

## Brazilian Regulation in Pharmacovigilance: A Review

Mastroianni PC\*, Varallo FR and Dagli-Hernandez C

Department of Drugs and Medications, School of Pharmaceutical Sciences, UNESP-Univ Estadual Paulista Paulista, Araraquara, Sao Paulo, Brazil

\*Corresponding author: Mastroianni PC, Department of Drugs and Medications, School of Pharmaceutical Sciences, University of Estadual Paulista, Araraquara, Sao Paulo, Brazil, Tel: +55 16 3301-6977; Fax: +55 16 3322-0073; E-mail: [pmastro@fcar.unesp.br](mailto:pmastro@fcar.unesp.br)

Received date: April 25, 2016; Accepted date: May 13, 2016; Published date: May 18, 2016

Copyright: © 2016 Mastroianni PC, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Brazilian health legislation on drug surveillance has been available for only four decades. This study aimed to analyze the chronological evolution of the pharmacovigilance legislation in Brazil. A critical review of the legislations and communications published between 1976 and 2015 was conducted. Sixty-two (62) documents were identified. Advancements in the assessment of health technologies occurred only after the publication of the National Drug Policy (1998), the foundation of the National Health Surveillance Agency (ANVISA), and the creation of the National Center for Drug Monitoring (2001). From 2009, pharmacovigilance practices became mandatory for marketing authorization holders. Despite recent, the regulatory advancements in pharmacovigilance in Brazil are equivalent to international practices. However, there is still a lack of regulations for biosimilars and veterinary medicines, of agility in reporting non-serious risks to manufacturers and health care services, and of encouragement for reporting technical complaints and quality deviations, which could improve and control post-marketing drug quality. It is necessary to encourage and develop strategies for the decentralization of pharmacovigilance actions to the whole country.

**Keywords:** Pharmacovigilance; Product surveillance; Post-marketing; Drug information services; Health legislation; Regulation pharmaceutical policy

### Introduction

The risk-benefit assessment of drugs is conducted during their whole lifecycle [1,2]. Randomized clinical trials assess the risk-benefit ratio in ideal conditions, where variables such as age, sex, the presence of morbidities or comorbidities, polypharmacy and exposure time to the drug are controlled.

In Brazil, a drug is considered as "new" in the first five years of commercialization. Drug registration is renewed by submitting a pharmacovigilance safety update report and a risk minimization plan [3].

Effective pharmacovigilance measures allow to improve the risk-benefit ratio by providing information about drug safety under real conditions of use [4] that is, on different age groups, in patients with morbidities, comorbidities, and genetic polymorphisms, and after prolonged exposure time to the drug. Cultural differences between countries, the use of traditional medicine (supplementation and medicinal plants) and the different quality standards in the manufacturing process of drug products can also affect drug safety [5]. These variables influence the creation of laws that regulate and monitor the safety, quality and effectiveness of these products.

Pharmacovigilance actions are constantly changing, adding resources to proactively detect drug-related problems. Prevalence data obtained on post-marketing surveillance have been used to identify genetic biomarkers [6,7], aiming to improve the safety and effectiveness of the pharmacotherapy [7].

In this context, this study aimed to assess the Brazilian legislation on pharmacovigilance, in order to identify the conceptual changes and actions in drug post-marketing surveillance over the years.

### Methods

A critical review of the Brazilian legislations was conducted using a descriptive study of historical nature [8].

The strategy comprised a search in the legislation database of the Brazilian health authority (National Health Surveillance Agency [ANVISA])–Saude Legis (Health Legislation System) and VISALEGIS (Health Surveillance Legislation System) to identify legislations that regulate pharmacovigilance practice in Brazil. A search was also conducted in the website of the Ministry of Health, in the field "legislation" within "The Ministry", and in the portal of the Federal Government legislation [9]. Another search for legislations was performed in the websites of the Pharmacovigilance Centers of the states of Bahia, Parana, Rio de Janeiro, Santa Catarina and Sao Paulo, which were registered at ANVISA's website [10].

The search was conducted by the type of legislation, with no restrictions to the period, origin, source and situation (revoked or current), and using the following keywords, "drug safety", "marketing authorization holders", "pharmacovigilance" and "patient safety".

