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Drug Quality in South Africa: A Field Test

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ABSTRACT

To assess drug quality and pharmaceutical care in South Africa, "mystery" (i.e., anonymous) customers collected 316 samples from July to September 2016. Solid dosage forms containing amoxicillin alone or in combination with clavulanic acid as well as analgesics containing paracetamol alone or in combination with other drugs were sampled in a randomized fashion from the formal market (pharmacies) and by convenient sampling from the informal market. Visual inspection, uniformity of dosage units, and dissolution testing were performed to evaluate adherence to pharmacopoeial quality standards and to identify counterfeit, degraded, or substandard drugs. Although no counterfeited products were identified, only 55.4% (173/312) of samples were able to fulfill all pharmacopeial requirements for quality. Most of the 139 samples that failed were unable to pass the visual inspection due to inappropriate labeling and packaging. In addition, several substandard products were identified: 17 (5.4%) samples failed dissolution testing and 15 (4.8%) failed the content uniformity test. To improve drug quality and the quality of pharmaceutical care, better education of pharmaceutical professionals and monitoring of the pharmaceutical supply chain in South Africa are needed. Further field studies are necessary to evaluate risks and quality issues for other drug classes and distribution channels.

Introduction

Access to good quality essential medicines is a key component of assuring not only individual health but also, in the long run, public health and national prosperity.[1] Poor quality drugs, which include substandard drugs, degraded drugs and counterfeit drugs, can result in increased morbidity, mortality,[2] and loss of confidence in the health care system. An insufficient dosage of the active pharmaceutical ingredient (API) may lead to therapeutic failure, and in the case of antibiotics, to possible emergence of resistance or even epidemics since inadequately treated patients are infectious for longer.[3,4] Toxic impurities are an additional source of danger.[5] These could arise as a result of degradation of the API, low quality raw materials, or inadequate manufacturing controls.

During the last decade, the number of reports about poor quality and especially counterfeit drugs, as well as media attention to these issues, has increased. However, field tests meeting rigorous criteria (e.g., those proposed by Newton et al.[6]) are few, despite their utility in identifying risks in the medicine supply chain. A recent review of literature studies published in the last decade revealed that appropriate data are lacking for most countries.[7] Indeed, apart from antimalarials and antibiotics, field tests are lacking for most drug products. The field test reported in the present study helps to close these gaps with a particular focus on South Africa, which has not previously been investigated in detail with respect to the prevalence of poor quality drugs.[7]

Over-the-counter (OTC) products containing paracetamol and prescription (Rx) medicines containing amoxicillin in combination with clavulanic acid were chosen as drugs of interest. These substances were selected for several reasons: first, to identify whether there are quality differences between OTC and Rx-medicines; second, because products containing amoxicillin or paracetamol are frequently prescribed and purchased in South Africa and are thus most likely to be targeted for possible counterfeiting; third, counterfeit or substandard products containing these APIs would pose a major public health risk, possibly affecting hundreds or even thousands of people.

In South Africa, medicines are categorized into 8 schedules according to their safety profiles, necessity for consultation and potential for abuse.[8] Amoxicillin, a beta-lactam antibiotic, is the standard treatment for respiratory and urinary tract infections. Since it is inactivated by penicillinases, this drug is often used in

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combination with clavulanic acid, which is a β-lactamase inhibitor.[9] Amoxiclav is categorized as a schedule 4 medicine, which necessitates a prescription. By contrast, paracetamol and drugs containing a mixture of paracetamol, aspirin, and caffeine are available without prescription. These schedule 0 drugs can be sold not only in pharmacies but also in any open shop, and no prescription or medical consultation is necessary.[10]

Until now, no internationally recognized definitions of poor quality, counterfeit, substandard, and degraded drugs exist.[11] Even the World Health Organization definitions are undergoing a continuous development process.[12-14] Terms such as "substandard," "spurious," "falsely-labelled," "falsified," and "counterfeit" are not always used in the same way.[7] The definitions used for this publication are oriented toward the World Health Organization publications and the MEDQUARG guidelines.[15] Consequently, for the purpose of this report, the term "poor quality drugs" includes all products which do not comply with national regulations or do not fulfill the requirements of the pharmacopeia. "Substandard" drugs are defined as authorized products, produced by the genuine manufacturer, but which fail to meet the requirements of the pharmacopeia because of manufacturing errors.[16] "Degraded drugs" are those which were produced in a proper way but are out of specification because of inappropriate storage.[15] "Counterfeit drugs" describe medicines that are deliberately and or fraudulently mislabeled regarding identity,[17] composition, or source. During the last few years, some interest groups have suggested restricting the term "counterfeit drugs" to those which infringe trademarks, while "falsified drugs" should describe all cases of fraudulently and deliberately mislabeled drugs.[13,18-20] However, in this publication, the terms "counterfeit" and "falsified" are used synonymously.

