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RESEARCH ARTICLE

Counterfeit of Medicinal Products and Parallel Trade: What Consequences for the Patient's Health?

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ABSTRACT

Counterfeit medicinals (so-called "fake drugs") and the "parallel trade" are widespread practices all over the world and especially in developing countries, the causes of which are often to be found in the lack of commercial products available due to the lack of interest of pharmaceutical companies in these countries. In this article, based on the data available in the literature, we want to briefly describe what are the causes of these correlated phenomena and also the consequences in terms of patients' health, both relating to the consumption of counterfeit medicines and the periodic shortage of industrial medicines and the possible need for parallel trade.

Keywords: Counterfeiting of medicines, pharmacovigilance, excipients, drug misuse

INTRODUCTION

A counterfeit ("fake") drug is a drug or pharmaceutical product manufactured and sold with the intent to misrepresent its origin, authenticity, or efficacy by impersonating real, licensed drugs. Pharmaceuticals are among the counterfeit products with the greatest potential to harm consumers' health. However, for such a dangerous threat, the topic has received a negligible amount of media and general public attention.[1] The World Health Organization (WHO) defined counterfeit pharmaceutical products as those that are deliberately and fraudulently mislabeled with respect to identity and/or source.[2] Recently, the WHO has introduced the more specific term "substandard and falsified medical products."[3] Substandard medical products - also called "out of specification" products - are authorized medical products that fail to meet necessary quality standards or specifications. Counterfeit medicines have become a highly profitable criminal industry run by transnational criminal organizations.[4] The WHO has determined that counterfeit products could comprise about 50% of the drug market worldwide; many of these products arise from developing countries.[5] According to reports sent to the WHO from 20 different countries, most falsified drugs fell into one of the following three categories: Products containing no active ingredient: About 30%; products containing an incorrect quantity of the active ingredient: About 20%; and products containing wrong contents: About 20%.[6,7] According to an estimate, one in 10 pharmaceutical products are substandard or even falsified in low- and middle-income countries [Figure 1]. Antimalarial medications are the most taking place counterfeit drugs, exhibiting about 20% of the total counterfeit products and drugs reported in the year 2017.[8] The predominance of counterfeit products is highest in developing countries in Africa, Asia, and Latin America,

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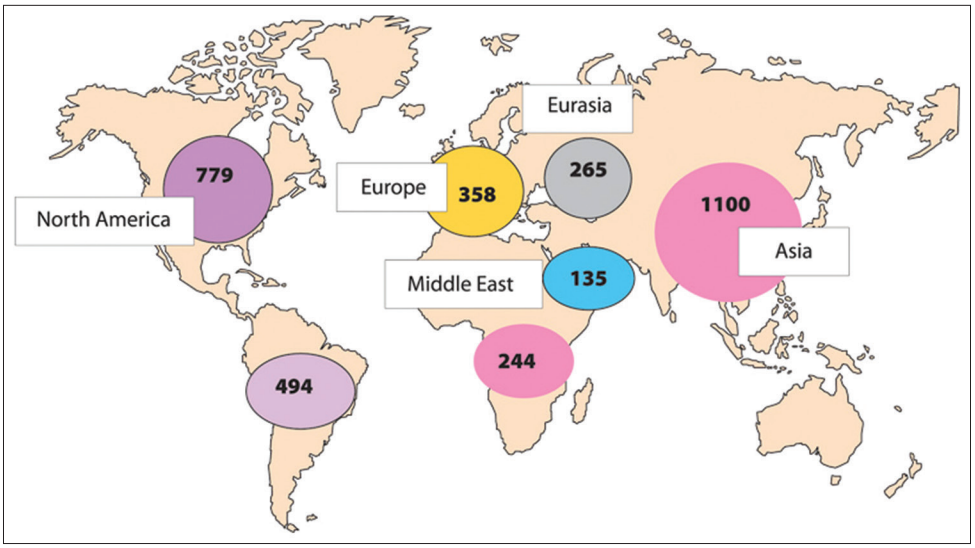

Figure 1: Global incidence of medicine falsification

comprising about 30–60% of all drugs in the market. Worldwide, it is estimated that 10–15% of drugs are counterfeit. Approximately 35–75% of the fake or counterfeit products that arise globally are made in India.[9,10]

