

## Are Counterfeit or Substandard Anti-Infective Products the Cause of Treatment Failure in Papua New Guinea?

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**ABSTRACT:** Counterfeit and substandard products present a big challenge to any national plan or policy devised to improve public health. Poor quality drug products are especially a problem in lower income countries where product information and drug regulation enforcement are scant or absent. The primary aim of the present study was to evaluate the quality of amodiaquine and amoxicillin formulations sold in Papua New Guinea (PNG) and to detect the presence of counterfeit or substandard drugs in circulation, if any. Fourteen samples, collected from five registered pharmacies in Port Moresby, PNG, were subjected to visual inspection, quality control tests, and verification of product authenticity. The quality control tests included weight variation, content uniformity, thin layer chromatography, and dissolution. None of the products complied with all of the evaluation criteria. Two products, one of which was purportedly distributed by a company which proved to be nonexistent, contained no detectable amodiaquine. The present study confirms that counterfeit and substandard amodiaquine and amoxicillin products are finding their way into the distribution chain in Port Moresby, PNG. This quality problem with anti-infective products is of great concern, as it not only exposes patients to poor quality products but also fosters the development of resistant bacterial strains. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 100:5859–5068, 2011  
**Keywords:** anti-infectives; content uniformity; drug resistance; dissolution; HPLC (high-performance/pressure liquid chromatography)

### INTRODUCTION

The poor quality of drug products in many less developed countries has been linked to chemical instability (especially a problem in tropical climates), poor quality control during medicine manufacture, and counterfeiting of medicines.<sup>1</sup>

Substandard products are those that are manufactured or repacked by legitimate manufacturers but do not meet the pharmacopoeial specifications.<sup>2</sup> These include both products for which adequate control of raw materials and the manufacturing process are not in place, those which are inadequately packaged to withstand the conditions of storage over the shelf life, and those which may have been exposed to incorrect

storage conditions, resulting in unforeseen stability problems.

Counterfeit drugs are a global problem which not only “eats into” the profits of legitimate manufacturers but also has a highly negative impact on public health. Such products subject patients to a high risk of inadequate treatment and/or exposure to adverse effects. Recognizing the scale of the counterfeiting problem and the impact it has on public health, the World Health Organization (WHO) has published guidelines for the development of measures to combat counterfeit drugs. These guidelines also discuss the possible factors that facilitate counterfeiting, which include absence of or a weak national drug regulatory authority, lack of appropriate legislation, lack of enforcement of existing legislation, demand exceeding supply, and high prices, to list a few.<sup>3</sup>

Papua New Guinea (PNG), one of the largest nations in the Pacific, is a low to middle-income country in which more than 87% of the population lives

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in rural areas. The leading health problems of PNG continue to be communicable diseases, with malaria, tuberculosis, diarrheal diseases, and acute respiratory diseases being the major causes of morbidity and death.<sup>4,5</sup> In 2009, the WHO updated the “health data bank” figures, which revealed pneumonia and malaria to be the top two diseases with respect to mortality and morbidity in PNG.<sup>6</sup>

Reports from the PNG Health Department reveal that the national prevalence of malaria has not declined in the past three decades. Failure of treatment of chloroquine and amodiaquine therapy, the recommended first line drugs, has been reported despite good compliance on the part of the patients.<sup>7</sup> Malarial drug resistance was suggested to be one of the possible causes of this treatment failure.<sup>7,8</sup> Consequently, continued use of chloroquine and amodiaquine as first line drugs in standard treatment of malaria in PNG was questioned and other effective antimalarials were recommended. The development of drug resistance despite compliance raises a further question concerning the probable cause of treatment failure, that is, whether counterfeit and/or substandard medicines are finding their way into the distribution chain. This question is particularly legitimate in PNG, a country which (as of this writing) imports all its medicines but has a weak national drug regulatory authority, poor enforcement mechanisms for drug legislations, and no government laboratories to monitor drug quality.<sup>6</sup>

Drugs that are in high demand are generally the first choice for counterfeiting or substandard manufacturing due to the high-profit returns. Amoxicillin, like amodiaquine, is a commonly prescribed drug in PNG, where it is recommended for the treatment of pneumonia, especially in children. Previous studies on amoxicillin products sold in other countries reveal that these are often substandard,<sup>9</sup> for example, Kyriacos et al.<sup>10</sup> evaluated the quality of amoxicillin formulations sold in Arab countries and found that 56% of the capsules did not meet the United States Pharmacopoeia (USP) standards.

