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The plague of unexpected drug recalls and the pandemic of falsified medications in cardiovascular medicine as a threat to patient safety and global public health: A brief review

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Abstract

Valsartan, losartan, and irbesartan, are widely used in the treatment strategies of cardiovascular medicine diseases, including hypertension and heart failure. Recently, many formulations for the aforementioned diseases contained active pharmaceutical ingredients and had been abruptly recalled from the market due to safety concerns mainly associated with unwanted impurities — nitrosamines, which are highly carcinogenic substances accidentally produced during manufacturing. Along with cardiovascular medications, formulations containing ranitidine were also recalled from the market. This poses a particular threat to public health due to the non-prescription status of these drugs. Regulatory authorities, including the Food and Drug Administration and European Medicines Agency among others, have taken action to minimize patient risk and improve the manufacturing quality as well as re-checking current guidelines and recommendations. While these steps are necessary to avoid further recalls, authorities should remember the growing concerns of patients regarding the safety and efficacy of pharmacotherapy. Apart from the genuine manufacturing mistakes mentioned above, falsified and counterfeit medications should be at the heart of global attention. The lack of a well-accepted definition of falsified/counterfeit medications has impeded political and scientific efforts to mitigate risk of this phenomenon. Falsified Medicines Directive should be considered the most pivotal legislation recently enacted to harmonize international cooperation. In summary, one should remember that only international and direct collaboration between patients, stakeholders, and authorities be considered a remedy for a pandemic of falsified medicines and plague of unexpected recalls due to safety concerns. (Cardiol J)

Key words: drug recalls, counterfeit drugs, pharmacovigilance, public health, angiotensin II type 1 receptor blockers

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Introduction: The complexities of pharmaceutical policy

One of the primary purposes of pharmaceutical policy is to ensure that patients have access to effective and safe medicines, safe not only in terms of acceptable risk associated with the treatment but also regarding the quality of drug formulation [1]. International differences, complex characteristics of the pharmaceutical market with sometimes conflicting objectives among stakeholders, and the rapid development of pharmaceutical and medical sciences have multiplied problems with good governance of the pharmaceutical market, and have constituted a significant challenge for contemporary authorities [2]. Moreover, any reasonable and well-planned pharmaceutical policy should minimize drug shortages — an issue that is increasingly difficult to cope with [3]. Drug re-importation in countries with a well-developed pharmaceutical market can, however, decrease the risk of drug shortages, and should be planned as part of pharmaceutical strategy authorized by governments responsible for public health [4, 5]. On the other hand, re-importation and parallel import, the latter known commonly in the European Union, can introduce drugs of unknown and substandard quality into the market, not to mention falsified and counterfeit medications [6].

Due to the fact that medications should have the highest possible quality, both governments and scientific bodies have created a set of legal and ethical guidelines aimed at ensuring patient safety [7, 8]. From the perspective of clinical importance, clinical drug effectiveness is tested extensively during clinical evaluations, mostly randomized controlled trials [9, 10]. When drugs are introduced into the market, post-authorization safety studies are conducted to detect adverse events, which cannot be noticed in pre-marketing phases, and must be established in epidemiological studies, predominantly in the field of pharmacoepidemiology [11].

While much is known about clinical significance, less attention has been paid to drug formulation, at least from the healthcare providers' perspective [12]. However, recent unintended drug recalls have forced us to reframe drug quality mostly as an international problem connecting all parties involved in drug production and distribution. Nagaich and Sadhna [13] listed several causes behind drug recalls, inter alia, label error in terms of declared dose, non-satisfactory stability, and, in recent cases, unwanted and potentially harmful substances. As a consequence, drug recalls due to safety issues may be one of the many causes responsible, at least temporarily, for drug shortages.

Thus, it is no surprise that effective mechanisms aimed at recalling a drug from the market, whenever necessary to ensure patient safety, must be implemented in harmony with a legal framework, and routine practice. The community pharmacy is importantly placed in this process and implies a core role of pharmacists in the protection of public health and patient safety [14]. Greater access to new media and the internet can facilitate this role significantly, on the other hand, and it may lead to an unwanted dissemination of false information and create unnecessary fear among chronically ill patients [15].

This paper aims to outline the recent drug recall events and their consequences for patient safety and global health and provide a brief commentary on the phenomenon of falsified medicines. Both issues are discussed, whenever possible, in the light of medications used in cardiovascular medicine, the treatment of hypertension, and heart failure. What should be stressed here is that the societal perspective remains at the core of deliberations and to emphasize public health implications from a plague of unexpected drug recalls and the pandemic of falsified medications, particularly with respect to medication adherence when it comes to trust in the medical profession and conventional medicine.

What are SSFFC? Drug recall versus drug withdrawal

Before talking about drug recalls based on safety issues, the acronym 'SSFFC' should be mentioned here (S — substandard, S — spurious, F — falsely labeled, F — falsified, C — counterfeit), as suggested by the World Health Organization (WHO) (Table 1). Although this classification seems to be useful, there is still no universally agreed definition of falsified/counterfeit drugs; thus, scientific deliberation and discussion are significantly impeded, which has also affected the international cooperation necessary to eliminate this phenomenon from the market.

