REVIEW
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Characterization and representation of substandard drugs in the area of pharmacovigilance scope: a narrative review

Caracterização e representatividade dos desvios da qualidade de medicamentos no âmbito da farmacovigilância: uma revisão narrativa

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ABSTRACT

Introdução: Os desvios da qualidade de medicamentos (DQM) apresentam grande relevância no âmbito da farmacovigilância, devendo ser investigados e monitorados, uma vez que podem levar a uma grande variedade de desfechos clínicos. **Objetivo:** Discutir sobre a caracterização dos DQM no âmbito da farmacovigilância por meio de uma revisão narrativa da literatura. **Método:** Foi realizada uma busca abrangente em bases de dados utilizando-se os descritores: "farmacovigilância", "queixas técnicas (QT)", "DQM" e "sistemas de notificação", incluindo estudos relacionados diretamente ao tema proposto, realizados no Brasil e publicados no período de 2005 a 2020. **Resultados:** Os DQM podem estar relacionados a alterações no próprio medicamento, ao conteúdo e integridade da embalagem e à rotulagem. Dos 18 estudos selecionados (14 artigos, dois capítulos de livro e duas dissertações) contendo notificações de DQM na forma de QT de medicamentos, dois avaliaram exclusivamente notificações de QT de medicamentos (100,0%), enquanto o restante apontou que estas representavam de 0,6% a 70,0% do total de notificações realizadas em estabelecimentos de saúde do país. Os principais DQM evidenciados foram alterações no aspecto do produto, ausência/redução na quantidade do medicamento e problemas nas embalagens. **Conclusões:** Considera-se que as notificações envolvendo DQM representem um excelente indicador de qualidade dos medicamentos disponíveis no mercado, vindo a contribuir na qualificação de fornecedores e distribuição de produtos conformes à população.

PALAVRAS-CHAVE: Farmacovigilância; Notificação; Controle de Qualidade; Preparações Farmacêuticas

RESUMO

Introduction: Substandard drugs (SD) present great relevance in the area of pharmacovigilance and should be investigated and monitored as they can lead to several clinical outcomes. **Objective:** To discuss the characteristics of SD in the area of pharmacovigilance through a narrative review. **Method:** A comprehensive search was performed on databases using the descriptors "pharmacovigilance", "technical complaints (TC)", "SD" and "notification systems" including studies directly concerning the subject conducted in Brazil and published between 2005 and 2020. **Results:** SD issues might be associated with drug product alterations, content and integrity of the package and labeling. Among the 18 selected studies (14 articles, two book chapters and two dissertations) regarding SD notifications reported as drug TC, two exclusively evaluated drug TC notifications (100.0%), while the rest showed that this type of notification represented 0.6% to 70.0% of the total of notifications made in national health establishments. The main SD issues found were: alterations on the product aspect; absence/reduction in the amount of drug product; and, package problems. **Conclusions:** Notifications involving SD issues are considered an excellent quality indicator for the drugs available in the market, which contributes to suppliers' qualification and provision of consistent products for the population.

KEYWORDS: Pharmacovigilance; Notification; Quality Control; Pharmaceutical Preparations

INTRODUCTION

Drugs available in the pharmaceutical market are monitored by pharmacovigilance, whose objective is to detect, assess, understand and prevent not only adverse drug reactions (ADRs), but also drug-related problems (DRPs). A DRP is any undesirable result related to a drug-based treatment that actually or potentially interferes with the expected results of such treatment[1].

Therefore, the scope of pharmacovigilance activities comprises: 1. suspected ADR; 2. adverse events due to substandard drugs (SSD); 3. adverse events resulting from off-label drug use; 4. drug interactions; 5. total or partial therapeutic ineffectiveness; 6. Intoxication related to drug use; 7. drug abuse and 8. potential and actual medication errors[1,2].