Considering the present public health situation in PNG, the aim of this study was to evaluate the quality of amodiaquine and amoxicillin products sold in PNG and to detect the presence of any counterfeit or substandard drugs in circulation, if any.

## MATERIALS

### Chemicals and Reagents

Analytical grade amodiaquine hydrochloride (lot #038F0993) and amoxicillin trihydrate (lot #108K0449) were purchased from Sigma–Aldrich Chemie GmbH, Steinheim, Germany. Orthophosphoric acid (85%) was obtained from VWR BDH Prolabo,

Fontenay su Bois, France. Sodium dihydrogen phosphate monohydrate, methanol, ethyl acetate, acetone, glacial acetic acid, and acetonitrile were purchased from Merck KGaA, Darmstadt, Germany. Concentrated ammonia solution was procured from Aug. Hedinger, Stuttgart, Germany. All the chemicals used for the tests were of analytical grade.

## METHODS

### Product Sampling

The capital of PNG, Port Moresby, was selected as the sampling area for this study. Sampling was performed in the month of November 2009. A total of 25 pharmacies registered by the PNG Pharmacy Board operate in Port Moresby. These pharmacies were divided into five groups (according to geographical location), each consisting of five pharmacies. One pharmacy from each of these five groups was then randomly selected for sample collection. The products were purchased by locals from the pharmacies without disclosing the purpose. Amodiaquine and amoxicillin products, including pediatric formulations, were purchased from these pharmacies. Some samples were repacked products, dispensed by the pharmacies for individual patient use. In total, six tablet samples (coded ADQ1–ADQ6, amodiaquine) and eight solid dosage formulations (coded AMX1–AMX8, amoxicillin), respectively labeled as containing amodiaquine or amoxicillin as the active ingredient, were collected for the study. Samples from the same manufacturer but with a different batch number were treated as a separate sample.

### Product Evaluation

Product evaluation was based on three attributes: (a) visual inspection and label evaluation, (b) quality control tests, and (c) verification of the product authenticity.

#### *Visual Inspection and Label Evaluation*

Visual inspection and label evaluation were carried out according to the International Pharmaceutical Federation’s (FIP) checklist for visual inspection of counterfeit products.<sup>11</sup>

#### *Quality Control Tests*

Thin layer chromatography (TLC), weight variation, content uniformity, and dissolution testing were performed on the samples according to the methods specified in the pharmacopoeias. The drug regulation of PNG recommends the British Pharmacopoeia (BP) as the compendial standard for drug products. Amoxicillin products were compared with the limits specified in the BP.<sup>12</sup> As BP has no monographs for amodiaquine preparations, all results were compared with

**Table 1.** Table showing the HPLC conditions used in the quantitative estimation of amodiaquine and amoxicillin formulations.

HPLC variables	Amoxicillin <sup>18</sup>	Amodiaquine <sup>19</sup>
Mobile phase	Methanol: (1.25%) acetic acid (20:80)	Acetonitrile: 0.08M potassium hydrogen phosphate buffer (17:83), adjusted to pH 2.8 with 85% orthophosphoric acid.
Flow rate	1.2 ml/min	1 ml/min
Injection volume	10 $\mu$ l	20 $\mu$ l
Detection wavelength	230 nm	333 nm
Extraction medium	phosphate buffer pH 5.0 (50mM)	water

the limits specified for these tests in the amodiaquine tablet monograph in USP.<sup>13</sup>

### Chromatographic Techniques

Thin layer chromatography and high-performance liquid chromatography (HPLC) were utilized in product evaluation. The former was performed as a semi-quantitative evaluation method in order to test for the presence/absence of the active pharmaceutical ingredient (API) in the products, whereas the latter was used to determine the content uniformity in each of sampled products.

**Thin Layer Chromatography.** A reference standard solution containing 5 mg/mL of amodiaquine hydrochloride was prepared in water. The mobile phase constituted of methanol, ethyl acetate, and concentrated ammonia solution in a ratio of 40:10:1.<sup>14</sup> Silica gel 60 F<sub>254</sub> plate (Merck, Darmstadt, Germany) was used as the stationary phase. Sample preparation was carried out by extracting the amodiaquine from each tablet in 100 mL water using ultrasonication and then suitably diluting the filtered solution to obtain a theoretical concentration of 5 mg/mL (based on the stated label strength). The TLC chamber was saturated with the mobile phase prior to developing the chromatogram. Approximately 10  $\mu$ L of each sample solution was spotted on the TLC plates along with the reference solution. The plates were developed in the chamber, air dried, and the spots were observed under ultraviolet (UV) light at 254 nm. The products were evaluated by comparing the  $R_f$  value of each sample with that of the reference substance.  $R_f$  value was calculated using the following equation:

$$\text{Sample } R_f = \frac{\text{Distance travelled by the spot}}{\text{Distance traveled by the solvent front}}$$

In case of amoxicillin capsules, a similar method was used except that the drug was extracted from the capsule contents into acidified acetone (Concentrated HCL, water, acetone, 1:9:40).<sup>14</sup> The mobile phase constituted of ethyl acetate, glacial acetic acid, and water (3:1:1).

