

Pharmacovigilance risk mitigation plans: action in public health to promote the safe use of medication

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Abstract Risk mitigation plans (RMP) are an innovative and important strategy for monitoring the sanitary risks of medication. The scope of the study was to identify RMPs for drugs registered with the Food and Drug Administration (FDA) and the actions to minimize risks established by the Brazilian Health Surveillance Agency (Anvisa) and the manufacturers of these drugs. This is a quantitative and descriptive study including a survey together with the pharmaceutical industries and research on sites and databases of Anvisa, the FDA and pharmaceutical industries. Forty drugs with RMPs filed with the FDA were also registered with Anvisa. Only 4 laboratories (10%) reported RMPs developed in Brazil. Safety information for 15 drugs (37.5%) were located on the Anvisa site. In 91.4% of Brazilian user package leaflets there is safety information equivalent to actions to promote safe use described in RMPs available on the FDA website. The actions of communication on drug safety and sanitary risk of drugs needs to be expanded by Anvisa. The RMP is an important strategy in public health for managing new risks, monitoring known risks and, especially, for promoting the safe use of medication. **Key words** Pharmacovigilance, Adverse effects, Medication, Sanitary vigilance

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Introduction

Current methods of development of drugs – chemical synthesis, pharmacogenetics and biotechnology – have helped incorporate new therapeutic classes into clinical practice: leading examples are the monoclonal antibodies, and drugs used in molecular targeting therapies^{1,2}.

In spite of the modern regulatory measures, which take effect prior to the launch of drugs, concern with their safety has increased. The limitations of clinical trials underline this concern and re-emphasize the need to continue assessing and identifying: the more serious adverse effects of a drug; the emergence of new adverse reactions and/or confirmation of the frequency with which those already described occur; the therapeutic value; and new indications over the whole of the period of marketing and sale¹⁻³.

This is where the responsibility of pharmacovigilance begins, with its mission of monitoring the risk/benefit relationship of drugs that are sold¹⁻⁵. Voluntary notification of adverse reactions, addressed to the drug manufacturers and pharmacovigilance centers, is a non-interventionist method which generates signals for low cost, has been adopted in several countries, and is a useful tool in elucidating drug safety in the post-marketing phase. But nowadays more up-to-date safety strategies for monitoring the safety of new drugs are employed, especially in developed countries. They include: networks of population databases for surveillance, use of data mining (computer processes for finding patterns in large databases), integration of various sources of information to improve prediction and identification of adverse events, and preparation of Risk Minimization Action Plans (RiskMAPs)^{5,6}.

The RiskMAP, a new strategy in pharmacovigilance, comprises: evaluation of the risk/benefit of a drug; identification, characterization, prevention or minimization of risks, including the evaluation of effectiveness of these interventions, with the goal of helping to monitor the safety of drugs⁴⁻⁸. The US Food and Drug Administration (FDA), a benchmark in questions of drug safety, was the pioneer in implementation of the RiskMAP, followed by the European drugs agency and those of other countries^{5,6}. The regulatory framework for pharmacovigilance in Brazil specifies development of a RiskMAP by drug manufacturers established in Brazil⁹.

The process of a RiskMAP is interactive, and consists of evaluation of the risk/benefit relationship for patients that will begin a new treatment,

and also monitoring of the safety of the patients during the treatment, to guarantee safe and appropriate use of the drug^{4,7,8}.

To be efficacious, risk minimization activities require communication with both patients and health professionals, and intercommunication between these two groups. Communication of information in pharmacovigilance is very complex, but is an essential element for improving information on drug safety⁹.

In view of the growing concern with the safety of new drugs, and in view of the incorporation of RiskMAPs as a risk management strategy by the principal regulatory agencies, the objective of this study was to identify the drugs sold in Brazil that have RiskMAPs registered in the FDA, and the risk minimization actions put in place in Brazil by Anvisa and by the drug manufacturers.

Methods

This is a descriptive, documentary, quantitative study, consisting of research on sites and databases of the drug regulatory agencies and questioning of pharmaceutical companies by correspondence sent to the web addresses of their customer service departments - CSDs.

The FDA site was accessed and in the section on drug safety the relationship between those with a RiskMAP approved up to the access date (July 5, 2012)¹⁰ was identified. These drugs were researched for availability in the Brazilian pharmaceutical market.