DRPs are frequent in hospitalized patients and can result in prolonged hospitalization, disability, injury and/or death, in addition to increased consumption of health resources[3,4]. Actions to enable the fast identification of DRPs to prevent, minimize or eliminate risks to the health of patients make pharmacovigilance an important strategy to connect drug regulation and clinical practice[3,5]. These actions occur mainly through therapeutic follow-up activities[5].

Although ADRs are more frequently explored, investigating SSDs is also very relevant in the field of pharmacovigilance[6]. SSDs are defined as any deviation from the quality standards required from a product or process for their approval and marketing authorization. SSDs may or may not cause harm to the patient's health[1].

Therefore, not every SSD leads to negative clinical outcomes. If the deviation is found before the drug is dispensed/administered, there will be no harm to the user and the event will be described as a technical complaint (TC)[1]. A TC is defined as suspected changes or irregularities in a product or company related to technical or legal aspects, such as drug non-compliance problems associated with performance, quality or safety issues[6]. However, when a positive association between the SSD and the harm to the patient can be established, then there is an adverse drug event (ADE)[1]. In any case, suspected substandard drugs should be investigated and monitored, as they can lead to a wide variety of clinical outcomes.

This study aimed to discuss the characterization of SSDs within the scope of pharmacovigilance through a narrative review of the literature. To this end, several bibliographic sources were retrieved both to contextualize the topic and to survey the representativeness of SSDs at the national level in Brazil.

METHOD

Narrative review study to explore the following question: what is the representativeness of SSDs described in scientific studies conducted in Brazil and how to characterize them based on the findings?

A comprehensive search was performed in the Scientific Electronic Library Online (SciELO) and Latin American and Caribbean Literature on Health Sciences (LILACS) databases, using the following descriptors: "Pharmacovigilance", "Technical Complaint", "Substandard Drugs" and "Reporting Systems", in both Portuguese and English. A supplementary search was performed in the references of the studies found, in addition to official documents from health surveillance bodies, textbooks and academic dissertations. Content published from 2005 to 2020 was considered.

In total, 782 articles were retrieved from both databases. After the exclusion criteria were applied (selected period and language), 526 articles were excluded. Critical reading was applied to the title/abstract of the remaining 256 articles, and those that were not of interest to this review were excluded, that is, those that involved the exclusive analysis of other types of DRP, those that were conducted outside Brazil, and those that appeared in more than one of our databases.

Finally, the review was based on 18 articles, three books, three dissertations and ten standards and documents from official bodies, including studies selected from the references of previously identified materials, totaling 36 references. The representativeness of SSDs was obtained through the lowest and the highest value referring to the TC reports described in the selected articles.

The results and discussion were organized according to the following topics: "Representativeness of substandard drugs in the form of technical complaints in the Brazilian context", "Characterization of substandard drugs", "Surveillance of substandard drugs" and "Substandard drugs and pharmaceutical care". These topics were selected to contextualize the review and complement the narrative by placing the discussion on SSD within the scope of pharmaceutical care.

RESULTS AND DISCUSSION

Representativeness of substandard drugs in the form of technical complaints in the Brazilian context

All studies found (14 articles, two book chapters and two dissertations) that discussed data from SSD reports published in the described period (2005-2020) and carried out in Brazil were included in this survey (Chart).

The studies selected through the bibliographic survey have shown that drug-related TC reports account for 0.6% to 70.0% of the total reports made in the described healthcare services[9,10,11,12,13,14, 15,16,17,18,19,20,21,22,23,24]. There were also two studies that exclusively analyzed drug-related TC reports (100.0%)[7,8].

Among the other types of reports analyzed in the studies, ADR reports were the most common (90.6%)[21], followed by

Chart. Summary of the studies selected in the bibliographic survey on the representativeness of substandard drugs in the form of technical complaints in the Brazilian context.