**High-Performance Liquid Chromatography.** Quantitative assay was performed using a HPLC, consist-

ing of an autosampler (Merck Hitachi L-7200, Tokyo, Japan), a pump (model L-7110), and a UV detector (model L-7400). Analyses were performed on a RP-18e LichroCART<sup>®</sup> (Merck KGaA, Darmstadt, Germany) analytical column (125  $\times$  4 mm, 5  $\mu$ m for amodiaquine and 250  $\times$  4 mm, 5  $\mu$ m for amoxicillin) fitted with a precolumn. Table 1 shows the HPLC conditions used in the analysis.

Samples were prepared by dispersing a tablet or content of an individual capsule into the respective extraction medium and sonicating for 15 min. This solution was filtered, suitably diluted, and analyzed by HPLC. Calibration curves for each API were prepared in the corresponding extraction media and were run on each analytical day. Ten units per sample were analyzed by this method.

### Dissolution Methodology

Dissolution tests were performed on the amodiaquine tablets and amoxicillin capsules containing 500 mg of amoxicillin as specified in the USP using a DT 80 paddle apparatus (Erweka, Heusenstamm, Germany).<sup>13,17,18</sup> No dissolution test was recommended for amoxicillin capsules according to BP. For amoxicillin capsules (250 mg), the basket apparatus was utilized to comply with the USP specifications. Freshly degassed water at 37°C  $\pm$  0.5°C was used as the dissolution medium. The filtered samples were appropriately diluted with the medium, their absorbances were measured at 342 (amodiaquine) and 254 nm (amoxicillin) against suitable blank and compared with calibration curves of the reference API in the respective dissolution medium. Six units per sample were evaluated for dissolution.

### Product Authenticity Verification

Every effort was made to verify the authenticity of the products by contacting the manufacturer declared on the label. This was achieved by first cross-checking whether the product is listed on the official web page of the company stated on the label. If this was the case, attempts were made to contact the company to cross-check the product details with them, in order to ensure that the batch had been manufactured by that company. This was achieved by writing e-mails to the companies with pictures of the respective products along with a product description and the batch

number, together with a request to confirm whether the batch was manufactured by that company. Any relevant information on the internet or in publications which supported or questioned the product, its manufacturer, or the distributor's genuineness was also taken into account to determine product authenticity.

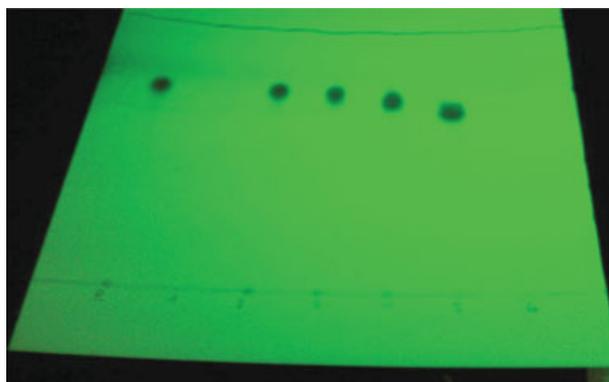
## RESULTS

Fourteen formulations were collected from five registered pharmacies in Port Moresby, PNG. The samples included eight products in their original packs and six repacked products (AMX3, AMX4, AMX7, AMX8, ADQ4, and ADQ6). Samples AMX6 and ADQ5 were blister packed and filled into a cardboard carton along with a product leaflet. Sample AMX7 consisted of blister-packed capsules, which were dispensed in a labeled resealable polythene bag. By contrast, sample AMX8 was dispensed as loose capsules in a resealable polythene bag, which provided minimum protection for the capsules against light, moisture, or transport. The other products were packed in small plastic bottles with plastic screw caps. Table 2,2a summarizes the results of the tests performed on the sampled products. None of the 14 formulations collected from registered pharmacies in Port Moresby was able to comply with all three sets of evaluation criteria: visual evaluation, quality control specifications, and product authenticity.

