Accepted Manuscript

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PII: S0022-3549(18)30345-9

DOI: 10.1016/j.xphs.2018.06.012

Reference: XPHS 1192

To appear in: *Journal of Pharmaceutical Sciences*

Received Date: 1 March 2018

Revised Date: 4 June 2018

Accepted Date: 12 June 2018

Please cite this article as: Lehmann A, Katerere D, Dressman J, Drug Quality In South Africa: A Field Test, *Journal of Pharmaceutical Sciences* (2018), doi: 10.1016/j.xphs.2018.06.012.

Drug Quality in South Africa: A field test

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Keywords: Medicine Quality, Field Test, South Africa, substandard, degraded, counterfeit, falsified, dissolution test, HPLC.

1. *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 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 using validated methods 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. Additionally, 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.

2. 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 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 due to results 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. 2009 [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 missing 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 purchased and prescribed in South Africa, and are thus most likely to be targeted for possible counterfeiting; third, counterfeit or substandard products containing these APIs would pose major public health possibly affecting hundreds or even thousands of people.

In South Africa, medicines are categorized into eight schedules according to their safety profiles, necessity for consultation and potential for abuse [8]. Amoxicillin is a beta-lactam antibiotic, which is the standard treatment for respiratory and urinary tract infections. Since it is inactivated by penicillinases this drug is often used in 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 WHO 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 towards the WHO 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” describes medicines that are deliberately and or fraudulently mislabeled regarding identity, composition or source [17]. 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 [18–20, 13]. However, in this publication, the terms “counterfeit” and “falsified” are used synonymously.

3. Methods

3.1 Sampling

3.1.1 Sample Size and Location

A total of 316 samples were purchased in three provinces of South Africa between the 11th of July and 5th of September 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. Additionally, 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 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 in order to arrive at a statistically meaningful outcome for counterfeit products.

3.1.2 Collectors and Protocol

“Mystery” (i.e. anonymous) customers, who had lived in South Africa for at least one 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, since 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 three 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 two locals were asked for help. If it was still not possible to access 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, so all of them were included 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 five 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 as well as the details of the product (name, batch number, expiry date and price). The invoice, if provided, was glued on the protocol.

3.2 Visual Inspection

During September 2016, visual inspections were performed by pharmacy students at the Tshwane University of Technology (TUT) in Pretoria. The package, package-insert and dosage form were compared to the reference product, which was purchased from a reliable wholesaler. Additionally, a modified inspection protocol was developed using the "Tool for Visual Inspection of Medicines" provided by the International Pharmaceutical Federation (FIP) (supplement 2) [25]. The inspection tool was modified to reflect the legal specifics of South Africa regarding labelling 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.

3.3 Chemical Analysis

Table 1: Details of the HPLC method and key results of the method validation for amoxicillin and clavulanic acid, as well as for paracetamol, aspirin and caffeine.

[TABLE 1]

The chemical analyses were performed on a blinded basis (with respect to the visual inspection) between October 2016 and September 2017 using HPLC-UV. All HPLC methods were validated according to ICH guidelines and took the requirements of the European Pharmacopeia into consideration. Table 2 provides an overview of the method and validation data.

For each sample, a *dissolution test (USP <711>)* and a check of the *Uniformity of Dosage Units (USP <905>)* were performed [26]. As only a limited number of tablets per sample was available, it was necessary to prioritize the analyses. Stage one of *Uniformity of Dosage Units* (10 tablets) was carried out for all samples as the highest priority. If possible, stage S_1 of dissolution testing was also carried out. Where appropriate and possible, stage S_2 of dissolution testing was additionally performed.

For the test of *Uniformity of Dosage Units* ten dosage forms per sample were stirred for 30 min on a magnetic stirrer (500 rpm) in one liter of purified water (room temperature). Afterwards each

standard flask was placed in an ultrasonic bath for 10 min (45 °C for samples containing paracetamol and room temperature for amoxicillin). After filtration (0.45 µm PTFE filter by VWR International), the concentration was measured using the HPLC methods shown in Table 1. The acceptance value was calculated according to the pharmacopeial method as follows:

$$AV = |M - \bar{X}| + ks$$

(AV: acceptance value; M: reference value; X: mean; k acceptance constant; s: relative standard deviation)

Dissolution testing was carried out according to the USP monographs. A mechanical qualification according to FDA [27] and a performance verification test according to USP [28] were carried out in October 2016 on the dissolution tester (ERWEKA DT 720) prior to performing the analyses. Table 2 shows which samples were analyzed and the corresponding settings for the dissolution tester.

Table 2: Parameters used for dissolution testing of the samples according to USP

[TABLE 2]

3.4 Data analysis

SPSS 24 by IBM was used to record and organize all data as well as for the statistical tests. Microsoft Excel 2016 was applied to further processing the data and to create charts.

3.4.1 Assessment of price differentials

The Kruskal-Wallis-Test was used to assess the dependency of the price charged for prescription medicine on the economic status of the area in which the pharmacy is situated. For this purpose, the pharmacies were classified into pharmacies located in low-income, mid-income or high-income areas based on the documented impressions of the mystery customer and with the help of google maps.

On a regular basis, the South African Medicine Price Registry updates its database of medicine prices. This database contains all important prices, fees and taxes for every approved medicine. The maximum price a pharmacy is allowed to charge for every specific amoxicillin containing medicine was located in the database (accessed on the 8th August 2016)[29, 30]. Using the Kruskal-Wallis-Test the

price charged in the specific pharmacy (expressed as a percentage of the maximum allowed price) was related to the income category in the area where the pharmacy was located.