To identify registry in Brazil, the drug database of the Brazilian National Health Supervision Agency (Anvisa) was consulted, and the following information collected: The date of first registry in Brazil; the manufacturer; and the name of the pharmaceutical specialty classified as the reference drug¹¹. To identify the reference drug, the specific list available on the Anvisa site in the drugs section was used as source of research¹².

The RiskMAPs of the drugs registered in the United States and in Brazil were analyzed to identify the measures employed and the key aspects involved in minimization of risk. Existence in Brazil was verified by email sent to the customer CSD of the manufacturer that produces the reference drug in Brazil. The email requested that, if the information was not available in the CSD, the message should be sent to the manufacturer's pharmacovigilance service.

In the pharmacovigilance section of the Anvisa website¹³, the authors accessed warnings,

notices and letters to health professionals related to drugs that were registered in Brazil and have a RiskMAP with the FDA.

Research was also undertaken in the page of the Anvisa¹⁴ site about package leaflet information to verify the safety information and the monitoring measures on the package leaflets of the Brazilian drugs. For those which did not have package leaflet content available on the site, research was done in the pharmaceutical specialties dictionary (2011/2012¹⁵edition), or on the manufacturer's own site, or by contact (via telephone or email) with the CSD of the manufacturer that sells the drug in Brazil.

The active principles of the drugs were classified according to Level 3 – therapeutic/pharmacological subgroup – of the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization¹⁶.

For organization of the data, an instrument of collection was prepared grounded on a literature review about strategies for minimization of risks. A database was developed in Epidata 3.1 and double-typing entry employed. The descriptive statistical analysis, made in SPSS 18.0, comprised determination of absolute and relative frequency for various categories.

Results

40 drugs were identified that had a RiskMAP registered in the FDA and were registered with Anvisa.

As to the nature of the drug, 29 (72.5%) were obtained by chemical synthesis, and 11 (27.5%) by biotechnological processes.

The drugs with a RiskMAP that were registered in the FDA belonged to 20 therapeutic classes in ATC classification level 3. Among these, those with the greatest absolute frequently (Table 1) were inhalable adrenal stimulants (7), immunosuppressants (6) and drugs that reduce glycaemia, excluding insulins (4).

Table 1 shows that on the Anvisa site, information about the safety of use was available for only 15 drugs (37.5%). On the package leaflets of the Brazilian drugs, information with use safety warnings was found in 32 (91.4%) of the 35 drugs which had a RiskMAP in the FDA and were also registered with Anvisa.

Risk minimization actions were directed to health professionals and patients. It was found that 35 of the 40 RiskMAPs had actions in which the target was health professionals, while for 23

the patient or drug user was the target. There were cases of both being referred to in a single RiskMAP. Among the actions directed to health professionals, specific actions for doctors, nurses and pharmacists were identified.

The actions for promotion of safety of drugs contained in the RiskMAPs registered with the FDA are presented in Table 2. Information on risks associated with use and in relation to possible adverse drug reactions was the most prevalent. It was found that the strategies most referred to for disseminating information about safety of the drugs with a RiskMAP were: A letter to the health professional, educative material, creation of a specific site, and a letter to the health professionals' association.

After consultation of the drug manufacturers, it was found that the manufacturers stated that they were developing a RiskMAP in Brazil for only four drugs (Table 1), these being the same as those of the USA, and they referenced the site of the FDA, in the English language, as a mechanism for access to the RiskMAP. Information on these four drugs registered in Brazil with RiskMAPs is presented in Chart 1. Of the 36 (90.0%) remaining drugs, it was found that two (5.0%) did not present a RiskMAP – Metoclopramide (Plasil®) and Vigabatrin (Sabril®); for nine (22.5%), the manufacturers contacted said it was not possible to make such information available; and for 18 (45.0%) the manufacturers did not respond to the email sent. We report that seven (17.5%) drugs did not present a RiskMAP, since five of these no longer have a registry in Brazil (formoterol fumarate in solution for inhalation, rosiglitazone, rosiglitazone + metformin, testosterone gel and vigabatrin oral solution); and two – dronedarone tablets (Multaq®) and buprenorphine patches (Restiva®) – are registered with Anvisa, but the manufacturers stated that they were not being sold in Brazil during the period in which the research was carried out.

Of the 40 drugs identified with a RiskMAP in the USA, 35 (87.5%) were registered in Brazil in the period during which the research was carried out. Among the drugs identified with registry in Brazil, 32 (91.4%) had the same manufacturer in the two countries.

