Journal of Pharmaceutical Sciences xxx (2017) 1-9

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Global Health Commentary

Poor-Quality and Counterfeit Drugs: A Systematic Assessment of Prevalence and Risks Based on Data Published From 2007 to 2016

Andreas Koczwara, Jennifer Dressman*

Institute of Pharmaceutical Technology, Goethe University Frankfurt am Main, Frankfurt am Main, Hessen, Germany

ARTICLE INFO

Article history:
Received 21 April 2017
Revised 15 May 2017
Accepted 16 May 2017

Keywords:
counterfeit drugs
poor-quality medicine
drug analysis
field test
dissolution
TLC
chromatography
bioequivalence
anti-infectives

ABSTRACT

Counterfeit drugs can hurt patients and harm the pharmaceutical industry. In 2006, the International Medical Products Anti-Counterfeiting Taskforce expressed a need to generate more and better data to calculate a worldwide prevalence of counterfeiting. This review analyzes field test data that were published in the time frame January 2007 to December 2016, were accessible via Pubmed, and which addressed the prevalence of counterfeit drugs. Based on the 41 studies identified, it is still not possible to make a reliable statement about the prevalence of counterfeit drugs due to the heterogeneity of the results. To make further progress in this area, both the quantity and quality of documented field tests should be increased. Without a differentiated analysis considering therapeutic class, source, and country of counterfeit drugs, it will remain difficult to identify the root causes of market infiltration and useful points of attack to combat them. Studies with high sample power and randomized sampling, packaging inspection, and detailed chemical analysis will be necessary to correctly identify (especially professional) counterfeit samples. The classification system presented in this review should help to calculate not only the prevalence of counterfeit drugs but also the risks to the patient associated with different types of counterfeited medicines.

Introduction

Poor-quality, and especially counterfeit, medicines can seriously harm patients.[1] For example, an insufficient dosage of an anti-infective drug can lead to bacterial resistance on the one hand and therapeutic failure on the other hand. Patients not receiving effective therapy are contagious for longer, which can lead to spread of the infection and in the worst case to an epidemic, with attendant loss of income, productivity, and national prosperity.[2,3] Additionally, patients and the public can lose confidence in the health care system if medicines are ineffective.[2] Toxic impurities, which are more common in counterfeit than in substandard drugs, can poison the patient and lead to persistent health problems or even death.[3] Consequently, not only individual patients but also society in general should be aware of the risks associated with poor-quality/counterfeit drugs and their distribution.

An increasing number of reports about counterfeit drugs submitted by member states to the World Health Organization (WHO) resulted in resolution WHA 41.16 in 1988. This resolution documented the need for an international program to combat manufacturing and trading of counterfeit drugs.[4] In 1992, the WHO published the first globally recognized definition of counterfeit drugs. According to that definition, a counterfeit drug is "one which is deliberately and fraudulently mislabeled with respect to identity and/or source."[4] Seven years later, the first "guidelines for the development of measures to combat counterfeit drugs" were published by the WHO.[4] Since then, scientific interest in counterfeit drugs has been steadily increasing (Fig. 1).

After the turn of the millennium, several associations were founded to combat counterfeit drugs. One example is the Pharmaceutical[5] Security Institute which was founded in 2002 and is a union of thirty pharmaceutical companies that aims to increase the security of pharmaceuticals and to document and decrease the prevalence of counterfeit drugs. Another association is the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) which is a collaboration of various governmental, intergovernmental, and nongovernmental institutions, agencies, and organizations. IMPACT was founded in 2006 in response to the Declaration of Rome. This declaration, published by the participants of the international WHO conference "Combating Counterfeit Drugs," condemned counterfeit drugs as a "serious criminal offence that puts human lives at risks."[6]

Until 2006, the often quoted prevalence of 10% counterfeit drugs worldwide was commonly accepted, and this figure was quoted in

* *Correspondence to:* Jennifer Dressman (Telephone: 0049-6979829680; Fax: 0049-6979829724).
E-mail address: dressman@em.uni-frankfurt.de (J. Dressman).

http://dx.doi.org/10.1016/j.xphs.2017.05.018
0022-3549/

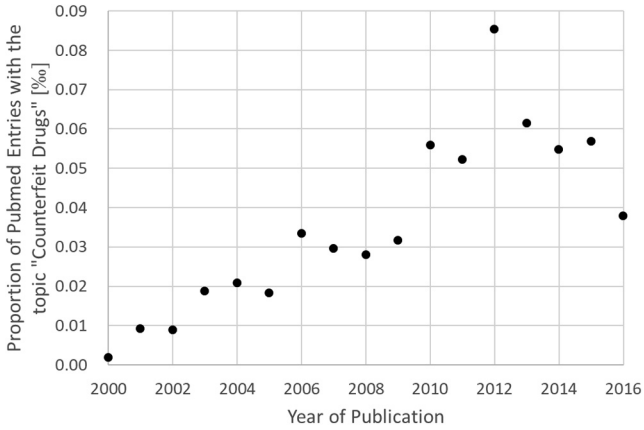

Figure 1. Proportion of total publications accessible via Pubmed.org with the topic "Counterfeit Drugs."