4. Results

4.1 Sampling

A total of 316 samples were collected. Three of the samples had to be excluded from the analyses because they were not sampled strictly according to the sampling plan. The distribution of the sources for the remaining 313 samples according to province (Gauteng, Northern Cape and Kwa-Zulu-Natal (eThekiwini Municipality)) is shown in Figure 1.

137 samples were collected in Gauteng, of which 118 were purchased in pharmacies and 19 were obtained from the informal market. Of the 80 pharmacies in Gauteng province that were randomly chosen (from a total of 1071 pharmacies registered in Gauteng), only 65 were visited. The remaining 15 could not be located; perhaps the information in the database of the South African Pharmacy Council was not completely up to date. In two pharmacies, the prescription was refused, since it was a photocopy of the original, and in a further four pharmacies there was not enough amoxicillin in stock to fill the prescription. In total, 59 amoxicillin and 59 paracetamol samples were acquired from the Gauteng pharmacies. In addition, 19 samples of analgesics containing paracetamol were collected in Gauteng from the informal market.

A similar situation occurred in Northern Cape area, where 62 pharmacies were listed in the database of registered pharmacies in June 2016. However, eight of these 62 pharmacies were actually located in neighboring provinces, like Western Cape or Free State. On the other hand, one pharmacy registered in Free State was identified to actually be in Northern Cape. Another two pharmacies registered in Northern Cape did not exist and one further pharmacy, the existence of which was checked with a phone call, could not be found. One pharmacy had no stock and referred the

customer to the closest pharmacy and another pharmacy refused to dispense the medicine because the prescription was partly photocopied. As a result, it was only possible to collect samples from 50 pharmacies instead of the 58 samples per API planned for Northern Cape. No informal markets were visited in this area, since the mystery customers were not indigenous to the province and sampling would have been impossible without attracting attention.

For Kwa-Zulu-Natal 634 pharmacies were registered at the time of the sampling. 35 pharmacies located in eThekiwini were randomly chosen from the database. One pharmacy did not have enough stock to fill the prescription, two pharmacies did not exist and three pharmacies could not be located even though their existence was checked. Therefore, 29 samples each of amoxicillin and paracetamol were acquired from pharmacies in this area. Eighteen further paracetamol samples were purchased from the informal market.

It should be mentioned that eight pharmacies dispensed a different dosage strength of Amoxiclav than the one prescribed, without offering another option like ordering the medicine overnight or referring the customer to a nearby pharmacy. In three cases Amoxiclav 375 was dispensed instead of 625 mg. Although the pharmacists explained that the customer should take double the number of tablets a day, this change of dosage was decided upon without consultation with the prescribing doctor. Consequently, the patient would have taken double the amount of clavulanic acid, since the same amount (125 mg) of clavulanic acid is included in both dosage strengths. This substitution of dosage strength by the pharmacists does not comply with the professional medical information provided by the companies. In two further cases, the situation was reversed: instead of Amoxiclav 625 mg, Amoxiclav 1000 mg was dispensed to the customer. In the first case, the pharmacist recommended taking two tablets a day, which would have led to a daily dose of 1750 mg amoxicillin and 250 mg clavulanic acid instead of 1500 mg and 375 mg per day as prescribed. In the second case, the pharmacist recommended that the customer take only one tablet a day, which would have led to insufficient dosing, with only 875 mg amoxicillin per day. Additionally, three pharmacies supplied

500 mg amoxicillin without clavulanic acid. In times of antibiotic resistance and multi-resistant bacteria this misconduct represents a risk to both the individual patient and the broader community.

[FIGURE 1]

Figure 1: Number of samples purchased per API and province as well as the location of random selected pharmacies (symbolized by a blue star).

4.2 Visual Inspection

After all samples had been inspected, failures were classified into five categories (

Table 3). The number of substandard samples provided by pharmacies was alarmingly high with almost 32 % not complying with Good Pharmaceutical Practice (GPP) regulations. In 77 of these 88 cases, the pharmacist did not attach a dispensing label or forgot to add important aspects like instructions or the names of the patient and dispenser (see Figure 2).

Table 3: Results of visual inspection according to type of outlet and API. The second part of the table indicates the reason for visual inspection failure.

[TABLE 3]

This incorrect or non-existent labelling could easily lead to dosage failures and/or confusion on the part of the patient. Furthermore, three pharmacies used inappropriate packaging to repack the Amoxiclav tablets. In reality, this number underestimates the real prevalence. After the first three cases in which the pharmacist repacked (properly packed) Amoxiclav tablets in inappropriate packaging in order to merge two 15 tablet packages into one, the customer subsequently requested that the medicine be dispensed in the original container in the rest of the pharmacies. In 15 additional cases the customer documented in their sampling protocol that the pharmacist wanted to

repack the medicine in a simple packaging and would have done so, if they had not been stopped and asked for the original packaging. This spontaneous modification of the sampling plan was done for two reasons. First, because one of the main goals of this field test was to identify potential counterfeit drugs. If the original container is missing, a distinction between substandard, degraded and counterfeit drugs is no longer possible.

[FIGURE 2]

Figure 2: Examples for inappropriate labeling and broken or chipped off tablets.

