerized drugs prescription requires a change of mentality and a restructuring of the whole process; for these reasons, it's still struggling to be used extensively. The Italian Medicines Agency (AIFA) has developed a treatment registration form and can monitor and control in real time the correct use of the drug. The first regulatory experience was the cancer drugs register.[2] Based on this experience, AIFA has extended the scope to the following areas: ophthalmology, rheumatology, dermatology, orphan drugs, cardiology, diabetology, respiratory, and neurological diseases. It involves more than 60 drugs (most of them with managed entry agreements (MEAs) on a population of over 400 000 patients (Table 1) and is available from http://monitoraggio-farmaci.agenziafarmaco.it.

Through this network, AIFA will implement the monitoring process and the exchange of data between the pharmacist, clinicians, and patients under control of the regulatory authority with centralized management of all the information required by law.[3]

Data entry

The monitoring is totally web based and allows the physician to issue an electronic request for a precise dose of the drug regarding a patient whose diagnosis corresponds to parameters of the authorized therapeutic indication (Fig. 1). The electronic form application, valid for a single administration, is automatically sent by email to the hospital pharmacy, which proceeds to close the form by formally and practically dispensing the requested drug. The system is accessible from any computer connected to the internet through the use of a username and password. It is also targeted to non-computer experts and does not require specific training. The procedures for entering and managing the data are standardized; however, the flows depend on the specificity of the drug and its therapeutic indication.

For each prompt, the system offers additional compile a number of forms relating to the follow-up.

In addition, and not least, is very important also to analyse the use of the innovative therapies directly with the pharmaceutical companies, according to the principle of risk sharing or pay by result: the awareness and evaluation of results of clinical practice and the purpose of defining the right cost to be incurred by the national health system. Currently, the web based reimbursement procedures within the registries network are active (referred fifteen drugs). It is obvious that strict control procedures are needed on the number of patients treated and their registry follow-up files. This is possible thanks to pharmacies carrying out administrative and accounting measurements. The MEAs was a scientific, economic, and cultural revolution[4,5] (Fig. 2) and the formulas are as follows: CS is the

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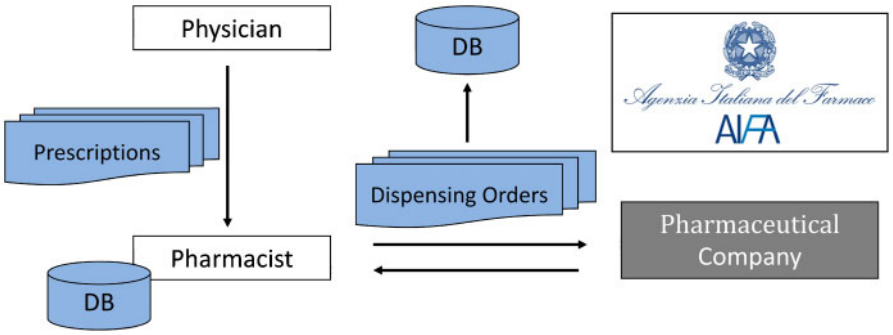

Figure 1 Patients' case report forms must be filled in, in a specific web-based monitoring register (RFM). The register tracks the eligibility of the registered patients and the complete flow of the treatments

cost share as special discount applied to the initial cycles of therapy for all eligible patients; RS is the risk share as special discount applied to the initial cycles for non responder patients after re-evaluation; PbR is the payment by result (or performance) as total refund applied to the initial cycles for non-responder patients after re-evaluation.

The parties involved may enter their registration by filling out the online request form available according to the different profiles: physician and pharmacist. The registration form provides the inclusion of personal identification and references to the hospital structure. These can be entered by directly consulting the Italian hospital database.

The application of managed entry agreements

The web-based reimbursement procedures within the registries network are active (referred to 24 oncologic drugs). In this process, the pharmacist role is crucial and very important.

The pharmacist must report the data of the pharmacy and the name or code that characterize the pharmacy inside the Italian pharmacy database. This way, each hospital can distinguish or choose the reference pharmacy connected directly to the hospital (internal pharmacy). After filling out the relative forms, the system automatically sends the credentials by email, in conformity with the demands of security and privacy regulations (Fig. 3).

The physician provides insertion, update, and accessing data from patient treatment, performs the registration, fills out the clinical data card and, after obtaining the eligibility, enters the drug request as reported in Fig. 1. The physician also, provides data on health patient status reporting any toxicity or adverse drug reaction, where it occurs, and proceeds by entering the end treatment form to close the process. The drug request form must indicate the dispensing reference pharmacy. If the pharmacy is a hospital one, the system automatically sends an email to the reference pharmacy to notify the new request: a link allows direct access for the pharmacist to dispense the drug, thus completing the dispensing form. The correct completion of the dispensing form is a crucial and important step: it provides valuable data for the later analysis through the regional dashboard (Cruscotto Informativo Regionale Registri — CIRR).

