

Pharmacovigilance and the Italian Medicines Agency

Giuseppe Pimpinella, Loriana Tartaglia

Pharmacovigilance Unit, Italian Medicines Agency, Via del Tritone, Rome, Italy

ABSTRACT

The new European Union (EU) regulations on pharmacovigilance require that the national systems are strengthened in order to fit the new requirements. The Italian Pharmacovigilance System, coordinated by the Italian Medicines Agency (AIFA), is made by local and regional structures. In 2007, a program for funding active pharmacovigilance projects in the Italian Regions was established by the National law. The AIFA is responsible for the preparation of guidelines aimed at the identification of research areas and for the approval of the projects submitted by the regions. In April 2012, the AIFA started a program of visits at the regional pharmacovigilance centers (RPCs), aimed at monitoring their performances, evaluating the quality of the activities in order to understand the main differences and discrepancies and with a view to start a program of harmonization of the procedures in place. The outcome of the visits program highlighted major differences among the quality management systems of the various centers; hence, AIFA has decided to launch an initiative to promote in the next months the harmonization of procedures. The synergy among AIFA, regional structures, RPCs, and local structure responsible for pharmacovigilance is needed in order to establish a robust pharmacovigilance system working in full compliance with the provisions of the new EU legislation.

Key words: Italian Medicines Agency, AIFA, Italian Pharmacovigilance System, pharmacovigilance

INTRODUCTION

European Union (EU) provisions regulating pharmacovigilance have been modified in 2010 by means of the adoption of Regulation 1235/2010/EC^[1] and of Directive 2010/84/EC.^[2] The modifications that have been introduced in the provisions have the aim to strengthen the timeliness, effectiveness, and transparency of pharmacovigilance actions, in order to make the whole system more robust. The changes highlight the need of a more integrated system, based on a network of closely

interconnected structures, all cooperating in order to achieve a common goal: Good pharmacovigilance practice^[3] (GVP). Hence the Italian Pharmacovigilance System is facing the challenge of the new tasks established by the recent provisions that will require adequate human and technological resources.^[4]

THE ITALIAN PROGRAM FOR FUNDING ACTIVE PHARMACOVIGILANCE PROJECTS

The Italian Pharmacovigilance System, coordinated by the Italian Medicines Agency (AIFA), consists of local structure responsible for pharmacovigilance (LRP), regional pharmacovigilance centers (RPCs) and Italian regions. Hence, local and especially regional structures are essential for making the whole national pharmacovigilance system work properly. Local structures strictly cooperate with AIFA, singularly or in association, providing the fundamental elements needed for a proper evaluation of benefits and risks of medicinal products.

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.120940

Address for correspondence:

Giuseppe Pimpinella, Pharmacovigilance Unit, Italian Medicines Agency (AIFA), Via del Tritone, 181, 00187, Rome, Italy. E-mail: g.pimpinella@aifa.gov.it

In fact, they are responsible for the collection of adverse drug reactions (ADRs) reports on the territory and also provide data on drug utilization and prescription monitoring by utilizing the regional monitoring programs on pharmaceutical prescriptions. Regional structures also cooperate with AIFA in order to disseminate safety information and to provide the training of health professionals on pharmacovigilance duties. As in other EU countries, regions may utilize RPCs to support their activities. Furthermore, they are involved in the national program of active pharmacovigilance in cooperation with AIFA.

In this regard, in 2007 the national law established a program for funding active pharmacovigilance projects in the Italian regions.^[5,6] A specific agreement has been signed between the Italian State and the regional structures identifying areas of interest for research and regulating the allocation of funds.

Furthermore, AIFA is responsible for the preparation of guidelines aimed at the identification of research areas and for the approval of the projects submitted by the regions.

Following the agreement adopted on 28 October 2010, the resources available for years 2008-2009 (50 million Euros) have been allocated.

Guidelines have been agreed with the regional structures including initiatives to improve the knowledge of the benefit-risk profile of drugs in the postmarketing phase.^[7] The following main areas of interest have been identified:

- Studies on selected ADRs, either on the basis of the analysis of spontaneous reports, or by conducting epidemiological studies
- Evaluation of drug utilization and promotion of drug prescription appropriateness
- Drug information and training initiatives directed to health professionals with the aim to stimulate spontaneous reporting
- Strengthening of the pharmacovigilance activities of ethical committees in the context of clinical trials; and
- Set up and/or maintenance of RPCs.

Monitoring of funded projects is a further important activity performed by AIFA in this context. Regional structures which receive funding commit, in the framework of the agreement with the state, to provide to the AIFA an interim report on the work progress. Once the studies have been completed they provide a final report that describes the achieved results.