Second, repackaging of medicine leads to a loss of information about the pharmaceutical producer including details like batch number and expiry date, since the pharmacist does not always transfer this information to the label. Thus, it would have been impossible to trace substandard medicine back to the original manufacture. Such information is essential to inform the responsible company and the regulatory authorities so they can investigate the failures in detail and improve their processes for the future.

4.2.1 Chemical Analysis: Content Uniformity

The use of inappropriate packaging was not only a theoretical issue, but had ramifications for the analysis of content uniformity. Three samples of Amoxiclav were dispensed in simple plastic boxes without any moisture protection. Two of these samples (analyzed 6th June 2017 and 28th June 2017, respectively) failed the content uniformity test because the clavulanic acid was degraded and an insufficient amount was recovered [31]. The degradation was already apparent during sample preparation from the yellow color of the solution. The third sample (analyzed 21st November 2016) passed the test. The combination of inappropriate packaging and longer time of exposure to the ambient environment explains the difference in analytical results between the failed and passed samples. It is hypothesized that due to inadequate protection from humidity, water vapor was able

to penetrate through holes in the coating (which were visible to the naked eye in some samples) and accelerate the degradation of the clavulanic acid.

Of the 313 samples which underwent visual inspection, 312 were analyzed for content uniformity and 304 for dissolution. One sample obtained from a pharmacy in Gauteng was a package of repacked “Stilpane” which should contain paracetamol, codeine and meprobamate. Since no suitable and validated HPLC method was established for two of these APIs, this sample had to be excluded from chemical analysis. Stilpane is categorized as a schedule 5 (S5) medicine in South Africa due to its abuse potential which means a prescription must be presented in the pharmacy[10]. In this case the customer did not present a prescription for Stilpane, but simply asked for paracetamol, and yet was sold an S5 product.

Table 4: Failures of chemical analysis

[TABLE 4]

Of the 133 paracetamol samples provided by pharmacies, only one sample failed during the content uniformity test (sampling code: 5XPLZ). This sample had already failed visual inspection because the tablets were broken or chipped. Therefore, the acceptance value of 17.8 % (mean content of paracetamol 97.7 % with an RSD of 6.9 %) was not unexpected. The failure rate of 8.1 % (11 of 135) in samples from the formal market containing amoxicillin and clavulanic acid was much higher. As mentioned earlier, two samples were degraded most likely because of inappropriate repackaging by the dispensing pharmacist (sampling codes 2NFFR & QFFBJ). In two additional cases degradation also appeared to be responsible for the poor performance (F8FTF & HCUK7). In sample F8TFT one tablet had degraded because the rim of the tablet had penetrated through the blister, enabling moisture to enter (Figure 3). This one tablet increased the RSD of clavulanic acid to 35.1 %, resulting in an acceptance value of 95.2 % (for clavulanic acid), which is clearly over the 15 % limit. In the second case (HCUK7), inappropriate storage in the pharmacy may have been the culprit. This pharmacy was

described as a “very poor standard” pharmacy situated in a township. The pharmacist recommended an incorrect dosage and sold a squashed packaging of dubious origin. Thus, the competence and possibly the authenticity of the pharmacist also have to be called into question. All tablets of this sample were slightly yellowed and only 89.0 % clavulanic acid was recovered, resulting in an acceptance value of 40.9 %.

Figure 3: A yellow color, corresponding to degraded clavulanic acid was already noticeable during sample preparation (F8FTF). Right top: the tablet is also colored yellow. Right bottom: Tiny cut in the blister caused by the sharp rim of the tablet.

[FIGURE 3]

Three other samples failed with acceptance values for clavulanic acid of 16.6 % (TVDX8), 15.9 % (DP67S) and 17.0 % (VME4J), all just above the L1-limit of the pharmacopeia (15 %). However, it is likely that these three samples would have passed stage two of the content uniformity test. Additionally, it should be mentioned that all three samples were comprised of two batches, of which five tablets each were analyzed. The results from the batches differed from each other, which led to a higher standard deviation than would have been the case if all ten tablets had been taken from the same batch. For this reason, these three failures are perhaps attributable to the study and analysis plan rather than to low quality. The remaining four failures (CA2FX, FZK3T, GFJ2T and TP224), characterized by high standard deviations for clavulanic acid, had been produced by the same manufacturer (Actor Pharma (Pty) Ltd) and had the same batch number (CD5015011-A). There appears to be an issue with this particular batch, since all four samples from that batch were classified as substandard drugs; other samples produced by the same company but with a different batch number passed the test.

Only three of 37 analyzed samples from the informal market failed the content uniformity test. All three samples were combination products. In all three cases, only one of the three APIs in the

formulation (aspirin, paracetamol, caffeine) failed, and then only marginally (MA7Q5, GKSLU & X4B9V).

Table 5: Results of dissolution testing according to type of market, API and dosage form, as well as stage of dissolution test.

[TABLE 5]

4.2.2 Chemical Analysis: Dissolution Testing

Dissolution testing was performed on 304 of the 312 samples. Six samples were powders, for which no dissolution testing was necessary. Two samples contained only 10 tablets, all which were used for the content uniformity test. For a further nine samples, fewer than six tablets were available for dissolution testing. These nine samples were nevertheless tested to get an impression of the dissolution behavior. However, they were excluded from the calculation of proportion of failures. The majority of samples passed stage one dissolution testing (255 samples); while 23 samples passed only after stage two testing. 17 samples failed S2 as well as S1 dissolution testing (Table 5).