The mean time of registry with Anvisa was 5.1 years (Standard Deviation = 4.8).

Of the drugs included in the RiskMAPs registered with the FDA, 25 (62.5%) were used both for ambulatory and in the hospital context; 10 (25.0%) were for ambulatory use.

Table 1. Absolute frequency of drugs with RiskMAP and safety warnings on package leaflet and website, by regulatory agency.

Drug Level 3 ACT classification	RiskMAP		Warning on package leaflet		Warning on website	
	FDA	ANVISA	FDA	ANVISA	FDA	ANVISA
	N	N	N	N	N	N
R03A – adrenergics, inhalants	7	0	7	6*	7	7
L04A – immunosuppressants	6	2	6	6	6	1
A10B – blood glucose lowering drugs, excl. insulins	4	0	4	2*	4	3
L01X – other antineoplastic agents	3	1	3	3	3	0
B01A – antithrombotic agents	2	0	2	1	2	0
C02K – other antihypertensives	2	0	2	2	2	0
M03A – muscle relaxants, peripherally acting agents	2	1	2	2	2	2
N03A – antiepileptics	2	0	2	1*	2	0
A03F – propulsives	1	0	1	1	1	0
B02B – vitamin k and other hemostatics	1	0	1	1	1	0
B03X – other antianemic preparations	1	0	1	1	1	0
B05D – peritoneal dialytics	1	0	1	1	1	0
C01B – antiarrhythmics, Class I and III	1	0	1	0*	1	1
G03X – other sex hormones and modulators of the genital system	1	0	1	0	1	0
H05A – parathyroid hormones and analogs	1	0	1	1	1	0
M05B – drugs affecting bone structure and mineralization	1	0	1	1	1	0
N02A – opioids	1	0	1	0	1	0
N05A – antipsychotics	1	0	1	1	1	1
N06A – antidepressants	1	0	1	1	1	0
N07B – drugs used in addictive disorders	1	0	1	1	1	0
Total	40	4	40	35	40	15

* A drug of this therapeutic class was registered in Brazil, but the package leaflet is not available because it was not sold in the period under the research.

Table 2. Actions for promotion of safe use of drugs contained in the RiskMAPs registered with the FDA.

Action	Yes		No		Total	
	N	%	N	%	N	%
Inform risks	39	97.5	1	2.5	40	100
Information on adverse drug reactions	36	90.0	4	10.0	40	100
Orientation on safe use of the drug	20	50.0	20	50.0	40	100
Inform risk of death	9	22.5	31	77.5	40	100
Risk/benefit relationship	5	12.5	35	87.5	40	100
Warning on risk of medication error	4	10.0	36	90.0	40	100
Minimize risks of teratogenicity	4	10.0	36	90.0	40	100
Minimize drug interactions/incompatibilities	3	7.5	37	92.5	40	100
Inform on dosage for use concurrent with other drugs	1	2.5	39	97.5	40	100

Discussion

Development of RiskMAPs by drug manufacturers established in Brazil is still at an incipient

stage, since only four manufacturers say that they have them. This shows a different reality from that of the USA, which has a larger number of RiskMAPs. It is important to highlight that

Chart 1. Information on the four drugs registered in Brazil that have RiskMAPs.

Drug	Same manufacturer in Brazil as in the USA	Main factor in the RiskMAP	RiskMAP strategy	Safety warning on the package leaflet	Safety warning on Anvisa website
Balatacepte (Nulojix®)	Yes	Increased risk of progressive multifocal leukoencephalopathy (PML)	Educational material. Communication plan: letter to the health professional, and creation of a site for the drug.	Yes	No
Ipilimumabe (Yervoy®)	Yes	Risks of serious adverse reactions: fatal immune mediated enterocolitis, fatal immune mediated hepatitis, fatal immune mediated medication-induced skin disorders, fatal neurotoxicity, and endocrinopathies. Presents instructions for dealing with the reactions.	Communications plan: letter to associations of health professionals.	Yes	No
Natalizumabe (Tysabri®)	Yes	Risk of PML, including increase of risk of PLM with longer duration of treatment and prior use of immunosuppressants.	Educational material. Accreditation of prescribers and pharmacies/hospitals. Registry of the user.	Yes	No
Botulinum toxin (Botox®)	Yes	Risk of medication errors related to the lack of permutability with botulinum toxins of other manufacturers.	Educational material. Communications plan: letter to health professionals.	Yes	Yes

22.5% of the Brazilian manufacturers said that it was not possible to make information about RiskMAPs available. This underlines the need for improvement in the means of communication, with the creation of a space on the site of Anvisa, as is the case with the FDA, for publication of RiskMAPs. Another problem that is an obstacle to communication about the health risk of the drug is publication of the RiskMAP in a language other than Portuguese, since language is also an important instrument for understanding of information published.