Methods

Sampling

Sample Size and Location

A total of 316 samples were purchased in 3 provinces of South Africa between July 11 and September 5, 2016. Previously published results of field tests investigating drug quality had indicated possible differences between rural and urban areas.[21] Therefore, Gauteng (with the highest population density) and Northern Cape (with the lowest population density) were chosen as the main provinces of interest. In addition, the greater area of Durban (situated in Kwa-Zulu-Natal) was investigated because South African experts were concerned that Durban, with its harbor, could be a main portal for the introduction of illegal drugs.

The sample size for each cluster was calculated using the Clopper-Pearson equation.[22] The confidence interval (CI) for the prevalence of counterfeit drugs was determined not to be greater than 5% for Gauteng and Northern Cape and not greater than 10% for Durban. Since in the literature only one case of counterfeit drugs in South African pharmacies during the last decade has been reported,[23] we did not expect to obtain counterfeit products from formal sources using our sample size. Applying a statistical power of 0.9, it was calculated that at least 29 samples for Durban and 58 samples for Gauteng and Northern Cape would need to be collected to arrive at a statistically meaningful outcome for counterfeit products.

Collectors and Protocol

"Mystery" (i.e., anonymous) customers, who had lived in South Africa for at least 1 year were given instructions about how to collect the samples. For collection in pharmacies, the customers were provided with a prescription for 30 tablets of Amoxiclav 625 mg. The customers were advised to hand over the prescription and ask additionally for "a cheap brand of paracetamol" (at least 20 tablets). For the informal market, only analgesic medicines with paracetamol were purchased because in a pilot study, no antibiotics were found to be available for purchase in this market.

The pharmacies were chosen randomly as follows: in June 2016, all community pharmacies registered in the 3 provinces were retrieved from the database of registered pharmacies, which is accessible on the homepage of the South African Pharmacy Council.[24] Using a random generator, 58 pharmacies were chosen in Gauteng and 29 in Durban. For each pharmacy, the physical address was entered in Maps (by Microsoft), to identify the location. If the customer could not locate a pharmacy, at least 2 locals were asked for help. If it was still not possible to locate the pharmacy or if the pharmacy had no stock, a new pharmacy was chosen randomly from the database. This procedure was not used for the Northern Cape. For this province, there are only 62 community pharmacies listed in the database; therefore, all of them were included in the data set.

Because of their nature, a database with all vendors of the informal market cannot exist. Therefore, for these shops, which were mainly "spaza" shops (i.e., a small, informal shop in a township) and supermarkets in low-income areas, convenience sampling was performed, meaning that the customers could freely choose vendors.

Each customer was equipped with sampling protocols (see Supplement 1) and zip-lock bags. After the purchase was made, the protocol was discretely filled out, and the samples were marked with stickers containing a unique 5 digit alphanumeric sampling code (e.g., QR3H5), both written out and as a QR-code. Each sample was stored in an individual zip-lock bag also containing the QR-code. From sample collection to analysis, all samples were handled (transported and stored) according to the storage instructions (dry and <25°C). The protocol information recorded by the customer included the location, name and type of vendor, address of the vendor, and any deviations from Good Pharmaceutical Practice (GPP) as well as the details of the product (name, batch number, expiry date, and price). The invoice, if provided, was glued on the protocol.

Visual Inspection

During September 2016, visual inspections were performed by pharmacy students at the Tshwane University of Technology in Pretoria. The package, package insert, and dosage form were compared to the reference product, which was purchased from a reliable wholesaler. In addition, a modified inspection protocol was developed using the "Tool for Visual Inspection of Medicines" provided by the International Pharmaceutical Federation (Supplement 2).[25] The inspection tool was modified to reflect the legal specifics of South Africa regarding labeling of medicine and was filled out for each sample. Before the samples were transported by temperature controlled airmail to the Goethe University in Frankfurt for chemical analysis, each package, together with its visual inspection protocol, was photographed.

Chemical Analysis

The chemical analyses were performed on a blinded basis (with respect to the visual inspection) between October 2016 and September 2017 using high-performance liquid chromatography (HPLC)—ultraviolet. All HPLC methods were validated according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and took the requirements of the European Pharmacopeia into consideration. Table 1 provides an overview of the method and validation data.