The OECD-EUIPO [Figure 2] report finds that most of the counterfeit drugs seized over 2014-16 were fake antibiotics, male impotence pills, painkillers and medication for malaria, diabetes, epilepsy, heart disease, HIV/AIDS, cancers, high blood pressure, and allergies.[11] The vast majority contain incorrect proportions of active ingredients, meaning that they are unlikely to work.[12] Many contain undeclared substances that can pose serious health risks.[13] Forensic tests of suspect samples show that in 90% of cases, counterfeit medicines can harm patients.[14] Strong global demand, high-profit margins, and a low risk of detection make pharmaceuticals, especially vulnerable to counterfeiting.[15] Criminal groups may traffic medicines made with substandard ingredients or steal legitimate pharmaceuticals destined for hospitals to sell on the street at cut prices, often storing them in poor conditions that reduce their effectiveness.[16] The volume of fake or defective pharmaceuticals in circulation has ballooned with the rise of rogue online pharmacies - 96% of websites offering pharmaceuticals are operating illegally - and with the surge in the use of postal services, where inadequate labeling makes detection and interception difficult.[17] More than

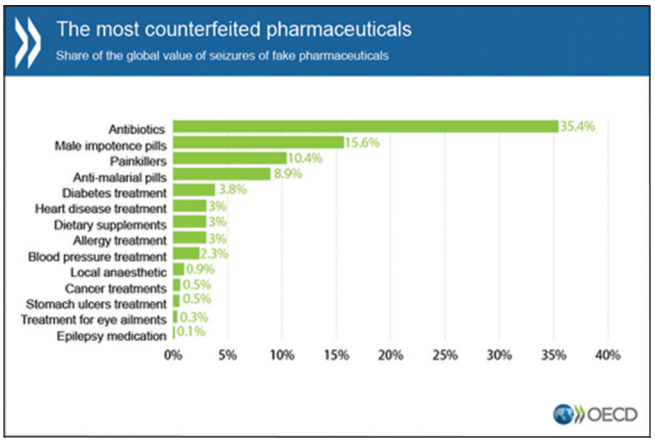

Figure 2: OECD-EUIPO report over 2014-2016 on counterfeit medicinals

half the fake medicines seized in recent years originated in India and nearly a third came from China with the main destinations being Africa, Europe, and the United States. Singapore and Hong Kong are key transit points in the supply chain, with other routes running through the United Arab Emirates, Egypt, Cameroon, and Turkey. Pharmaceutical companies from the US, EU, and Switzerland are the hardest hit by counterfeiting.[18]

In this article, we will try to describe what are the risks associated with counterfeiting medicines, which ones are most involved by ATC categories and what the consequences may be on the consumer and on the trade of medicines in general.[19]

MATERIALS AND METHODS

We searched PubMed, Google Scholar, and ResearchGate for papers and documents relating to the trade and use of counterfeit medicines around the world. We have selected research articles and systematic reviews from 1990 to 2023, with the aim of both evaluating which classes of medicines are most often involved and with what geographical distribution and also to evaluate the possible consequences on the health of patients. We have not focused on the individual pharmacological characteristics.

DISCUSSION

The term "counterfeiting" refers to the idea of "falsifying" the content that an original product intends to transmit, causing a misunderstanding for the consumer regarding the identity of such product.[20] Thus, adulterated, fake, or counterfeit drugs are the ones that deliberately/fraudulently have a false presentation of identity (packaging, labeling, name, composition of excipients, and active ingredients or their quantities), origin (manufacturer, country of manufacture, or marketing authorization holder), or history (records or distribution documents), excluding those with unintended defects (the World Health Organization, 2018; the European Parliament and the Council of the European Union, 2011).[21] Counterfeit products may include:

- Products with the correct ingredients or the wrong ingredients.
- Products with insufficient or no active ingredients.
- Products with fake packaging.
- Medicines with active ingredients different from what is stated on the package.
- Expired medicines relabeled with the purpose to extend the shelf-life.
- Products without the name and address of the manufacturer.
- Expired products.
- Drugs with no expiry date.
- Medicines which do not contain any of the specified active ingredients despite what is written on the label.
- Products which contain the correct strength of the specified active ingredient.
- Products which contain the different quantity of impurities.