The collected material was examined using the content analysis technique, which is a data processing technique used to objectively, quantitatively, and systematically describe the selected content [11].

From the initial reading of the selected material, the following variables were defined: year of publication, scope (federal or state), type of legislation (laws, decrees, resolutions, ordinances and communications), to whom it is applied (industries; health care services; pharmacies and drugstores; regulatory organs and health

professionals), and what it regulates (what should be done by whom it is applied).

During data processing, the content of the texts was analyzed, in order to assess the historical evolution of concepts, competences and responsibilities in pharmacovigilance of each sector involved. We also evaluated whether there are sectors not covered by current regulations in pharmacovigilance.

## Results

The Brazilian pharmacovigilance legislation dates from 1976 to 2015 (Table 1). The Health Surveillance Center of the State of São Paulo

(CVS-SP) and ANVISA are responsible for regulating and monitoring the pharmacovigilance actions at a state and national level, respectively. The regulated sectors are health care assistance services (Public health care establishments, pharmacies, drugstores, particular clinics and hospitals), drug manufacturers, Marketing Authorization Holders (MAH), and health care professionals (Table 1). Existing policies cover all health care levels (primary, secondary and tertiary levels) and spheres involved in the drug chain. However, there were no relevant legislations on the pharmacovigilance of bio similar and veterinary products.

Before founding ANVISA (1976-1999)				After founding ANVISA							
				Focused on drug safety (1999-2015)				Focused on patient safety (2013-2015)			
Law	Level	Enforcer	Regulation	Law	Level	Enforcer	Regulation	Law	Level	Enforcer	Regulation
Law No. 6360	National	MAH	ADR reporting and efficacy assessment	Law No. 9782	National	ANVISA	To control, monitor, and regulate products and services that involve risks to health	Ord. No. 529	National	Health care services	Establishes the National Program of Patient Safety, to enable promoting the mitigation of the occurrence of ADE in health care
Decree No.79094	National	MAH	ADR reporting <sup>a</sup>	Res. No. 328	National	Pharmacies Drugstores	Risk communication (ADR and drug interactions)				
Ord. 577	National	Technical Council	Pharmacological surveillance system (ADR reporting, assessment and record)	Res. No. 33	State (SP)	CVS-SP	Approves an instrument for risk communication				
Federal Constitution	National	State	To ensure safety and prevent health damage	Res. No. 33	National	Pharmacies	Pharmacovigilance studies	RD C No. 36	National	Health care services	Establishes actions for patient safety and risk communication (ADE) and sets deadlines for reporting
Ord. No. 17	State	Surveillance Center	Establishment of pharmacovigilance <sup>a</sup>	Ord. No. 696	National	CNMM	To structure post-marketing drug surveillance in Brazilian territory				
Law No. 8080	National	Health care services	To identify and prevent health damage	Ord. No. 239	National	ANVISA	Establishes the Pharmacovigilance Unit	Ord. No. 2647	National	REBRACIM	Contributes to the National System of Pharmacovigilance and the National Program of Patient Safety on safety in medication use
Res. No. 300	National	Hospitals	Establishes the hospital pharmacovigilance	Res. No. 863	National	MAH	Post-registration pharmacovigilance reports (stability test)				
Res. No. 72	State (SP)	CVS-SP	Establishes a post-marketing drug surveillance program	Res. No. 136	National	MAH	Renewal of registration of new drugs by submitting a pharmacovigilance report				
Res. No. 132	State (SP)	CVS-SP	Creation of a Commission of Iatrogenic Control	Res. No. 138	National	MAH	Renewal of registration of new drugs and classification of the sales category according to	RDC No. 53	National	Health care services	Establishes the period of 180 days after the publication of the RDC No. 36 for implementing