Study	Data collection period	Sentinel hospital	Municipality (state)	Total reports	Drug TC reports	SSD	Other reports	Reporting party's role
Bitencourt et al.[7]	04/2016 - 09/2016	No (primary and secondary care units)	Belo Horizonte (MG)	276 (five excluded for technical reasons, totaling 271)	100.0% (total of 329 SSDs - average of 1.21/record)	Package content (47%); package integrity (26%); changes in medication (22%); labeling (5%)	-	-
Chaves et al.[8]	01/2016 - 06/2017	Yes	Fortaleza (CE)	49	100.0% (total of 92 SSDs - average of 1.88/record)	Foreign body/suspended material (32.6%); crack/bubble/leak (28.6%); absence of label/content (8.2%); amount lower than that reported (8.2%); color change (6.1%); ineffectiveness or decrease in therapeutic effect (6.1%); color change with the presence of a foreign body (4.1%); illegible/inadequate label (4.1%); others (2.0%)	-	Nurses (57.2%); pharmacists (26.5%); pharmacy interns (4.1%); nursing technicians (4.1%); assistant physicians (2.0%); laboratory technicians (2.0%); not informed (4.1%)
Lima et al.[9]	01/2009 - 12/2010	Yes	Botucatu (SP)	199	70.0%	Leak (17.3%); color change (10.8%); difficulty opening the bottle (10.0%); absence of product in the bottle (9.4%); broken pills (6.5%); precipitated solution (6.5%); others	Therapeutic ineffectiveness (21.0%) and ADR (9.0%)	Pharmacists (38.2%); nurses (36.7%); physicians (20.1%); nursing technicians and assistants (4.5%) and secretaries (0.5%)
Caon et al.[10]	04/2010 - 03/2011	Yes	Porto Alegre (RS)	169	66.3% (1.8% excluded for technical reasons, totaling 64.5%)	Packaging problems (54.1%); content aspect (21.1%); absence of full label/missing information (16.5%); smaller amount than informed on the label (5.5%); integrity of the pharmaceutical form (4.6%); absence of drug in the package (0.9%)	RAM (33.7%)	-
Duarte et al.[11]	01/2008 - 12/2012	Yes	João Pessoa (PB)	34	61.8%	General changes (57.1%); color changes (19.0%); ineffectiveness (14.4%); physical and chemical changes (9.5%)	RAM (38.2%)	Pharmacists (73.5%); nurses (11.8%); nursing technicians (8.8%); physicians (5.9%)
Visacri et al.[12]	2010	Yes	- (SP)	68	60.3%	Broken bottles/ampoule (20.9%); absence or reduction in the amount of the product (20.9%); physical and chemical changes (11.7%); absence of identification (11.6%); packaging problems (11.6%); presence of foreign material (9.3%); poor quality information (7.0%) and organoleptic changes (7.0%)	RAM (39.7%)	-
Bezerra et al.[13]	01/2006 - 08/2008	Yes	Goiânia (GO)	100	55.0%	-	TC of hospital and medical supplies (26.0%); adverse events of blood products (11.0%) and drugs (8.0%)	Nurses (35%); nursing technicians (14%); pharmacists (13%); doctors (5%); other areas (7%); no identification (26%)
Sobreira et al.[14]	2015	Yes	Campina Grande (PB)	71	50.7%	Unlabeled ampoule; broken ampoule; ampoule containing foreign body; no dispenser	Adverse events (8.5%) and techno-surveillance TC (40.8%)	-
Mahmud et al.[15]	04/2002 - 07/2003	Currently yes, but it does not mention if it was at the time of the study	Porto Alegre (RS)	254	35.8%	Packaging/label (38.4%); physical and chemical changes (24.1%); organoleptic changes (25.2%); therapeutic ineffectiveness (10.9%); other changes (1.4%)	RAM (64.2%)	Pharmacists, nurses, drug technicians, physicians, residents and nursing technicians/assistants
Basile et al.[16]	01/2009 - 12/2014	Yes	Botucatu (SP)	188 (potentially hazardous drugs)	32.4%	Absence of label (21.3%); difficulty opening the package (11.4%); presence of foreign material (8.2%); color change (8.2%); content reduction (8.2%); inappropriate bottle (6.6%); change in appearance (6.6%); missing/broken ampoule (6.6%); empty cavity in blister pack (6.6%); absence of product in the bottle/ampoule (4.9%); broken tablet (3.3%); leak (3.3%); excess content (1.6%); defective bottle (1.6%); difficulty aspirating the content (1.6%)	Therapeutic ineffectiveness (36.7%); ADR (16.0%); phlebitis (7.4%); leakage (5.1%); dispensing error (1.1%); administration error (0.5%) and medication error (0.5%)	Nurses (41.5%); physicians (28.7%); pharmacists (16.5%) and professionals who did not identify themselves (13.3%)