almost all publications. Even today, the number is often used to underline the importance of the topic.[2,7-11] But already in 2006, an IMPACT publication questioned this frequently quoted figure due to the lack of reliable data.[12] The question arises as to whether the data which have been collected in the ensuing last 10 years are meaningful enough to now draw a conclusion about the prevalence of counterfeit drugs worldwide. To investigate this question, it is necessary to rely on published scientific studies investigating the distribution of counterfeit or poor-quality drugs, rather than on lay press reports or subjective statements. Only with a differentiated knowledge of prevalence (e.g., rural vs. urban areas, developed vs. undeveloped countries, etc.), distribution channels, and potential risks, can suitable countermeasures be realized. Four years ago, Almuzaini et al.[13] systematically reviewed the available scientific data regarding counterfeit and substandard drugs and identified that there was a continuing need for "well-designed studies." In their review, scientific publications from 1948 until January 2013 were summarized and evaluated according to 12 quality criteria from the Medicine Quality Assessment Reporting Guidelines checklist. This checklist is a part of a guideline for performing field surveys investigating the quality of medicines that was proposed by Newton et al.[14] in 2009.

One important aspect of improving the ability to draw conclusions from scientific studies is to harmonize the definitions of poor-quality, counterfeit, and substandard drugs. Alternative definitions of counterfeit drugs include "a counterfeit sample contains none of the stated active drug"[15] or "those which are sold under a product name without proper authorization."[16] Counterfeit drugs should be differentiated from substandard drugs, which are "genuine drug products" that do not fulfill the requirements of the pharmacopeia.[17]

But sometimes, the terms "counterfeit" and "substandard" are used synonymously or are not properly differentiated.[13] In studies published in the last 10 years, substandard, counterfeit, and degraded drugs (quality deficiencies because of improper storage) are often summarized as "poor-quality drugs"[14,18] or "SSFFC medicine,"[19,20] which stands for substandard, spurious, falsely labeled, falsified and counterfeit. Although Newton et al. differentiate between degraded and substandard drugs, the WHO classifies degraded drugs as a subgroup of substandard drugs. Such discrepancies point to an ongoing need to establish globally accepted definitions and categories because otherwise the reported prevalence of counterfeit drugs or substandard drugs will continue to vary among studies and publications according to the definition applied. To assist with correct interpretation of the data, Newton et al.[14] recommended in their Medicine Quality Assessment Reporting Guidelines to document which definitions of counterfeit, substandard, and poor-quality drugs were applied in the study. Within this review, we use the definitions published by the WHO and which were specified by Newton et al. For this reason, the prevalence of counterfeit drugs reported here may deviate from the figures given in the original source.

Because counterfeit drugs may potentially contain the right amount of active pharmaceutical ingredient (API) and fulfill all requirements of the pharmacopeia, even if they are not produced by the genuine manufacturer, an in-depth packaging analysis is often necessary to distinguish between counterfeit drugs and genuine drugs.[14,21] Ideally, this is performed by comparing the samples with a guaranteed genuine package, provided by the genuine manufacturer. However, even without the availability of a reliable reference product, checklists are available to enable detailed evaluation of the package and identification of suspicious products. For example, the International Pharmaceutical Federation together with the US Pharmacopeia published a "Tool for Visual Inspection of Medicines."[22] This visual inspection should be performed blinded to the chemical analysis, that is, researchers working on inspection should be separate and independent from those performing the chemical analysis.[14] This approach avoids any prejudice on the part of the chemical analysts or the packaging inspections or vice versa.

Different analytical methods are available to analyze and evaluate drug quality. A discussion of the advantages and disadvantages of the main methods used to identify counterfeit drugs can be found in 2 recent reviews.[11,23] Summarizing briefly, easy, inexpensive methods like thin-layer chromatography (TLC), color reactions, and disintegration tests, provided, for example, by the Minilab® (Global Pharma Health Fund e.V.)[24] are beneficial for laboratories in countries that have limited resources. However, TLC methods are not accurate substitutes for highly sensitive methods.[25-27] High-performance liquid chromatography (HPLC) is the gold standard to verify the identity and content of a drug.[11] Using HPLC, even small deviations in the content or small amounts of toxic impurities can be detected. Furthermore, spectroscopy methods like near-infrared spectroscopy and Raman spectroscopy can be used to differentiate between various formulations containing the same API. These 2 methods are well established, fast and easy to perform, and yield precise results but have the drawback that a database of reference spectra for each product is essential for their implementation.[10,11,28]

This review retrospectively analyzes studies that investigated the quality of drugs published during the period 2007-2016. This time frame was chosen, first because at the end of 2006, IMPACT called for additional literature that could be used to calculate a worldwide prevalence of counterfeit drugs and second because political campaigns and changes can improve or worsen the pharmaceutical supply of countries and affected areas.[29] The main aim was to evaluate whether the data are now sufficient to draw conclusions about prevalence, distribution, and risks of counterfeit drugs worldwide. Further aims are to identify any deficiencies in studies from this time frame and to provide suggestions for improving the quality and comparability of future studies in this area.

Methods

Using the bibliographic software Citavi 5.4.02, the database Pubmed was searched for the terms "counterfeit" and "fake" in combination with "drug(s)" and "medicine(s)" on January 2, 2017. All abstracts offered in English and published between 2007 and 2016 were viewed. Publications identified within that time frame