Most commonly, adulterations are related to the composition, since counterfeit drugs may not contain an active pharmaceutical ingredient (API), contain a wrong or different dosage of API, or may contain undesired substances, making them illegal and harmful to the population's health. In 2013, a semi-quantitative thin-layer chromatography analysis was performed on 713 samples of two first-line antituberculosis medicines collected from low and middle-income countries in Africa, China, India, and Brazil. Samples showed less than 80% rifampicin or isoniazid, and 36 samples demonstrated less than 10% of both APIs. In 2017, 13 confiscated tablets falsely labeled as "Viagra," circulating in the Brazilian market, were examined by infrared spectroscopy. 10 tablets demonstrated reduced dosages of sildenafil, 8 tablets contained starch, and 6 tablets contained calcium sulfate as undesired substances.[22] The counterfeiting of medicines is a huge and worldwide crisis that has escalated in the past two decades.[23] At present, counterfeit medicines are a global crisis that affects and is mostly caused by developing countries in Asia, Africa, and Latin America. These countries lack strict law enforcement against this practice and have low-income populations with medicinal needs. Lately, the crisis has escalated, impacting developed countries as well, e.g., the US and the EU, mainly through the Internet. Despite this extension, some current laws aim to control and minimize the crisis' magnitude. Falsification of medicines maintains an illegitimate supply chain that is connected to the legitimate one, both of which are extremely complex, making such falsification difficult to control.[24] Furthermore, political and economic causes are related to the crisis' hasty growth, causing serious consequences for individuals and public health, as well as for the economy of different countries.[25] Recently, organizations, technologies, and initiatives have been created to overcome the situation. Nevertheless, the development of more effective measures that

could aggregate all the existing strategies into a large functioning network could help prevent the acquisition of counterfeit medicines and create awareness among the general population.[26] Due to a rapid globalization, 10% of all medicines sold worldwide estimated as counterfeits (Fantasy, Vooys, 2018). The main factors contributing to its spread are related to the high costs of medicines and treatments, failures in the legal supply chain, gaps in legislation, easy access to technologies, poverty, as well as lack of strict law enforcement. Developing countries in Asia, Africa, and Latin America have been heavily affected by the counterfeit drug market, considering that they present many of the previously mentioned factors and have large low-income populations with medicinal needs.[27] In those countries, counterfeit or poor-quality medicines are appraised to be more than 30% of all marketed medicines, with this rate higher than 50% in certain regions (Jackson *et al*., 2010; Yadav, Rawal, 2015). The consequences of using counterfeit medicines are:

- A risk of reduction of therapeutic efficacy, linked to the possible shortage of APIs within the pharmaceutical form with consequent failure.
- A risk of toxic effects linked to an excess of API compared to the legal prescription on the market or to the presence of undeclared contaminants-excipients or present in excess.[28]

In fact, all pharmaceutical products marketed by companies or sold as Galenic products in pharmacies must comply with certain quality requirements, a fundamental prerequisite for efficacy and safety. Figure 3 shows, for example, the physiological path of a solid formulation after oral intake.[29] The excipients are also essential to ensure that the medicinal product has adequate bioavailability and a biopharmaceutical suitable for the type of formulation.[30] One of the most serious aspects of fake drugs is that the excipients are often changed, using cheap and easily preventable adulterants which, however, alter the biopharmaceuticals of the compound. Before being marketed by the pharmaceutical company, a medicinal product must undergo *in vitro* tests such as dissolution, bioequivalence, resistance or

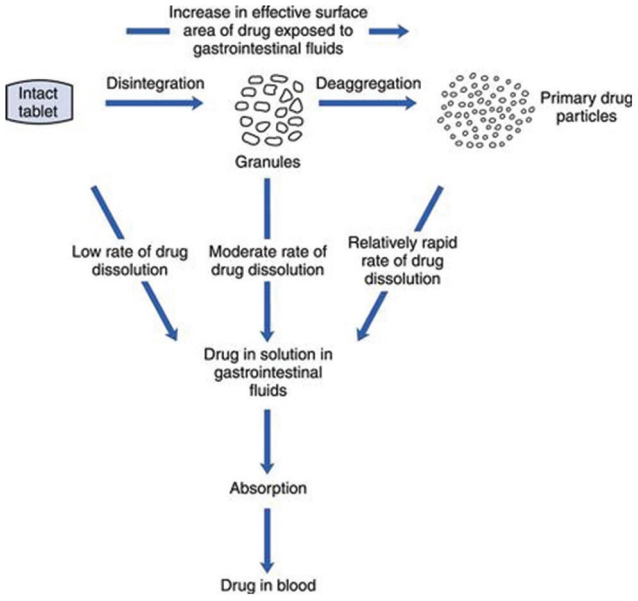

Figure 3: Drug pathway after oral intake

otherwise to disaggregation, etc. which guarantee that the product put on the market is of quality, which is not done in the case of counterfeit medicines.[30]