Only one S2 failure was a paracetamol-containing tablet. The failure was a sample of Panado produced by Adcock Ingram (EBH57). Surprisingly, a few tablets failed to disintegrate during the dissolution test and only partly released the API. In total, we analyzed 57 Panado samples. The average release of API after 30 min of these 57 samples was 100.4 % of labelled API content, whereas the sample that did not pass S2 dissolution testing released on average only 76.3 % with a range from 52 to 94 %. The fact that the only other paracetamol sample that had to go through S2 dissolution

testing was also Panado, with the same batch number as the sample that failed, suggests a batch-specific issue during manufacturing. The failed sample was therefore classified as a substandard drug.

[FIGURE 4]

Figure 4: Box-Whisker-Plots illustrating the mean results of the dissolution tests for Amoxiclav products (amoxicillin dotted and clavulanic acid striped). Please refer to the text for a detailed description of which products failed dissolution.

Three amoxicillin samples were capsules, one of which failed dissolution testing (Table 5). The sample that failed was purchased at a pharmacy in Soweto (9NH47). The mystery customer described the pharmacy and the consultation as "poor". The pharmacist did not keep the prescription and instead of 30 tablets Amoxiclav 625 mg, he handed out 90 capsules of amoxicillin 500 mg. The capsules were not packed in the original blister but in zipper plastic bags. Therefore, it is difficult to determine whether the drug was substandard or an alteration in the capsule shell (e.g. crosslinking) was responsible for the poor results. According to the report of the customer, the most probable explanation would be inappropriate storage.

Of the 134 Amoxiclav tablets analyzed, 15 (12 %) failed. It is not surprising that both Amoxiclav samples (2NFFR & QFFBJ) which failed content uniformity because of inappropriate packaging also failed stage two of dissolution testing. The other 13 samples were produced by Austell (11 samples Austell Co-Amoxiclav 625) and Ranbaxy (2 Ranclav samples of 375 and 625 mg each). While the majority of Austell's samples were under Q of 85 %, Ranbaxy's samples were mostly slightly over the Q-limit (Figure 4). Nevertheless, for both companies the problem appears to be more general, as more than one batch was involved.

Putting all results together, 44.6 % of all samples failed at least one quality test. While the failure rate was higher for products obtained from the informal market, there was no difference between analgesics and antibiotics at the formal market regarding poor quality. No counterfeit drugs were detected (Table 6).

Table 6: Numbers of poor quality drugs according province, type of market and API and prevalence of counterfeit drugs.

[TABLE 6]

4.3 Evaluation of price levels in relation to economic area

It was possible to categorize 133 pharmacies selling Amoxiclav into low-income (n=24), middle-income (n=80) and high-income (n=29) areas. The results of the Kruskal-Wallis Test indicated that pharmacies charge different prices depending on their location ($p < 0.001$). Interestingly, pharmacies situated in low-income areas charged the most with a mean of 101.1 % of the maximum permitted price compared to middle-income areas with 88.3 % ($p < 0.026$) and high-income areas with 76.2 % ($p < 0.001$) of the maximum permitted price. The p-value indicates significant differences between low-income areas and middle-income as well as high-income areas. Seven of the 24 pharmacies located in low-income areas charged up to 50 % more than the maximum price permitted (Figure 5).

Figure 5: Box-Whisker-Plot summarizing the distribution of charged prices in relation to the economical surroundings of the pharmacy.

[FIGURE 5]

5. Discussion

In this field test, no samples were identified as being counterfeits. Although we did not expect to find counterfeit drugs in the formal market based on previous reports, the results for the informal market were a pleasant surprise. Generally, the results are similar to previous field-tests conducted to identify counterfeit drugs. During the last decade, not one study that was conducted with adequate statistical power identified a high prevalence of counterfeit antibiotics in any country [7, 32, 33, 11]. If only studies with a 95 % confidence interval smaller than 20 % are considered [7], the highest prevalence of counterfeit antibiotics in the formal market was reported for Cambodia with 0.6 % [32]. Similar to our

study, the Cambodian study did not find any counterfeit drugs on the informal market. While several studies have been conducted to investigate the situation regarding antibiotics, studies with adequate statistical power are not available for nonsteroidal analgesics obtained from either the formal or for the informal market [7]. Due to the large number of samples collected in our field test, the results generated for counterfeit drugs can be characterized with a narrow confidence interval. By calculating the 95 %-Clopper-Pearson confidence interval, it can be concluded that less than 1.2 % of Amoxiclav and paracetamol containing drugs are counterfeited in South Africa (Table 6). Thus, the often-quoted prevalence of 10 % counterfeit drugs worldwide and 30 % counterfeit drugs in developing countries [34] could not be confirmed in this study for South Africa.

The situation is very different regarding poor quality drugs. With a prevalence of 37.8 % (CI: 32.1-43.8 %) for the formal market and 94.6 % (CI: 81.8-99.3 %) for the informal market, the results are *prima facie* worse than for most other countries [7]. However, it is necessary to distinguish between repackaging problems, insufficient labeling and failures in chemical analysis. If only the chemical analysis failures are considered, the prevalence is clearly much lower. However, since 9.5 % (CI: 6.3-13.6 %) of the samples obtained from the formal and 8.1 % (CI: 1.7-21.9 %) from the informal market were not able to fulfill the pharmacopeial requirements for chemical analysis, it appears that around 10 % of the drug products studied are substandard due to manufacturing and storage problems. With this prevalence, South Africa falls within the range of other emerging markets [7].