It is worth highlight this language aspect, since the manufacturers with RiskMAPs in Brazil gave information on the RiskMAP implemented

in the USA, referencing the site of the FDA in the English language.

To achieve the objectives of putting RiskMAPs in place the manufacturers should make them available and Anvisa should make access to them possible for health professionals.

Considering that 80.0% of the manufacturers that have RiskMAPs in the USA have drugs registered in Brazil, one can see that it is feasible to improve the strategies for dissemination of risk information and the measures contained in the RiskMAPs, since there is already familiarity with this strategy of promotion of safety in the post marketing phase. Setting aside of an area on Anvisa's site for publication of RiskMAPs would be

an appropriate measure, since it would contribute to the safe use of drugs, and would increase the effectiveness of actions of pharmacovigilance.

To optimize results in pharmacovigilance the contribution of health professionals and of the patients themselves – who are considered to be the priority targets of RiskMAPs – is essential. The choice of the appropriate means of communication is essential to reach the target public and achieve the expected objectives⁸. The involvement of the whole of the health team is important in achieving the positive results arising from RiskMAPs, and for this reason doctors, nurses, and pharmacists including those responsible for community/hospital pharmacies are the health professionals that are also part of some RiskMAPs registered in the FDA.

In terms of communication, no strategy should be generic, since no strategy in particular can provide the same results when applied to different publics. It is ideal for there to be more than one type of communication for each target group, and also repetition of messages to achieve a result in the long term⁹. This can be shown by looking at the frequency of the strategies for promotion of safe use of drugs in this study. From the results, it is seen that there is more than one means of communication available for reaching the desired publics, and some can be used to notify health professionals and the patients simultaneously.

Supply of educational material is a predominant strategy in RiskMAPs, since providing it can minimize risks relatively easily, that is to say, it is simple to produce and implement as well as being able to cover various target publics⁸.

In Brazil actions for communication of health risk of drugs is still at an incipient phase. There are only a few drug safety warnings available on the site of Anvisa, and indeed for only some 40% of those that have a RiskMAP with the FDA. On the package leaflet there is a larger number of warnings: for 91.4% of the 35 drugs sold in Brazil. However, there are some limitations to communication of a warning through the package leaflet of a drug, making other means of communication necessary. One drug that attracted attention in relation to the risk communication strategy was Thalidomide. Anvisa created a blog making a range of information about this drug available to the public¹⁷. It is clear that Anvisa has carried out intensive work to guarantee safe use of this drug and to establish an appropriate communication with health professionals and patients, but it is essential that the manufactur-

er should also participate in these actions, since the blog does not explicitly refer to actions in relation to the manufacturer. Some children were born after 1965 with birth defects compatible with the phenotype of embryopathy caused by thalidomide – showing that control of use and dispensation of the drug failed in the country¹⁸. Actions by Anvisa to amplify the publication of information about the safety of Thalidomide contribute to optimization of control of its use and dispensation.

New drugs need more active pharmacovigilance, especially the biological drugs, since limited information about the therapeutic action and adverse reactions of these products narrows their safety profile in comparison to those of a chemical nature. Some of the aspects that determine the safety of drugs that contain biological agents are related to the complexity of the production processes and of purification, and to the high potential for formation of antibodies¹⁹. The new technologies constitute a challenge for health surveillance because it is their competency to monitor the adverse effects (and risks) of the technological resources, products and services used by the health system²⁰. The large number of pharmaceutical specialties in the Brazilian market; the problems relating to their safety and quality; and the registry of new biological drugs and nanotechnologies show the dimension of the challenge and the importance of the health regulatory action of Anvisa^{20,21}.

Of the drugs with RiskMAPs registered with the FDA, 62.5% are for hospital and ambulatory use. The health professionals that work at these levels of care should know what the risks associated with these drugs are, with a view to minimizing them within the institutions, through systems of surveillance and risk management. Surveillance actions should be developed to cover both hospital and ambulatory care. Notifications of adverse drug reactions and other adverse drug events included in the RiskMAP should be a priority target for risk management actions¹⁹.