Continue

Continuation

Study	Data collection period	Sentinel hospital	Municipality (state)	Total reports	Drug TC reports	SSD	Other reports	Reporting party's role
Azulino et al.[17]	03/2009 - 06/2011	Yes	Belém (PA)	50	30.0%	Empty blister packs (26.7%); label problems (26.7%); packaging problems (26.7%); organoleptic changes (13.4%); sealed bottle/ampoule without substance (6.7%)	TC of medical and hospital articles (70.0%)	Nursing staff (80.0%) and pharmacists (20.0%)
Furini[18]	08/2015 - 07/2016	Yes	Ribeirão Preto (SP)	807	27.4%	-	Dispensing, prescription and administration errors (50.6%); ADR (9.8%); therapeutic ineffectiveness (3.1%); problems with prescriptions (1.6%); off-label use (0.3%); among others	Nurses; pharmacists; pharmacy assistants; physicians; among others
Cavalcante et al.[19]	2015	No	- (CE)	66	21.0%	-	ADR (79.0%)	-
Oliveira et al.[20]	06/2012 - 07/2014	No	- (SP)	178	15.2%	Liquid leakage from packaging material (40.7%); color change (18.5%); presence of foreign particles (14.8%); damaged packaging material (14.8%); precipitation (11.1%)	ADR (84.8%)	-
Francelino[21]	1997 - 2005	No (Pharmacovigilance Center - Federal University of Ceará)	Fortaleza (CE)	1,293	9.4%	Color change (47.1%); therapeutic ineffectiveness (22.3%); precipitate formation (10.7%); liquid of difficult aspiration (5.8%); presence of a foreign body (3.3%); description error on the label (2.5%); among others	ADR (90.6%)	Nurses (56.2%); physicians (18.2%); pharmacists (18.2%); nursing assistants (4.1%); family (2.5%) and patients (0.8%)
Ribas et al.[22]	2016 - 2017	No	Southwest Region (BA)	232	8.2% related to: drug (10.5%); medical and hospital article (57.9%); cosmetics (5.3%); medical and hospital equipment (15.8%) and sanitizing product (10.5%)	-	Adverse events (91.8%) related to: pressure injury (38.2%); drugs (24.1%); surgery (7.5%); patient identification (5.7%); phlebitis (5.7%); fall (4.2%); others (14.6%)	Nurses (61.9%); nursing technicians (24.8%); interns (11.9%); pharmacists/physicians (1.5%)
Rodrigues et al.[23]	01/2015 - 12/2016	No	- (PA)	1,256	0.6%	-	Medication errors (73.7%); ADR (25.5%); ineffectiveness (0.2%)	-
Santos et al.[24]	01/2008 - 07/2012	Yes	Porto Alegre (RS)	191	-	Problems in primary packaging (27.7%); problems in the reconstitution of lyophilized powders (19.4%); suspected therapeutic failure (11.0%); presence of a foreign body (9.4%); major adverse drug reactions (6.8%); among others	Medication errors (12.6%) and serious ADRs (8.9%)	Pharmacy professionals (48.7%); nursing (35.1%) and physicians (8.9%)