Overall, 139 regional projects in 19 Italian regional structures and 8 multiregional projects with national relevance have been funded with the resources available for years 2008-2009.

A specific tranche (30%) of the available fund has been directly allocated to the regions with the purpose to establish

or to maintain RPCs. As mentioned above, in Italy the RPCs represent a strategic component for the proper functioning of the national pharmacovigilance system as well as a vital connecting node between the central and local structures.

The pharmacovigilance centers are regional structures with defined roles and responsibilities^[8]:

- Evaluation of ADRs reports coming from regions, with reference to quality of data and coding (medications and adverse reactions)
- Support to the LRP
- Causality assessment and listedness evaluation
- Support to LRPs in feedback and training activities directed to reporters; and
- Contribution to signal analysis on drugs and vaccines in cooperation with AIFA.

RPCs utilize multidisciplinary panels of experts (e.g. pharmacologists, epidemiologists, clinical pharmacists, specialized physicians, and biostatistics/informatics) in order to ensure specific expertise covering all areas of activity. Furthermore, for some peculiar issues, they must ensure interaction and synergy of actions with other structures (e.g. in the case of vaccines a close cooperation with prevention structures has to be put in place).

In Italy, eight RPCs used to operate since long time in the following Regions: Lombardia, Veneto, Liguria, Emilia-Romagna, Toscana, Campania, Basilicata, and Sicilia. As a consequence of the pharmacovigilance funding program for the years 2008 and 2009, eight further new RPCs have been recently established in Abruzzo, Calabria, Marche, Molise, Puglia, Umbria, Sardegna, and Friuli Venezia Giulia (it should be noted that such regions were already involved in pharmacovigilance activities before the establishment of the RPCs).

In April 2012, the AIFA started a program of visits at the RPCs, aimed at monitoring their performances, evaluating the quality of the activities performed, in order to understand the main differences and discrepancies among the different centers and with a view to start a program of harmonization of the procedures in place in the different centers. In fact, RPCs being an important part of the national pharmacovigilance system, they need to be in compliance with rigorous harmonized quality standards and have to follow detailed operating procedures, as established in the EU Guidelines on GVP, hence fulfilling the obligations provided in the new pharmacovigilance directive. On the basis of outcome of the visits program that has highlighted major differences among the quality management systems of the various centers, the AIFA has decided to launch an initiative to promote the harmonization of procedures supporting the RPCs in achieving this goal. The attainment of this objective is

considered very important in order to guarantee that the whole system works in a timely, efficient, and transparent way.

CONCLUSIONS

Pharmacovigilance has completed its evolution from a passive discipline, only taking actions in response to adverse reactions clusters, to a proactive dimension, focused on the early identification of risk factors in order to set preventative measures, such as post marketing efficacy and safety studies and perform information initiatives for health professionals, patients and the general public.

Both at national and community level, pharmacovigilance should not only be considered a responsibility of regulatory bodies, but of the whole health system. All subjects involved in the dispensation of sanitary services are responsible for the monitoring of the efficacy and safety of medicines and the best way to reach such a goal is through professional education and continuous training.

The experience gathered in the early years of the application of the Italian provisions, that grant the regional structures a funding for pharmacovigilance activities by the state, is globally positive. Many projects and education activities have been agreed with the regional structures and have been successfully carried out thanks to the allocated resources.

New RPCs have been established and the number of projects involving the participation of multiple regions has increased. The projects dealing with active pharmacovigilance conducted so far have decisively contributed to the increasing trend in the number of ADRs reports per year and to the quality of the data in the national pharmacovigilance database. Besides this, active pharmacovigilance initiatives not only have the scope to increase the number and the quality of ADR reports, but also to encourage a deeper understanding of the rationale use of drugs in clinical practice. Hence, the ultimate goal is to promote appropriateness in prescribing, according to the guidelines developed by national and international scientific societies and, in general, according to the principles of the evidence-based medicine. The preliminary results of such studies are promising and it will be possible to fully evaluate the results of the funded projects in a mid-long term, especially where the funding has been used to create permanent structures, and for projects impacting on prescribing appropriateness, on education/training and on the preventability of ADRs. Thus,

the positive synergy among AIFA, regional structures, RPCs, and LRPs allows the integration of different strategies in order to establish a robust pharmacovigilance system, in accordance with the provisions of the new EU legislation, with the aim to ensure that all medicinal products that are on the market have a positive risk-benefit balance.

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How to cite this article: Pimpinella G, Tartaglia L. Pharmacovigilance and the Italian Medicines Agency. J Pharmacol Pharmacother 2013;4:4-6.
Source of Support: Nil, **Conflict of Interest:** None declared.