The reasons for the observed prevalence of poor quality drugs can be found at several points within the supply chain. First, chemical analysis revealed that some batches produced by a few manufacturers were substandard. Second, it appears that storage of drugs was sometimes inappropriate. This appears to have been a particular problem in pharmacies. Third, pharmacists did not always follow the rules of Good Pharmaceutical Practice during repackaging and labeling of the medicines. Furthermore, a few pharmacists gave dispensing advice that was professionally questionable and inappropriate.

The most explicit example of a substandard medicine produced by a pharmaceutical manufacturer was Austell Co-Amoxiclav 625. This medicine released only slightly more than 80 % of the label claim for amoxicillin after 30 min and therefore the samples often failed not only stage 1 but also stage 2 of dissolution testing (14 of 16 samples collected). As 12 different batches were tested, the quality appears to have been consistently poor. A low dissolution profile for amoxicillin may be problematic for therapy. Due to the rate of absorption of amoxicillin being higher in the proximal duodenum than in the distal intestine [35], not only the rate but also the extent of absorption is dependent on the release profile. The slower the dosage form releases the API, the less will be absorbed, jeopardizing maintenance of the minimum inhibitory concentration of the antibiotic in plasma. Further, any drug not absorbed will reach the colon, where it can disrupt the colonic microbiome, potentially resulting in diarrhea and encouraging the emergence of resistance [36].

It should be noted that the South African Medicine Control Council (MCC) tests identity and content of approved medicines only when there is a problem with a facility inspection, and dissolution testing is not conducted by the Council. Consequently, drugs with poor quality due to an improper release profile, microbiological or other impurities would only be detected if the manufacturer performs additional quality control studies for batch release or if severe quality issues are reported from the field. On the basis of the current data it is recommended that more rigorous quality testing of the product prior to batch release as well as more frequent inspections of manufacturing facilities be instigated to improve the quality of medicines in South Africa.

All companies which produced samples that failed chemical analysis were contacted at least twice by e-mail and by phone. Results of the analysis, explanatory approaches and recommendations about how to proceed were provided in the emails. Although some manufacturers eventually responded after multiple contacts, only one manufacturer provided us with their quality control results for the batch in question. The general lack of responsiveness suggests that standards of practice in pharmacovigilance and quality control departments at South African manufacturers need to be raised.

As well as substandard manufacturing procedures, poor quality drugs can be caused by inappropriate storage, as this too can lead to degradation of the API and/or changes in the dissolution characteristics of the dosage form. Since inappropriate storage can occur at different points in the supply chain i.e. before leaving the manufacturer, during transport and logistics, at the wholesaler or in the pharmacy, it is nearly impossible to reliably identify the responsible company or person in any given case. For one sample which failed content uniformity, the pharmacy was identified as the probable point of weakness in the supply chain. In this case, the mystery customer described the appearance of the pharmacy in the sampling protocol as suspect (for details see Results). In all other cases it was not possible to distinguish where inappropriate storage leading to degradation had taken place.

In total, 139 of 312 (44.6 %) examined samples failed at least one of three performed quality tests. Most of the failures had already been detected during visual inspection (see Table 3) and most of the time the pharmacy / informal source was responsible. Inappropriate packaging or insufficient labeling were the main reasons for the very large number of failures during visual inspections. Some pharmacists repacked (or intended to repack) amoxicillin in plastic containers without proper moisture protection. In two out of three cases, this approach affected the content of clavulanic acid, posing a threat to the efficacy of the antibiotic. If all pharmacists who initially intended to repack Amoxiclav had actually done so, the number of products containing less than the required amount of API would have been even higher. One the basis of the results in this study, it is recommended that the MCC evaluate whether repackaging, which is done to save money, should be prohibited. The indirect financial expenses resulting from bacterial resistance and therapy failures could well be higher than the savings accrued by using cheaper bulk wares. Alternatively, if repacking is to be continued, compulsory use of desiccants in the repackaging containers should be introduced.

The third striking quality defect identified in pharmacies was incorrect or even non-existent labeling. For both OTC and Rx medicine, dispensing labels were often incomplete or non-existent, thus in breach of legal provisions in both the Medicines Act and the Pharmacy Act. While inappropriate

packaging can be blamed for degradation of the clavulanic acid, missing labels may lead to confusion, under-dosing or over-dosing and other problems for the patients. Although some pharmacies explained the appropriate administration and dosing of the medicines, a missing or incomplete label could result in improper use of the medicines as patients tend to keep any unused medicines for possible illnesses in the future. In addition to possible incorrect storage in the home, the patient is unlikely to be aware of the expiry date and may not remember the indication and/or dosage regime at a later date. In these cases, the medicine could easily do more harm than good.

Similar problems occur if pharmacists dispense the wrong API or recommending a different dosage regimen than that prescribed by the doctor. In cases where an antibiotic is involved, bacterial resistance may develop, which could potentially lead to spread of the bacteria or even an epidemic. More generally, if therapeutic failures due to dispensing errors occur repeatedly, this will eventually lead to loss of confidence in the health care system.