							pharmacovigilance data				
Ord. No. 3916	National	HM	To ensure drug safety and efficacy and the rational use of drugs through pharmacovigilance	Ord. No. 23	State (SP)	Pharmacies Drugstores	Communication of risks (ADE) associated with retinoids <sup>a</sup>				the patient safety center in health care services
Ord. No. 6	National	HM	Establishes an instrument for risk communication (ADR) of drugs subject to special control. Establishes an instrument for risk communication (ADR) of retinoids	Ord. No. 24	State (SP)	Health care services	Establishes an instrument for risk communication (ADE) and provides deadlines for reporting <sup>a</sup>	Res. No. 12	State (SP)	CIPESP	Creates the Committee on the Implementation of the State Program for Patient Safety
				Res. No. 91	National	MAH	Post-registration pharmacovigilance reports of phytotherapies (stability)				
Law	Level	Enforcer	Regulation	Law	Level	Enforcer	Regulation	Law	Level	Enforcer	Regulation
				Ord. No. 4	State (SP)	Pharmacies Drugstores	Risk communication (ADR) associated with clozapine <sup>a</sup>				
				Ord. No. 8	State (SP)	Health care services	Establishes an instrument for risk communication (ADE) and provides deadlines for reporting <sup>a</sup>				
				Ord. No. 3	State (SP)	CVS-SP	Creates the Pharmacovigilance Center of the CVS-SP				
				Ord. No. 4	State (SP)	Health care services MAH user	Updates and establishes an instrument for risk communication (ADR) and DQD; Stipulates deadlines for reporting <sup>a</sup>				
				RDC No. 233	National	MAH, distributors importers	Pharmacovigilance study				
				RDC No. 315	National	MAH	New biological products post-registration pharmacovigilance report				

				Res. No. 2697	State (RJ)	Health Department	Creates the Pharmacovigilance Program and establishes an instrument for risk communication				
				Res. No. 398	State (RJ)	Health care services	Encourages ADE risk communication of Hexabrix 320 <sup>a</sup>				
				Ord. No. 95 Res. No. 39	National	ANVISA	Establishes the Coordinating Committee of Actions for the Rational Use of Drugs				
				Res. No. 40	National	ANVISA CRF	Establishes the Advisory Committee of the Notifying Pharmacy Program				
				RDC No. 16	National	MAH	Post-registration pharmacovigilance report (ADR and efficacy) for generic drugs <sup>a</sup>				
				RDC No. 17	National	MAH	Pre and post- registration pharmacovigilance reports for similar drugs				
<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>
				Ord. No. 92	National	Anvisa Health Surveillance Secretariat National Quality Control Institute of Oswaldo Cruz Foundation	Vaccines and Other Immunobiologicals Pharmacovigilance Program in the scope of the Single Health System				
				Ord. No. 113	State (SP)	CVS-SP	Determines precautionary prohibition of lumiracoxib due to accumulation of serious ADR reports <sup>a</sup>				
				Ord. No. 266	State (SP)	CVS-SP	Prohibition on marketing of rimonabant due to accumulation of serious ADR reports <sup>a</sup>				

				RDC No. 4	National	MAH	Provides for pharmacovigilance standards				
				RDC No. 44	National	Pharmacies Drugstores	ADE and technical complaints reporting				
				NI No. 14	National	MAH	Approves the Pharmacovigilance Guidelines for implementing the RDC No.4				
				Ord. No. 3252	National	Health Ministry	Funding of Health Surveillance actions, such as the Notifying Pharmacy Program, Sentinel Hospitals and Notivisa, by the Union, the States, the Federal District and Municipalities <sup>a</sup>				
				Ord. No. 1660	National	ANVISA	Establishes the Health Surveillance Reporting and Investigation System - VIGIPROS, responsible for monitoring, analyzing and investigating adverse events and technical complaints				
				RDC No. 67	National	MAH	Establishes the general requirements of technical surveillance <sup>a</sup>				
<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>
				RDC No. 2	National	Health services care	Risk communication (ADE and technical complaints) and management of health technologies				
				Ord. No. 5	State (SP)	MAH	Communication of serious and non-serious ADE risk in pregnant women; provides deadlines for reporting; defines the deployment of a risk management plan				
				Ord. No. 28	State (SP)	MAH	Determines the registration of marketing authorization holders (MAH)				