SSD: substandard drug; TC: technical complaint; ADR: adverse drug reactions; MG: Minas Gerais; CE: Ceará; SP: São Paulo; RS: Rio Grande do Sul; PB: Paraíba; GO: Goiás; PA: Pará; BA: Bahia.
Source: Prepared by the author, 2021.

medication errors (73.7%)[23], TCs of medical-hospital articles (70%)[17] and therapeutic ineffectiveness (36.7%)[16]. More than half of the studies that mentioned therapeutic ineffectiveness considered it as a SSD[11,15,21,24], while the rest did not[9,16,18,23]. Additionally, reports of medication errors and therapeutic ineffectiveness may be caused precisely by an SSD that was not detected before the drug was administered to the patient.

The main SSD problems found by the studies were changes in the appearance of the product[7,8,9,10,11,12,15,16,17,20,21], absence/reduction in the amount of drug[7,8,9,10,12,16,17] and problems in the packaging[7,8,10,12,14,15,17,20].

Most reporting professionals were nurses, nursing technicians and assistants, pharmacists, technicians and academics in pharmacy, and physicians[8,9,11,13,15,16,17,18,21,22,24].

Most of the studies were conducted in sentinel hospitals (66.7%). The South and Southeast regions (50.0%) and North, Northeast and Center-West regions of Brazil (50.0%) were covered. The Sentinel Network, coordinated by Brazil's National Health Surveillance Agency (Anvisa) in articulation with the bodies of the National Health Surveillance System (SNVS), does the surveillance of adverse events and TCs related to products subject to health surveillance and collects data for the assessment of risks related to the use of these products. The information thus produced supports decision-making processes to eliminate/reduce risks and minimize the damage resulting from the use of these products[1,5].

Characterization of substandard drugs

SSDs may be due to changes in the drug itself (color changes, difficulty in reconstituting suspensions, changes in the content of the active substance), or changes in the content and integrity of the package (broken seals, incomplete package content, blister packs with empty cavities) and labeling problems (illegible label, absence of label or missing information)[5].

In general, SSDs can have consequences for the product itself (contamination, loss of stability and risk of counterfeiting or tampering) and for the patients (medication error, adverse reactions, therapeutic ineffectiveness, intoxication and administration of under or overdoses), in addition to hindering pharmaceutical care by generating dispensing errors, loss of product traceability and work accidents[5].

Although many SSDs can be easily detected even before the drug is dispensed/administered to the patient and ADEs are therefore prevented, some are more critical and potentially harmful. These include absence of the active substance, active substance content below specification and insufficient dissolution of solid dosage forms when in a liquid medium. These types of SSDs can lead to therapeutic ineffectiveness, defined as a reduction or absence of expected therapeutic response after administration of the drug according to the prescription or on-label indication[1].

On the other hand, levels above the specification can have toxic effects, especially in the case of drugs that contain substances with a low therapeutic index. In this sense, any deviation associated with failures in the drug manufacturing process is potentially harmful, especially because it may be detected only after ADEs appear.

In addition, TCs related to drug identification can lead to medication errors. Absence of label, illegibility/absence of variable data (batch number, manufacture/expiration date) and absence/ambiguity in information related to drug preparation and route of administration can lead to ADEs if not verified before administration to the patient[5].

In this way, determining the risk associated with an SSD is of the utmost importance. Anvisa's joint board resolution (RDC) n. 55, of March 17, 2005, provides for the classification of health-related risks to which a population is exposed if exposed to a proven or suspected substandard drug. Risks are classified into three categories[7,25]:

- Class I: higher risk; high probability that the use/exposure to the drug could cause a health risk with death, threat to life or permanent harm.
- Class II: medium risk; high probability that the use/exposure to the drug may cause temporary or reversible harm by drug treatment.
- Class III: lower risk; low probability that the use/exposure to the drug may cause adverse health consequences.

The Figure presents the different types of SSDs found in healthcare, distributed according to the classification of health-related risks.