An important pharmacoeconomic finding from this study was the differential cost of medicines among areas of different incomes, as exemplified by Amoxiclav. We found that inhabitants of low-income areas paid the most for prescription medicine and in several cases were overcharged. There are various possible explanations for this observation. It is well-known that a high pharmacy density, which is more prevalent in high-incomes areas, creates competition, which in turn lowers prices. By contrast, pharmacies in low-income areas rarely have competitors since the pharmacy density is low and the patients have limited mobility. Therefore, pharmacies can use their local monopoly to charge higher prices. The imbalance may have been exacerbated by the fact that the customers did not attempt to bargain the price, which is a common strategy used by customers in these areas. Another driver of prices in the poor areas is the cost of overheads such as insurance and salaries because of the higher risk of crime. Nevertheless, overcharging is in breach of the Single Exit Price regulations [29].

Since a significant number of pharmacists in this study failed to follow the rules and requirements during packaging and labeling, these topics should be given more emphasis during pharmacy

education. Moreover, continuing education on this topic should be organized for practicing pharmacists. To improve the quality of pharmaceutical consultation, avoid incorrect dosage advice and ensure appropriate dispensing, the South African Pharmacy Council and MCC should consider including GPP compliance in their inspection protocols. Introduction of inspectors, posing as customers, would also help to identify and monitor violations of ethical and legal standards including proper pricing. In most if not all developed countries, such inspections are organized by the pharmacy professional association on a regular basis. For example, if a pharmacist dispenses a schedule 5 medicine to a patient without a prescription, disciplinary measures would follow.

Another important policy finding is that a considerable number of registered pharmacy database entries were incorrect or outdated. Sometimes, locals stated that the pharmacies of interest have already been closed for several years. Regular inspections of pharmacies would help to ensure that the database is maintained accurately.

Analgesics purchased from informal sources had the highest rate of failures during visual inspection. One explanation therefore is that almost all samples were taken from a bulk supply pack of the product. Each bulk supply pack contains several smaller two-tablet packages, which are more or less intended to be sold without a patient information leaflet or a package insert. The package insert is printed on the back of the bulk package, which stays in the shop. In the case of Panado for example, certain information, including dosage strength, a short overview about contra-indications, dosage recommendations, lot number and expiry date, is also printed directly on the primary package. But important information, such as the hepatotoxicity of paracetamol, is only described in the package insert. Since spaza shops sell the drugs without any medical advice in any open shop, it is questionable whether the information that reaches the patient via the primary package is sufficient to warn him/her about the possible side-effects. Paracetamol, which is responsible for thousands of hospitalizations and hundreds of deaths per year in other countries e.g. the USA [37], is an example for which such information is vital to an informed decision about how and when to take the drug. It is

the task of policymakers to reevaluate packaging and distribution channels to ensure a proper supply of medicine.

6. Conclusion

The results of this field study show that substandard drugs, degraded drugs and poor adherence to dispensing regulations in pharmacies, rather than counterfeit drugs, place the health and wellbeing of patients in South Africa at risk. Although the number of samples and APIs in the study was too low to verify a complete absence of counterfeit drugs in South Africa, it is reasonable to conclude that the role of counterfeit drugs is far lower than that estimated by various organizations for developing countries. Most of the quality issues that were identified in the study can be solved by improving the education of pharmaceutical actors and by introducing regular GPP inspection of pharmacies. Public awareness about sub-standard products and appropriate storage of medicines is also an important strategy. Specific recommendations are summarized in the following 5-point-agenda:

1. **Regular independent quality tests for approved medicines according to pharmacopeial methods. These should be introduced and enforced by the MCC.**
2. **Increasing financial and human resources at the MCC for monitoring of the production and supply chain of medicines.**
3. **Training courses for pharmacy students and all pharmacy personnel to improve the quality of pharmaceutical care and reinforce GPP.**
4. **Introduction of professional, anonymous inspections by SAPC to check the quality of pharmacies and their staff.**
5. **Independent studies to monitor the impact of structural, quality and policy changes over time.**

Even though this study was the largest scientific investigation of drug quality in South Africa to date, more data are necessary to complete the picture. It is possible that if high price medicines e.g.

anticancer drugs had been sampled or other supply chains like internet pharmacies were to be investigated, the results might be different. In this study, only community pharmacies and the informal market for OTC-medicine were evaluated. Hospital pharmacies and the small but growing internet market also need to be evaluated in order to calculate the overall risk of substandard and counterfeit medicines in South Africa.

Acknowledgments

Sampling: Rethabile Molapisane, Florence Msimango, Yvette Kodravale, Nano Shadung, Enock Kekana, Tshepo Senyeke; Visual Inspection: Bachelor of Pharmacy IV students at TUT and Rethabile Molapisane; Chemical Analysis: Marina Fischer, Elisabeth Herbert, Yaser Mansuroglu; Advice and further consultation: Griffith Molewa, Russel Coote, Dr Ncoza Dlova, Prof Gill Enslin, Dr Rosemary Kabahuma.

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Figures

Figure 1: Number of samples purchased per API and province as well as the location of random selected pharmacies (symbolized by a blue star).

Figure 2: Examples for inappropriate labeling and broken or chipped off tablets.

Figure 3: A yellow color, corresponding to degraded clavulanic acid was already noticeable during sample preparation (F8FTF). Right top: the tablet is also colored yellow. Right bottom: Tiny cut in the blister caused by the sharp rim of the tablet.

Figure 4: Box-Whisker-Plots illustrating the mean results of the dissolution tests for Amoxiclav products (amoxicillin dotted and clavulanic acid striped). Please refer to the text for a detailed description of which products failed dissolution.