The aesthetic aspect sometimes already helps in the recognition of counterfeit medicines [Figure 4]. In fact, often, precisely because of changes in the excipients, especially for coated formulations (coated pills, tablets, or capsules with film for gastroprotection or prolonged release, etc.), fake drugs show different colors or wordings compared to the original formulations.[31]

Medicines must be safe, effective, and of acceptable quality and should be used rationally to produce the desired effects with good clinical and therapeutic outcomes. Part of the reason for the poor quality of drugs is due to decomposition of the drug being well below stated amounts. The use of these preparations could lead to therapeutic failure. Fake and poor-quality drugs are rife in developing countries and are costing lives. The illicit trade in counterfeit drugs remains a great threat to the lives of people. All drugs should be labeled in a language that is easily understood, and the label on each individual container should at least contain the pharmacological name, batch number, dosage form, strength, formulation, name of manufacturer, quantity in the container, storage conditions, route of administration, and expiry date. Drugs should be

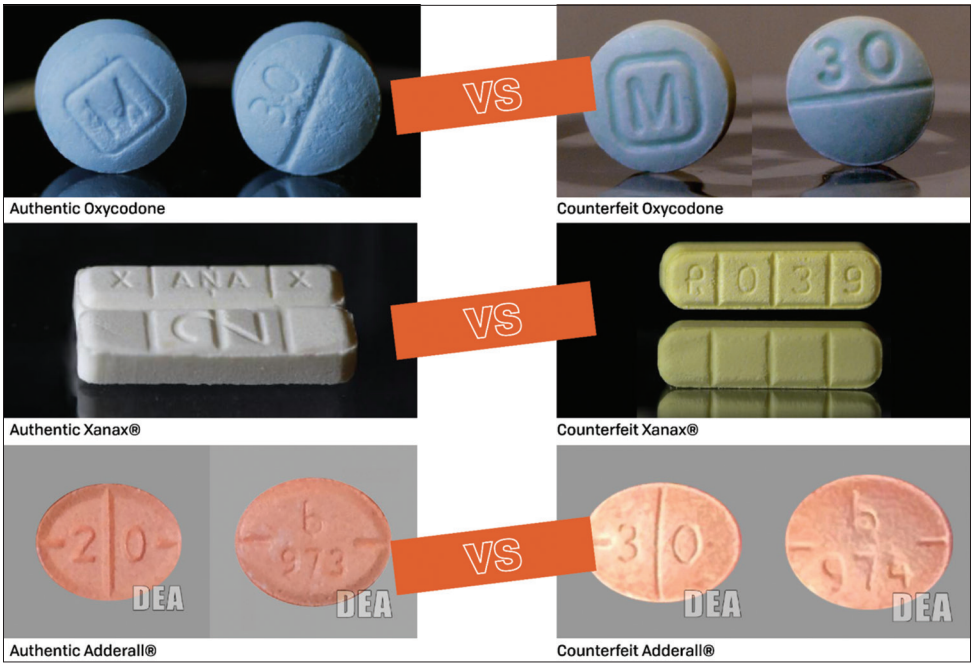

Figure 4: Esthetic differences between original and counterfeit drugs (note not only the possible changes in the color of the tablets but also some writings on them, important for identification also at a legal level)

obtained from a reliable source and comply with quality standards in the country. The only way for one to regain one's health is to take medications as prescribed by the doctor.

CONCLUSION

The sale and trade of counterfeit medicines represent a significant problem both for the patient and for the institutions and are unfortunately widespread all over the world and especially in countries with limited resources, as it can also concern important classes of medicines such as anti-infectives, psychopharmaceuticals, analgesics, and contraceptives.[32] Close monitoring is required both by health professionals and law enforcement agencies to reduce the phenomenon as much as possible, also reporting any seizures and the types of products involved.[33] The risks can be high, from reduced therapeutic efficacy to a dangerous increase in toxic effects linked to unknown excipients or undeclared or altered active ingredients, and therefore, patients should only rely on authorized pharmacies and avoid purchasing products through the internet on unsafe sites or in shops or points of sale of uncertain nature.[34]

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Nothing to declare.

CONSENT FOR PUBLICATION

All authors have consented to the publication.

AVAILABILITY OF DATA AND MATERIAL

Nothing to declare.

COMPETING INTERESTS

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