SSDs found in different batches of the same drug or in different drugs from the same manufacturer indicate problems related to the production process and non-compliance with Good Manufacturing Practices[7].

Surveillance of substandard drugs

Spontaneous reporting is the main source of information in pharmacovigilance. Several advantages are inherent in this activity, including identification of a broad range of DRPs; ability to identify ADEs that were not found during pre-marketing trials; and speed, since after a DRP is identified and reported, it is forwarded to health surveillance bodies straight away[1]. It is understood that Brazil's Unified Health System (SUS) is the right environment for this type of activity, since it has trained professionals at all levels of healthcare[5].

However, there are some shortcomings too, like reduced sensitivity of the method and late reports due to inadequate completion of the forms; difficulty in monitoring patients if there is no contact with the reporting party, since some reports are one-offs; and, most of all, the underreporting of DRPs, since healthcare professionals often fail to report them[1].

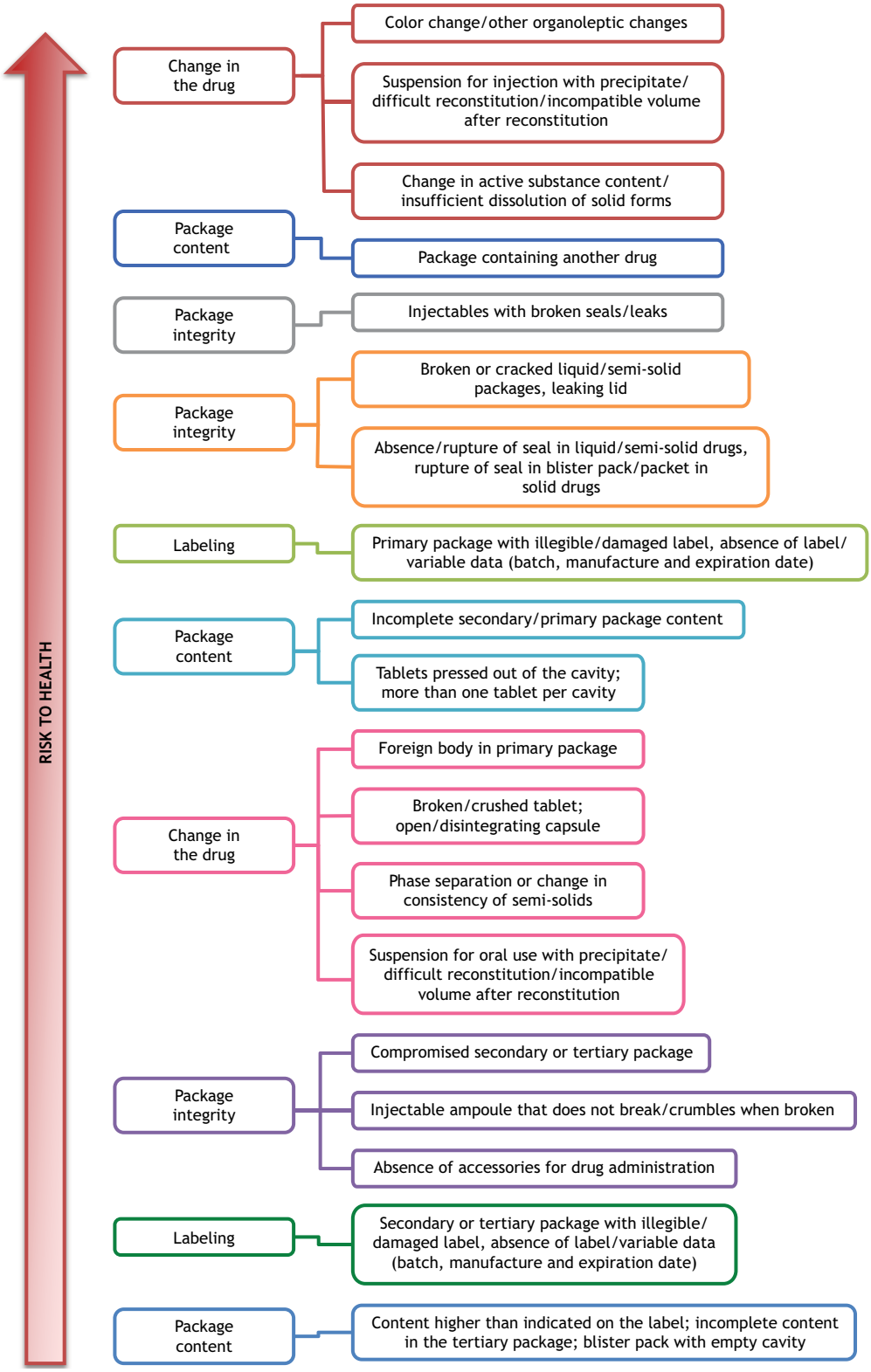
Pharmacovigilance investigations should be carried out to improve patient safety. In Brazil, pharmacovigilance activities are performed by health surveillance bodies under the three levels of public administration (municipal, state and federal), each with their own specific competences[4].