							based in the State of São Paulo in the online reporting system - PERIWEB				
				RDC No. 7	National	Hospital (ICU)	Risk management and ADE communication; risk minimization plans and reporting to the risk management				
				RDC No. 57	National	Blood center	Risk communication (ADR) associated with transfusion				
				RDC No. 52	National	MAH and health services care	Prohibition of manufacturing, importing, exporting, distributing, manipulation, prescribing, dispensing, providing, trading and using drugs or drug formulations containing the substances amfepramone, fenproporex and mazindol, their salts and isomers, as well as intermediaries <sup>a</sup>				
				Ord. No. 1	State (SP)	Health services care	Risk communication (ADE) related to the use of clozapine <sup>a</sup>				
				Res. 54	State (SP)	CVS-SP	Approves the Pharmacology Committee of the Health Department of the State of SP, which will implement actions and pharmacovigilance				
				Ord. No. 1378	National	Health services care	Risk communication (ADR) related to vaccines				
<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>	<b>Law</b>	<b>Level</b>
				Decree	National	MAH	Risk communication				

				No. 8077			(ADE and DQD), risk minimization plans of the products mentioned in the Law No. 6360				
				Res. No. 4162	National	MAH	Determines the suspension of the manufacture, importation, marketing, manipulation of lorcasein <sup>a</sup>				
				RDC No. 60	National	MAH	Submission of pharmacovigilance plans for concession and renewal of the registration of drugs with synthetic and semi-synthetic drug substances, classified as new, generic and similar				
				Law No. 13021	National	Pharmacies Drugstores	Risk communication of the health agency and MAH (adverse effects, ADR, intoxications [voluntary or not], pharmacodependence) observed and registered in pharmacovigilance practice				
				Law No. 13097	National	MAH	Changes the period for Drug Registration renewal, according to its effectiveness and safety				

**Table 1:** Brazilian regulation in pharmacovigilance <sup>a</sup>Revoked.

## Discussion

Brazilian pharmacovigilance regulations have been available for less than 50 years, but there was a significant advance in pharmacovigilance in Brazil. Before the 1990s, Brazil already had legislations for assessing drug safety aiming to detect adverse drug reactions (ADR). However, their implementation was considered unsuccessful [12], since the responsibility for pharmacovigilance practices was mainly of MAH. Also, safety assessment was not compulsory or monitored by national authorities at that time.

Strategies to enhance ADR and drug intoxication reporting started to be developed in the 1990s, when the CVS-SP first included educative interventions for health professionals and drug risk communication reporting as attributions of the pharmacovigilance practice.

The expansion to the whole national territory took place nine years later, with the publication of the National Drug Policy, the foundation of ANVISA, the inclusion of Brazil as a member of the World Health Organization's (WHO) International Drug Monitoring Programme, and the creation of the National Center for Drug Monitoring (CNMM). At this point, pharmacovigilance activities were



systematized, by developing tools describing how, when, and why to report; establishing deadlines for serious and non-serious adverse drug events (ADE) reporting; and developing strategies to minimize underreporting.

In 2002, the WHO widened the scope of pharmacovigilance [13], including not only ADR notifications, but any drug-related problem, such as quality deviations, drug ineffectiveness, and medication errors. At the same time, ANVISA launched the Sentinel Network project, whose main objective was regulating and monitoring health technologies used in the tertiary and secondary level of health care. Therefore, only teaching hospitals were responsible for reporting irregularities of health technologies to ANVISA, which would evaluate the safety, quality and effectiveness attributes of products available in the market.

In 2005, with the Reporting Pharmacy project, ADR and technical complaint monitoring was extended to the first health care level. However, the desired number of reports has not been obtained, although each notification is of great importance for patient safety in a qualitative point of view. This project is currently being regulated.

In 2009, pharmacovigilance standards were created for MAH of drugs for human use. In this resolution, pharmacovigilance is understood as "pharmacovigilance activities relating to the detection, assessment, understanding and prevention of adverse effects or other drug-related problems. Thus, the following adverse effects or other drug-related problems were considered for reporting: Suspected ADRs; Adverse Events due to drug quality deviations; Adverse Events due to the use off-label; Drug interactions; Total or partial therapeutic ineffectiveness; Drug abuse; Potential or actual medication errors [3].