The majority of the drugs with RiskMAPs registered with the FDA were the dosage form for parenteral administration. Since this route of administration has a higher risk of complications, with faster appearance of adverse events, and calls for greater care, actions for safety become important for a safe treatment, principally in the hospital setting where this route is widely used.

It is very important for the pharmacist to know which drugs are under a RiskMAP, and what is the principal information for ensuring

their safe use. With this information, patients using these drugs can be included in individual actions of monitoring the pharmacotherapy in such a way as to reduce the risk of adverse events.

The constitution of a multidisciplinary safety committee is fundamental for creating and coordinating programs and activities aiming for success in management of risks. The aim and purpose of a patient safety committee is the safety of the patient, through planning, development, control and evaluation of processes of care, so as to guarantee the quality of the services in the hospital².

Cooperation between pharmacovigilance and patient safety committees is also feasible in the preparation of measures to minimize risks to the patient. Also, coordinated actions between institutions and the country's regulatory agency result in more information for health professionals, minimizing the problem of drug safety, and may encourage them to make voluntary notifications^{1,2,22}. On this aspect, the inclusion of monitoring of patients that are using drugs which have RiskMAPs within the targets of the safety committee could be an action that might catalyze promotion of their safe use and might contribute to expanding knowledge of the risk/benefit relationship.

The information for promotion of safe use most frequently quoted in the RiskMAPs registered with the FDA was related to risk, adverse effects and specific orientation on safety of use. This shows the importance of pharmacovigilance for expanding knowledge of the safety profile of the drugs, principally because of the large number of RiskMAPs that have the objective of notifying adverse effects.

According to the RiskMAPs registered with the FDA, the level 3 ATC classification that was most frequent was that of inhalable adrenergics (17.5%), and a single drug could be presented in more than one dosage form, justifying the large number of drugs with that nomenclature. Immunosuppressant drugs (15.0%) with RiskMAPs registered with the FDA, in contrast to the inhalable adrenergics, were different within the class, showing that they present a greater potential for causing adverse drug reaction. This potential can be explained by the nature of the drug and because many of them are new drugs. In this present study, four of the six immunosuppressant drugs are of a biological nature and have been registered in Brazil for less than two years. Antineoplastic drugs are another class that has been registered with Anvisa for only a short time;

they are frequent among those with RiskMAPs registered with the FDA – and two of the three drugs in this study have been registered for less than one year. Most antineoplastic drugs, as well as being new, have a narrow therapeutic index, requiring greater monitoring, because there is a higher probability of adverse events.

Many of the drugs that have RiskMAPs are new drugs launched in the last five years, with safety warnings, and which need a greater degree of surveillance to ensure safety of use though this is not a rule. The need to inform risk is not related to the time of registry of a drug, but to ensuring safe use for the patient over all the time during which it is sold.

The panorama of the risk minimization actions in Brazil described in this investigation is limited by the fact that the majority of the drug manufacturers did not provide information about RiskMAPs, or did not respond to the email sent (45.0%), or because they did not make this information available (22.5%). However, it provided an opportunity to put the approaches to RiskMAPs in context from the point of view of the Brazilian drug industry and that of Anvisa. A positive contribution of the study was to show that information about risk, adverse events and safe use presented in the RiskMAPs in the USA is present on the package leaflets of drugs sold in Brazil. This is an important measure, but an insufficient one, because more effective results call for proactive measures, with development of RiskMAPs and adequate actions of communication to patients and health professionals.

Final considerations

The number of drugs sold in Brazil with RiskMAPs, as informed by the drug manufacturers that were researched, is small; they are drugs with a short time of registry in the country, produced by transnational drug manufacturers.

It is recommended that Anvisa should review the strategy of development of RiskMAPs specified in the current legislation, with a view to optimizing action and ensuring a more proactive character, with more effective measures of communication.

The plans for communication about safety of drugs call for mutual actions between the drug manufacturers and the regulatory agency, to achieve effective results from the program of pharmacovigilance. The RiskMAP is an important strategy for management of new risks in the

post-marketing period, in the monitoring of those that are known and, principally, for promotion of safe use of drugs.

Collaborations

SF Botelho participated in the conception, design of the study, analysis and interpretation of data, writing up of the article, critical revision and approval of the final version. AMM Reis participated in the conception, design of the study, critical revision and approval of the final version.

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Article submitted 08/04/2014

Approved 26/01/2015

Final version submitted 28/01/2015