Post-marketing surveillance of TCs gained importance after 2002, when a broader concept of pharmacovigilance was presented by the World Health Organization (WHO), covering several DRPs[5].

The creation of electronic reporting forms for products under health surveillance, in which reporting parties report confirmed

or suspected cases, is considered a milestone in the evolution of the pharmacovigilance system[5].

The Notivisa reporting form has fields related to the following topics: 1. TC (detailed description of the TC, date of problem



Source: Classification of substandard drugs in health-related risk categories according to RDC n. 55, of March 17, 2005[25], as proposed by Bitencourt, 2018[7].

Figure. Types of substandard drugs (categorized by change in drug, package content/integrity and labeling) and health risk inherent in each category.

identification, data on the place of occurrence); 2. product and company (registration number at Anvisa, National Registry of Legal Entities – CNPJ of the manufacturer or importer); 3. product data (trade name of the drug, presentation, pharmaceutical form, active substance, batch number, manufacture and expiration dates, whether the product is imported); 4. manufacturer or importer data (name/corporate name, full address, telephone/customer service) and 5. other important information (whether it was used following the manufacturer's instructions, place of purchase; whether there is an invoice of purchase; whether there was communication to the manufacturer/distributor; whether other actions were taken; whether there are complete samples for collection and, if so, how many; whether there are labels for collection; and a blank field for additional information[26].

SSDs must be reported as TC in Notivisa when the problem observed in the product is not associated with any adverse event until the time of reporting, that is, it has not yet caused any harm to any patient's health[5]. However, SSDs associated with adverse events, like therapeutic ineffectiveness, intoxication and medication errors, should be reclassified as such and reported on VigiMed, given the possibility of a causal relationship between both[5,27,28,29].

The VigiMed reporting form has topics related to reporting information (date of receipt, report type, qualification of the reporting party); patient (patient's initials or gender or date of birth or age at onset of reaction or age group, or whether the report is Parent-Child); case narrative and other information; medical and drug history; reaction (reaction/event as reported); drug (indication of at least one suspected drug or two drugs in interaction, drug name); tests and procedures; and causality assessment[30].

Reports received by the health surveillance body are analyzed according to severity, predictability, causal relationship between the described event vs. drug and health risk associated with ADE/TC. Notably, not all reports will generate immediate, individual health interventions; reports can be grouped together and wait for more information—or even a greater number of reports—to then be assessed[5].

The causality investigation of an event is not a simple process. Several factors can be involved in an SSD, therefore, several hypotheses must be considered in any attempt to elucidate the case.

Determining the health risk associated with an SSD is key in any analysis of a TC. However, this type of analysis is often complex and must take into account the characteristics of the drug and the potential damage that an SSD can cause[31]. A TC with the potential to trigger adverse events is considered severe and may include the presence of a foreign body in the product, suspected contamination and color changes. On the other hand, non-severe TCs are those that do not have such a direct implication, for example: a missing unit in a blister pack cavity or difficulty opening the bottle. This classification is important to inform the decision to take immediate action in hospital and health contexts[5].