Brazilian pharmacovigilance legislation demanded about three and a half decades to develop strategies for implementing post-marketing surveillance mainly focused on the drug. Currently, with the publication of new legislations focused on patient safety, the patient also starts to be the protagonist of the treatment process.

Furthermore, strategies for drug registration renewal by submitting periodic safety update reports and risk minimization plans were developed, and actions related to post-marketing surveillance were expanded to all spheres involved in the drug life cycle. Also, the new legislation of 2015 allows ANVISA to define deadlines for drug registration renewal, considering the nature of the product and the health risk involved in its use [14] (Table 1).

Nowadays, not only MAH are required to monitor their products, but health care services also started to be responsible for promoting patient safety, since they evaluate all the process of drug use (the need, safety, effectiveness, and adherence). This allows to analyze the profile of drug use, risk factors for the occurrence of ADEs [15], and problems related to ineffectiveness, such as polymorphisms [16], drug quality deviations and medication errors [17,18].

The reporting deadlines are important factors for improving drug risk communication. The legislation sets different deadlines for each sector. While Sentinel Hospitals are required to report serious or non-serious ADEs directly to ANVISA, MAH must report only serious ADEs within 7 or 15 days [3]. Non-serious ADEs will be reported only in the Periodic Safety Update Report during drug registration renewal.

To improve risk communication, the CVS-SP defined that adverse events that involve death must be reported, even when not confirmed by health care professionals [19]. Besides, MAH set in the State of Sao Paulo must report non-serious adverse events to the CVS-SP within 90

calendar days after knowledge of the case, possibly contributing to generate a rapid safety signal for a product.

Moreover, manufacturers do not have access to pharmacovigilance reports concerning their products or to ANVISA's assessment about these reports, since they are sent directly to ANVISA through the NOTIVISA system. It is important to provide this feedback to MAH, since it allows manufacturers to improve the quality and safety of their products. This process is currently ongoing, as the access of MAH to reports involving their products is planned for the version 2.0 of NOTIVISA, which is under construction [20].

Pharmacovigilance actions are conducted in a few services, such as Sentinel Hospitals, Notifying Pharmacies, and some centers and regions of Brazil linked to universities and teaching hospitals in the following states: Bahia, Cear (Northeast region); Brasília, Mato Grosso do Sul (Midwest region); Parana, Santa Catarina (South region); Rio de Janeiro Sao Paulo, Minas Gerais (Southeast region) [9,10]. Eighteen Brazilian states, especially in the North region, do not have pharmacovigilance services. The lack of centers in all regions leads to an unequal pharmacovigilance in Brazil, underreporting, and, consequently, failure in detecting signals of new ADEs [21].

Although pharmacovigilance in Brazil is strong in its legislation, other domains are not well structured, which contributes to the disparity of actions in different Brazilian states [22]. Thus, it is necessary to develop new requirements, such as transparency, accountability, information technology, among others, in order to minimize underreporting and promote equity of actions among the different Brazilian regions [22].

Another highlight is that RDC (resolution) 04/2009 [3] and Ordinance CVS-SP 05/2010 [19] only include the technical complaint reporting if an adverse event occurs due to drug quality deviations. Currently, technical complaints, important indicators of drug quality, are mostly reported by Sentinel Hospitals.

In Brazil, reporting events related to veterinary medicines, which are registered by the Ministry of Agriculture, Livestock and Supply (MAPA), that regulates drug registration and renewal, is not compulsory. Veterinary medicines also need a pharmacovigilance system to report ADEs in animals or ADEs observed by humans during drug handling and administration.

A trend for supervising Brazilian drugs would be the harmonization with the European Union, by adding a symbol of an inverted black triangle to the leaflet of new drugs with the following description: "This drug is subject to further monitoring". As drugs approved for less than five years must have their risk-benefit ratio assessed more frequently, this Brazilian legislation could be harmonized with the European legislation, alerting health care professionals and patients about the exposure to this drug and contributing to drug safety.

## Conclusion

The advancement of pharmacovigilance regulation is recent in Brazil. Regulatory advancements equivalent to international practices have been observed only after the publication of the National Drug Policy (1998), the foundation of ANVISA, and the creation of the CNMM (2001).