Similarly, the WHO approach is determined to distinguish medicinal products that are intentionally falsified from substandard products mainly introduced into the market as the result of an unintentional mistake [16]. In 2017, the WHO decided to push for greater transparency and simplification of terminology. According to WHO, i) substandard medicinal products are those drugs manufactured 'out of specification'; ii) unregistered/unlicensed products are

Table 1. Substandard and Falsified Medicinal Products according to World Health Organization (2011) — summary [54].

Term	Definition
S — Substandard	Medicines produced not in line with specifications, including intentional and negligent mistakes, not including genuine manufacturing errors
S — Spurious	Products falsely labeled or intended to deceive; the term used mostly in South Asia
F — Falsely labelled	Genuine products with false packaging
F — Falsified	Products introduced into the market with deliberate intention to mimic original formulation and deceive stakeholders; definition widely used in European legal framework
C — Counterfeit	Violation of intellectual property rights, mostly used in the United States

produced and distributed against national regulation, and iii) falsified products 'intentionally' misrepresent their identity, composition or source' [17].

Additionally, drug recall should be recognized as a different concept from drug withdrawal, when drugs are removed from the market due to unwanted drug events. Until new studies are provided, a particular medication which should no longer be used by patients. This procedure is illustrated by the cases of valdecoxib and rofecoxib, nonsteroidal anti-inflammatory drugs previously widely used in rheumatoid arthritis, withdrawn from the market due to increased cardiovascular risk among patients [18].

Falsified medications: A global challenge for the pharmaceutical policy

Although this paper aims not to describe falsified medications in great detail, some issues should be briefly highlighted with examples. As with recalled and withdrawn drugs, falsified medicines pose a challenge for pharmaceutical policy and international cooperation, and all actions aimed to mitigate the risk for patients are highly warranted [19]. One of the leading causes of this phenomenon has been the lack of international legislation; however, recently introduced Falsified Medicines Directive (FMD) and acts enacted by Food and Drug Administration (FDA) has significantly improved the situation. One can hardly underestimate the role of the above-mentioned legal acts in the global fight against falsified and counterfeit medications. Corruption, the complexity of stakeholders involved in drug distribution, high market prices, and many other factors have impacted globalization of the phenomenon. Considering this problem, there is also important financial and humanistic burden. On the one hand, this practice is associated with high income for parties involved in this crime. On the other hand, it may lead to a poorer prognosis, disability and, in some dramatic scenarios, death [20]. Finally, patient safety remains at significant risk whenever even a single falsified drug is made available on the market. Beyond reasonable doubt, it can be assumed that constant improvement in drug quality along with close and transparent cooperation between stakeholders can not only minimize the risk of the occurrence of unwanted falsified drugs in legal distribution but can also lead to better allocation of finite drug supplies [21].

It can be admitted here that there is a little terminological discrepancy between falsified medications, which are deliberately falsified and introduced into the market as an imitation of non-falsified drugs, and those medications which are produced in violation of intellectual property rights. European legislation, particularly in the FMD, falsified medicines are accepted as the best way to describe deliberate misrepresentation. Borup et al. [22] have noticed that creating the legal framework in the pharmaceutical sector is a complex task requiring a multidimensional approach and harmonization of national legislation with European legal acts, which was clearly seen in the FMD. At least in Europe, this act had started a broad discussion on the quality of drugs dispensed in legal distribution. According to the prior-mentioned study, legal purposes for instance; harmonization of definition were more established in the current European pharmaceutical policy than public health issues [22]. Moreover, the rigid approach authorized by the European Commission may not adequately respond to local needs [23, 24].

Falsified medications in cardiovascular medicine

Since cardiovascular diseases are highly prevalent in the population, cardiovascular medications are widely used, and due to the chronic nature of

cardiovascular diseases, in most cases, it is long-term therapy, from the initial diagnosis to death [25, 26]. In 2005, falsified atorvastatin was identified in the legal distribution in the United Kingdom [27]. Clopidogrel, an antiplatelet agent, was also falsified in the United Kingdom. It should be noted that falsified stocks were obtained via parallel distribution, and traceability was highly impeded in this case. It was eventually revealed that formulation had not contained a sufficient amount of the active substance, which might have affected clinical efficacy [28, 29]. It is worth remembering. One cannot forget the heparin adulteration, which occurred in the United States in 2008. As a consequence of this affair, 81 people were killed, and almost 800 patients were severely harmed. They have been living and will live with long-standing health problems for the rest of their lives [30]. Good Manufacturing Practice violations were also identified in the heparin-related case of 2016. However, it did not have direct severe repercussions on patient health [31].

Substandard and falsified medications are a serious problem for developing countries. Antignac et al. [32] investigated the quality of cardiovascular drugs in 10 Sub-Saharan Countries (The Seven Study), and revealed that almost 20% of analyzed formulations had been classified to be of poor quality. The authors did not decide to conduct a forensic investigation and trace whether a particular formulation was falsified or was substandard, which should be considered a significant limitation. According to available research, this paper is a unique study; since there is a lack of research aimed at a particular class of drugs used in a specialized field of medicine, as was stated in the original paper. The fake amlodipine was also distributed in Kenya in 2014. Patients were officially informed about the potential risks related to the use of this falsified medication. Moreover, the differences between the original and fake packages were provided in official communications [33].