The administration drug procedure could be executed from:

- 'Local Unit pharmacy: in this case, the physician will give the patient the drug release request form, which must be presented to the pharmacy area to obtain the drug. The paper form, therefore, contains a unique identifier code: this allows the patient to withdraw the drug from the nearest pharmacy.
- In the case of 'Hospital pharmacy' drug administration, the pharmacy receives an email request for the drug. The pharmacy checks the received data, fills out the form and delivers the drug.

Several quality and consistency controls are implemented during the data entry.

At the time of registration of the patient, the system performs a cross-check on homonyms and warns, if the same patient is registered in the database for the same drug, notifying the information to the physician

Table 1 CIRR update of 31 July 2012 (http://monitoraggio-farmaci.agenziafarmaco.it)

	N°
Hospital structures enabled	901
Drugs (total monitoring)	69
Drugs (active monitoring)	50
Therapeutic indications	88
Registered users	51 180
Eligible patients	428 969

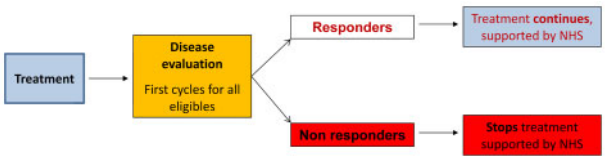

Figure 2 Risk sharing procedures: an innovative drug should be reimbursed only if effective; the welfare systems cannot take responsibility for the failures in front of such high costs. Identification of responders patients in order to ensure an effective therapy against the poor prediction of clinical response at the time of recruitment

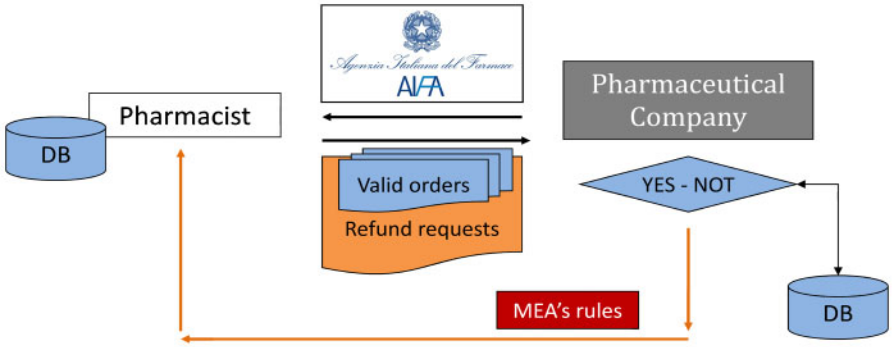

Figure 3 The MEAs procedure or risk sharing procedure: is a web-based system controlled directly by AIFA, with a free interaction between the hospitals and pharmaceutical companies

and tracking the path of care for patient treat with multiple drugs. The system also checks the parameters of eligibility for the treatment, if the correct use is not met, thus stopping the recording and reporting a detailed text alert about the inappropriateness of the request.

The regional dashboard

The dashboard calculates the cost of the drug usage according to the drug dispensing forms properly inserted in each log, and allows consultation of the reports for each region that can highlight in a simple, short and snappy way the information about drugs use in the territory of choice: consumer indicators, patient number, and patient agreement schemes. In detail, the dash allows to browse the data for local health unit and hospital centres (Fig. 4).

The data are presented as:

- multi-dimensional analysis (cubic): large quantities of information in aggregated view, with possibility of choosing independently the path analysis, multiple levels of disaggregation;
- static reports: tabular listing synthetic indicators (rates, percentages, ratios, medians, etc.) From a technical standpoint, the dashboard gives an overview of data from the registries (since 2006) and highlights in a concise and effective way the information of both clinical and economic governance.

The available information is:

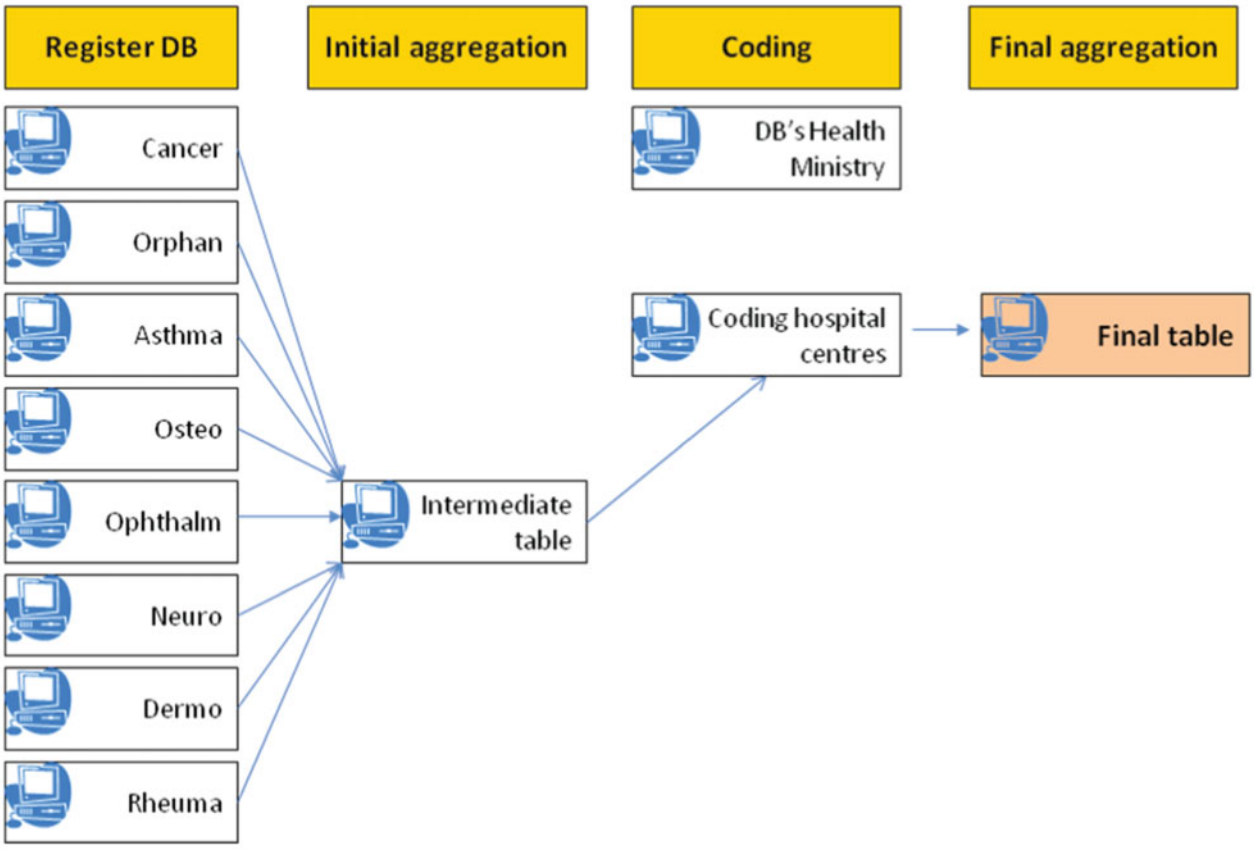

Figure 4 The data undergo an initial aggregation within an intermediate table of the dashboard. After the coding of all hospitals centers (through the database of the Ministry of Health), the system via a second data aggregation creates the final table

- clinical: eligible patients, treated patients, duration of treatment, end of therapy, ADR, per drug or therapeutic indication;
- economic/administrative: dispensed drugs per marketing authorisation, expenditure (per treated patient, pathology, difference among prescription sites), expenditure reimbursed by risk sharing and/or PbR;

The dashboard completes the information already collected in every single register, allowing AIFA and Regional Health Departments:

- to have an overview of data recorded in all Registers of Monitored Drugs (since 2006 over 400 000 cases);
- to obtain a brief and effective information of a clinical, economic and administrative nature;
- to have, for each Region, absolute and relative figures and indicators for national data comparison;
- to retrieve the requested information in a short time, searching the database by local and time parameters;
- to customize and save research criteria.

The data can be inspected at different levels: space (for each region, local health unit or clinical site), time (for year, semester or month), clinical (for therapeutic indication), and treatment (for each register e/or drug).

Project Vision

The mechanisms of monitoring by registries, the MEAs schemes and the information of regional dashboards are all intended to share costs and responsibilities with prescribers, companies, and authority in order to define the best ethical rules that should underlay the administrative job, as well as the multiple economical aspects concerned.

As a main result of this approach to appropriateness in prescribing, it gets easy to use new drugs with a better level of confidence in order to obtain early drug activity indicators and to better manage the expenditure controls.

Here are the benefits of all the actors involved:

- patients: rapid access to new drugs, supported by National Health Service (NHS) and monitoring of prescriptions and tolerability;
- institutions, healthcare communities and payers: balance between rapid access to market[6] and appropriateness, balance between costs and efficacy and new sources of relevant clinical data;
- pharmaceutical companies: access to market for the new drugs, supported by NHS and again, new sources of relevant clinical data.

On the other hand, sharing the risks of the new treatments between companies and institutional actors promotes an effective growth of patient's protection. For this reason, AIFA has put considerable effort in attempting a nationwide experiment in drug monitoring, despite its high managing complexity, combining regulatory, clinical and IT aspects.

The parties involved into the project are different: Italian Medicines Agency, IT service — Consortium of Universities CINECA; pharmaceutical companies (over fifteen), patients (over 400 000); clinicians (different therapeutic areas, over 20 000); hospital connected (more 1000), pharmacists (over 1200).

With the experience of more than 6 years of monitoring (profiled access to the projects over 90 000 000, public access to the projects over 110 000 000), AIFA has the opportunity to field test the impact of innovative drugs on clinical practice in Italy. The return and analysis of data logs to all those involved in the authorization mechanism, production, prescription, and administration of drugs monitored has always been one of the major elements of the philosophy of the registries that, since 2005, have been progressively refined and specialized. The new challenge may be, not only to continue this project, but also to add also improvements to the current structure. In this sense, one of the potential mean could be insert specific details about the disease for the duration of a drug monitoring process.

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