Figure 5: Box-Whisker-Plot summarizing the distribution of charged prices in relation to the economical surroundings of the pharmacy.

Table 1: Details of the HPLC method and key results of the method validation for amoxicillin and clavulanic acid, as well as for paracetamol, aspirin and caffeine.

	Amoxicillin and Clavulanic Acid		Paracetamol, Aspirin and Caffeine		
Method					
Column	LiChrospher 100 RP-18 (5µm) LiChroCART 125-4 by Merck KGaA				
Mobile Phase	4 % Acetonitrile 96 % H_2O 25 mmol KH_2PO_4 – pH: 2.5 (adjusted with H_3PO_4)		A: 7.5 % acetonitrile 92.5 % H_2O pH: 2.5 (adjusted with H_3PO_4) B: 22.0 % acetonitrile 78.0 % H_2O pH: 2.5 (adjusted with H_3PO_4)		
Flow Rate	1 mL/min		2 mL/min (Minute 0: 100% A – Minute 9.5: 100% B)		
wavelength	220 nm		207 nm		
Sample preparation	Filtration through a 0.45 µm filter		Filtration through a 0.45 µm filter and dilution 1:5 with mobile phase		
Validation					
	Clavulanic Acid	**Amoxicillin**	**Paracetamol**	**Aspirin**	**Caffeine**
Reference Standard	Lithium Clavulanate CRS – Eur. Pharmacopeia L0720000 Batch: 6.0	Amoxicillin Trihydrate – Sigma Aldrich PHR1127-1G Batch: LRAA8983	Acetaminophen – Sigma Aldrich PHR1005-1G Batch: LRAA7900	Aspirin – Sigma Aldrich PHR1003-1G Batch: LRAA7459	Caffeine – Sigma Aldrich PHR1009-1G Batch: LRAA7308
Retention times [min]	3.2	8.4	1.9	7.5	3.9
Peak Symmetry	1.1	1.1	1.18	1.07	1.45
Resolution	Clavulanic Acid compared with Amoxicillin: 14 Amoxicillin compared with Cefadroxil: 6.7		Paracetamol compared with 4-Aminophenol: 4.8 Aspirin with Salicylic Acid: 3.6		
Calibration curve	Y=65259x+200 [µg/mL]	Y=56581x+13419 [µg/mL]	Y=101327x+110083 [µg/mL]	Y=77418x+86307 [µg/mL]	Y=152691x+2881 [µg/mL]
Correlation coefficient	1.000	0.9999	1.000	1.000	1.000
LOQ	< 0.75 µg/mL	< 3.0 µg/mL	< 0.2 µg/mL		
Recovery	101.4 %	100.0%	98.7 %	98.8 %	98.5 %
Repeatability	RSD: 0.3 %	RSD: 0.4 %	RSD: 0.1 %	RSD: 0.1 %	RSD: 0.1 %
Reproducibility	RSD: 1.4 %	RSD: 1.3 %	RSD: 1.3 %	RSD: 1.8 %	RSD: 0.5 %

Table 2: Parameters used for dissolution testing of the samples according to USP

	Apparatus	**Media**	**Time**	**Acceptance Criteria**
500 mg Amoxicillin Capsules	Apparatus 2 - 75 rpm	900 mL water	60 min	Amoxicillin Q=80 %
Amoxicillin and Clavulanic Acid Tablets	Apparatus 2 - 75 rpm	900 mL water	30 min	Amoxicillin Q=85 % Clavulanic Acid Q=80 %
Paracetamol Tablets	Apparatus 2 - 50 rpm	900 mL Phosphate Buffer	30 min	Q=80 %
Paracetamol, Aspirin, Caffeine Tablets	Apparatus 2 – 100 rpm	900 mL water	60 min	For all Q=75 %

Table 3: Results of visual inspection according to type of outlet and API. The second part of the table indicates the reason for visual inspection failure.

		n	Correct	Incorrect	Neither PIL nor PI available	Dispensing label missing or clearly incomplete	Tablets broken or chipped off	Inappropriate packaging	False amount of tablets labeled
Formal	Paracetamol	138	86 (62.3 %)	52 (37.7 %)	1	44	3	0	4
	Amoxicillin	138	102 (73.9 %)	36 (26.1 %)	0	33	0	3	0
Informal	Paracetamol	37	2 (5.4 %)	35 (94.6 %)	33	2	0	0	0