Whenever the health surveillance body determines the need to further understand the problem brought about by the report, an investigation process will be opened and may include inspection of establishments and collection of samples for analysis in the fiscal modality, pursuant to laws n. 6.360, of September 23, 1976, and n. 6.437, of August 20, 1977[4,5,32,33]. Laboratory analysis of the potential SSD may confirm the suspicions/hypotheses raised during the investigation, therefore, samples should be collected and sent for analysis as soon as possible[4]. Potential SSDs are technically confirmed through the analysis of the drug in Central Public Health Laboratories (Lacen), via health surveillance.

Analysis by official methods (pharmacopoeic) is recommended to enable the assessment of the product appearance, identification and determination of the content of the active substance, uniformity of unit doses and dissolution, and the tests must be performed according to the pharmaceutical form in question. If the analytical report of fiscal analysis shows unsatisfactory results, investigating possible causes of the quality deviation is indispensable[4].

Several actions can be taken after the reports are investigated, like issuing notices and alerts, changing package inserts/labels, limiting use or trade, batch ban or even cancellation of marketing authorization[5,34].

An alert is defined as a piece of information related to a drug and a severe event that must be quickly and widely disseminated. A notice is defined as information related to a drug and an event that requires wide but not urgent dissemination. The urgency with which they should be published is what differentiates the two modes of communication[3].

Substandard drugs and pharmaceutical care

The lack of pharmacotherapeutic follow-up done by clinical pharmacists in outpatient settings is the reason why many DRPs go unnoticed, which may result in unfavorable outcomes for patients. In this way, pharmaceutical care services are key to reducing the underreporting of DRPs and strengthening the patient-healthcare professional relationship[1].

As discussed earlier, underreporting is the main weakness of the method based on voluntary reporting, so we can assume that current records do not reflect the totality of DRPs[5].

SSDs have a financial and clinical impact on pharmaceutical care. Without an established pharmacovigilance program, the return/replacement of unsafe units may not be possible. Furthermore, in the case of very frequent SSDs for the same product or the adoption of enforcement measures to remove the drug from circulation, even if temporarily, the supply of the health system can be compromised, with a particularly harsh impact on the SUS[5].

Although SSDs pose a potentially high risk to patients' health, they are sometimes underestimated by healthcare professionals in relation to ADRs and other DRPs[5,35]. However, it is emphasized that SSD-related reports are as important as ADR reports in the field of pharmacovigilance[6], since SSDs that are not identified before dispensing/administering the drug can result in serious ADE, like ineffective therapy and intoxication[5].

Therefore, spontaneous reporting should be encouraged through the promotion of educational interventions focused on discussing the importance of this initiative. These interventions have to emphasize what should be reported, who can file a report and the benefits for society (patient safety), healthcare facilities (reduction of unnecessary costs) and the pharmaceutical industry (control and regulation)[36].

CONCLUSIONS

Pharmacovigilance of SSDs directly supports the prevention of risks to patients' health. The studies that make up this review point to a significant representation of SSDs in healthcare facilities in Brazil, which confirms the importance of discussing this topic.

It is essential that healthcare professionals report potential cases of SSDs regardless of the associated health risk, since one of the criteria used by health surveillance in its analysis process is precisely the recurrence of reports.

Finally, SSD-related reports are considered an excellent indicator of the quality of medicines available on the market, which contributes to the qualification of suppliers and the distribution of compliant products to the population.

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Author's Contribution

Eserian JK – Conception, planning (study design), data acquisition, analysis and interpretation and writing of the manuscript. The author approved the final draft of the paper.

Disclosures

The author reports that there is no potential conflict of interest with peers and institutions, nor political or financial conflicts in this study.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.