The plague of 'unwanted' drug recalls

Valsartan recall has been widely discussed in international media [34–36]. The formulations containing valsartan were recalled due to identified contamination with N-nitroso dimethylamine (NDMA), a potentially cancerogenic substance, resulting from unintended changes in the manufacturing process in China. Since contamination was related to an active pharmaceutical ingredient production, more than one brand had to be removed from the market.

Moreover, due to the chronic nature of both arterial hypertension and congestive heart failure — two of the most common indications for its use — valsartan is often prescribed for long-term therapy, which could potentially cause prolonged exposure to a cancerogenic substance, leading to substantial risk for developing malignancy [37, 38]. So far, studies have highlighted minimal short-term risk. Nevertheless, the real consequences should be a matter for further scientific and clinical discussion, also in terms of preventive screening among those exposed to the contamination over a long period [39, 40].

Cable News Network provided a list of recommendations to minimize the dissemination of false information among patients who used valsartan-containing products. The first piece of advice emphasized that some formulations, still available on the market at that moment, were safe for patients and did not contain hazardous contaminants. The media corporation also suggested that there were safe alternatives for patients, mostly in terms of drug equivalents, e.g., drugs belonging to a different therapeutic group with a similar hypotensive effect and toxicity profile, which can be a reasonable alternative for valsartan. The next part of the article described the association between exposure to contamination and cancer growth. Finally, the last piece of advice explained that using drugs should not be understood as a substitute for a good lifestyle, which is generally true, and applied not only to valsartan recall [41]. European Medicines Agency (EMA) urged national regulatory agencies to take appropriate steps to monitor drugs containing valsartan, specifically those produced in China. Nevertheless, in an official press release, EMA emphasized that all actions taken by authorities were precautionary, and actual risk to patients remained under control [42].

The contamination with NDMA is also a key reason behind the recall of formulations containing ranitidine. The FDA announced that, though unintended contamination was detected, the risk to patients was minimal since the level of NDMA barely exceeded concentration in food eaten on a daily basis by the vast majority of people around the world [43]. FDA, in a set of official public releases, revealed various aspects of valsartan and ranitidine recalls. FDA emphasized that an essential part of the recall was to educate patients about possible alternatives for ranitidine, and that patients should not stop their treatment unless they receive personalized recommendations from healthcare professionals [44]. It is important to note that

press releases were highly reassuring, brought the emotional level down, and emphasized the role of patient-oriented education as a tool for securing safety [45]. In addition, the FDA also revealed unwanted deviations from Good Manufacturing Practice, e.g., lack of adequate written procedures and problems with cleaning equipment used in drug production. Canadian authorities indicated that the problem with drugs containing ranitidine shared many similarities with a previously-described case with valsartan; however, since ranitidine is available over-the-counter, practical implications may have more serious consequences [46].

In light of all cases, the EMA recommended taking a proactive role and to extend the experience gained in valsartan and ranitidine-related cases to all medications. All actions should be aimed at reassuring patients that medicines are safe, effective, and without potentially cancerogenic ingredients, at least from a clinically relevant point of view. A different set of regulations should be given to clarify how to prevent future contamination with the NMDA [47].

The unwanted contamination of medicinal products containing valsartan and ranitidine had multiple repercussions in less developed countries as well. Safety alerts and drug recalls were introduced in Pakistan, where seven products with valsartan had been recalled from the market immediately after an official statement was authorized by American and European agencies had been published [48]. On the other hand, Moldova does not have well-prepared procedures regarding drug recalls, and the current situation there remains unclear [49].

Losartan and irbesartan were also investigated in terms of nitrosamine impurities [50]. As a result of this investigation, formulations containing losartan and losartan with hydrochlorothiazide were also recalled from the market; however, it should be noted that some products were recalled voluntarily by manufacturers just after the first signals from the market [51]. The same procedure was also implemented in the case of products containing irbesartan. In both above-mentioned cases, media attention was less prominent compared with the 'plague' of valsartan recalls [52, 53].

Summary

Falsified and substandard medications are an important threat to patient safety and public health. The occurrence of falsified medications in legal distribution has been making this situation even worse, particularly since over-the-counter medications are among the most frequently falsified categories of medications. The examples of falsified cardiovascular medications have confirmed that this phenomenon is, however, not only limited to non-prescription drugs. The second problem described in the paper herein, refers to drug recalls due to safety concerns. In recent years, many formulations used in cardiovascular medicine have been recalled from the market due to unwanted impurities or potentially carcinogenic substances. Both phenomena may have an impact on a patients' perspective on the safety and effectiveness of pharmacotherapy, potentially including hard outcomes. In this field, further studies are strongly recommended. Similar situations of a mass drug recall, as well as drug counterfeiting, should not take place. Authorities and parties involved in creating pharmaceutical policy should focus on ensuring patient safety, both from a legal and a societal point of view.

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