Table 4: Failures of chemical analysis

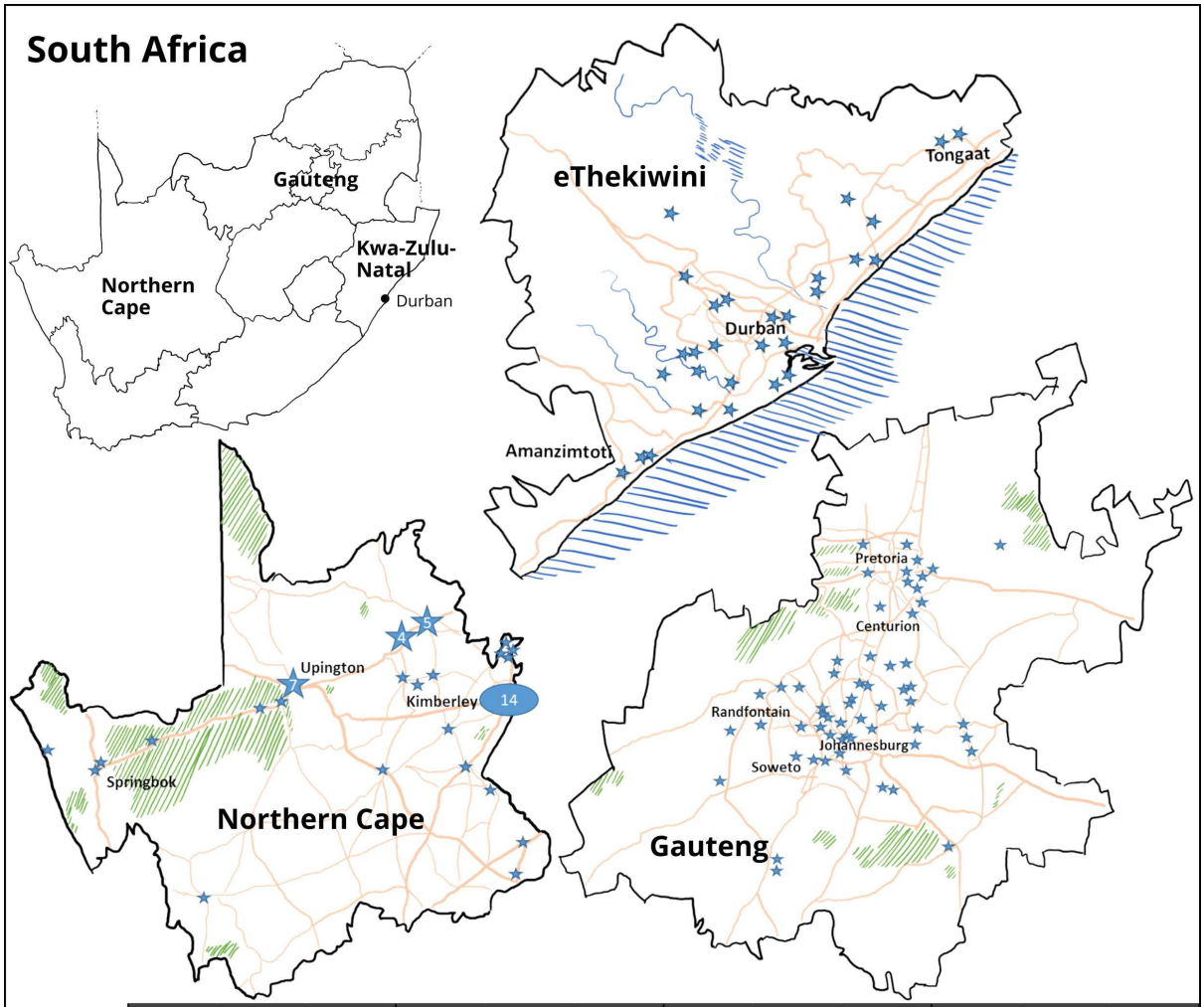
Market	API(s) contained in product	Total Failures	Content Uniformity Failures	Dissolution Failures
Formal	Only Paracetamol	**2 / 133**	1 / 133	1 / 133
	Combination with Paracetamol	**0 / 4**	0 / 4	0 / 4
	Only Amoxicillin	**1 / 3**	0 / 3	1 / 3
	Amoxicillin and Clavulanic Acid	**23 / 135**	11 / 135	15 / 125
Informal	Only Paracetamol	**0 / 24**	0 / 24	0 / 23
	Combination with Paracetamol	**3 / 13**	3 / 13	0 / 7

Table 5: Results of dissolution testing according to type of market, API and dosage form, as well as stage of dissolution test.

Market	Product	Analyzed	Less than 6 dosage forms	Passed S1	Passed S2	Failed
Formal	**Amoxicillin Capsules**	**3**		1	1	**1**
	Amoxiclav Tablets	**134**	9	89	21	**15**
	Paracetamol Tablets	**133**		131	1	**1**
	Combination with Paracetamol	**4**		4		
Informal	**Paracetamol Tablets**	**23**		23		
	Combination with Paracetamol	**7**		7		

Table 6: Numbers of poor quality drugs according province, type of market and API and prevalence of counterfeit drugs.

		Gauteng		Northern Cape		Kwa-Zulu-Natal		Total			
		Passed	**Failed**	**Passed**	**Failed**	**Passed**	**Failed**	**Passed**	**Failed**	**Poor-Quality-Drugs [%]**	**Counterfeits [%] (95%-Confidence Interval)**
Formal	**Analgesics**	43	15	29	21	13	16	85	52	38,0%	0.0 (0.0-2.7)
	Antibiotics	33	26	31	19	22	7	86	52	37,7%	0.0 (0.0-2.6)
Informal	**Analgesics**	1	18	0	0	1	17	2	35	94,6%	0.0 (0.0-9.5)



	Gauteng			Northern Cape			Kwa-Zulu-Natal (eThekiwini)			Total		
	Formal	Informal	Total	Formal	Informal	Total	Formal	Informal	Total	Formal	Informal	Total
Paracetamol	59	19	**78**	50	0	**50**	29	18	**47**	138	37	**175**
Amoxicillin	59	0	**59**	50	0	**50**	29	0	**29**	138	0	**138**
Total	**118**	**19**	**137**	**100**	**0**	**100**	**58**	**18**	**76**	**276**	**37**	**313**

Dispensing label missing or incomplete

Tablets broken or chipped off