However, the lack of decentralization of pharmacovigilance centers or services in all Brazilian states leads to underreporting and failure in signal detection, especially of non-serious ADE reports for health care



products and services. There is a lack of regulations for biosimilars and veterinary medicines and of agility in reporting non-serious risks to manufacturers and health care services.

It is necessary to encourage and to develop strategies for technical complaint and quality deviation reporting, in order to improve and control post-marketing drug quality. Also, there is a need for decentralization, leading to a higher equity between Brazilian regions in regards to risk communication related to the use of drugs.

## Acknowledgement

Support grant #2013/12681-2 and support grant #10263-9, São Paulo Research Foundation (FAPESP).

## References

1. Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, et al. (2010) A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. *Value Health* 13: 657-666.
2. Garrison LP, Towse A, Bresnahan BW (2007) Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. *Health Aff (Millwood)* 26: 684-695.
3. National Health Surveillance Agency (2009) Ministry of Health. National Agency for Sanitary Vigilance. Guidelines of pharmacovigilance for running DRC. Official Gazette Brasilia.
4. Buon M, Gaillard C, Martin J, Fedrizzi S, Mosquet B, et al. (2013) Risk of proton pump inhibitor-induced mild hypernatremia in older adults. *J Am Geriatr Soc* 61: 2052-2054.
5. Mazzitello C, Esposito S, De Francesco AE, Capuano A, Russo E, et al. (2013) Pharmacovigilance in Italy: An overview. *J Pharmacol Pharmacother* 4: S20-S28.
6. Awada Z, Zgheib NK (2014) Pharmacogenovigilance: A pharmacogenomics pharmacovigilance program. *Pharmacogenomics* 15: 845-856.
7. Blankstein S (2014) Pharmacogenomics: history, barriers, and regulatory solutions. *J Food Drug Law* 69: 273-314.
8. Godoy AS (1995) Introduction to qualitative research and its possibilities. *Rev Adm Empres* 35: 57-63.
9. BRASIL (2014) Federal government. Portal legislation. Federal laws of Brazil.
10. BRASIL (2016) National Agency for Sanitary Vigilance –ANVISA. Pharmacovigilance centers.
11. Bardin L (1977) Content analysis 70.
12. Pan American Health Organization (2002) Terms of reference for the meeting of the working group: Interface between Pharmaceutical Care and Pharmacovigilance. OPAS.
13. World Health Organization (2005) The importance of pharmacovigilance: drug safety monitoring.
14. Brazil (2015) It reduces to zero the rates of PIS/PASEP, COFINS and other measures. Official Gazette Law No. 13,097.
15. Varallo FR, Capucho HC, Silva Planeta C da, Carvalho Mastroianni P de (2014) Possible adverse drug events leading to hospital admission in a Brazilian teaching hospital. *Clin* 9: 163-167.
16. Capucho HC, Mastroianni PC, Cuffini S (2008) Pharmacovigilance in Brazil: The relationship between polymorphism of drugs, effectiveness and safety of medicines. *Cienc Farm Primary Apl* 29: 277-283.
17. Gavaza P, Brown CM, Lawson KA, Rascati KL, Steinhardt M, et al. (2012) Effect of social influences on pharmacists' intention to report adverse drug events. *J Am Pharm Assoc* 52: 622-629.
18. Sao Paulo (2010) Health Surveillance Center. CVS Ordinance No. 5. Update flow notifications pharmacovigilance for Drug Registration Holders of the State of Sao Paulo and gives related measures. *Diario Oficial do Estado de Sao Paulo*, Sao Paulo.
19. National Health Surveillance Agency – ANVISA (2013) Pharmacovigilance Bulletin 2.
20. Varallo FR, Guimaraes S de OP, Abjaude SAR, Mastroianni P de C (2014) Causes for the underreporting of adverse drug events by health professionals: a systematic review. *J Nursing of USP* 48: 739-747.
21. Madurga SM (2014) Pharmacovigilance, the "mother" of all surveillances. *OFIL Rev* 24: 201-203.
22. Uniao Europeia (2001) Directive of the european parliament and of the council amending, as regards pharmacovigilance, directive on the Community code relating to medicinal products for human use, pp: 348-374.