The label on sample ADQ1 claimed to contain amodiaquine as the hyclate derivative. However, amodiaquine is available only as a dihydrochloride salt form, not as the monohydrochloride hemiethanolate hemihydrate (hyclate). This indicates that the product was incorrectly labeled. Although the product passed the TLC test, it failed to pass the tests



**Figure 1.** Products ADQ2 and ADQ3 have similar labels but physically identical dosage forms.



**Figure 2.** TLC plate spotted with amodiaquine product samples (left to right: reference, ADQ5, ADQ3, ADQ2, ADQ1, ADQ4, and ADQ6), observed under 254 nm UV light. Products ADQ5 and ADQ6 show no spot for the API.

for assay and content uniformity. Based on these findings, ADQ1 was deemed to be substandard.

Samples ADQ2 and ADQ3, claimed to be manufactured by the same company, were labeled as a chewable tablet formulation and as an immediate release tablet formulation, respectively. However, the tablets were identical in appearance in terms of color, shape, and size and were in almost identical packaging, with only a slight difference in the artwork on the label (Figure 1). The address of the manufacturer was missing from both the product labels. On assaying the two products, ADQ2 (chewable tablets) failed to meet the pharmacopoeial limits. Further tests revealed that both the products failed to conform to the content uniformity test and therefore are substandard products. Additionally, ADQ2 appeared to be a possible counterfeit as the tablets looked physically identical (Figure 1) to ADQ3. However, due to lack of response from the manufacturer and the absence of availability of a confirmed original product, this could not be verified.

ADQ4 was repacked by the pharmacy; hence, the actual source of these products could not be traced. Several anomalies were seen in the dispensed label. Dispensing date, expiry date, and storage information were missing and the content of drug was indicated as 0.1 g instead of 100 mg on the label. The tablets failed tests for assay and content uniformity and hence the product was concluded to be substandard.

Sample ADQ5 was a clear case of a counterfeited, poor quality product. Product ADQ5 failed on several counts, including improper labeling as per WHO specifications for prepackaging of antimalarial medicines, poor organoleptic properties, nonuniformity of tablet weight (Table 2), and absence of API in the formulation (as substantiated by TLC and HPLC results) (Figure 2 and 3). The active ingredient was incorrectly described as "amodiaquine" instead of the dihydrochloride salt. Examination of the dosage form

**Table 2.** Summary of the Formulations Tested

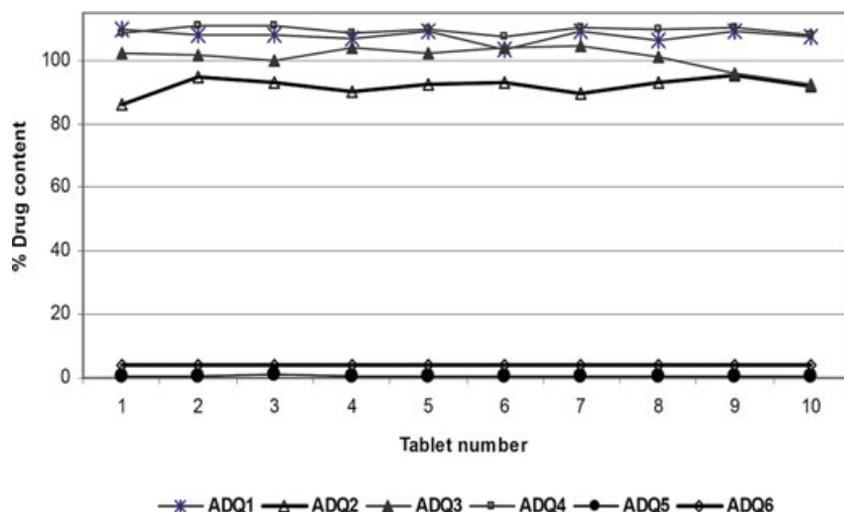
Product Code	Name of the product	Source according to label	Dosage form, batch no	Claimed active ingredient, strength	Weight variation	Assay% <sup>a,b</sup>	TLC	Content Uniformity <sup>a</sup> Mean % (min-max)	Visual Inspection	Product authenticity check response	Product quality assessment
<b>AMX1</b>	Amoxicillin capsules	North China Pharmaceutical Group Corporation, China	Capsule, #090503	Amoxicillin trihydrate, 500mg	passes	<b>112</b>	passes	<b>111.8 (107.8-115.5)</b>	Container could be opened without breaking "tamper proof" seal	No response	<b>Substandard:</b> fails assay, poor content uniformity, inappropriate packaging <b>Substandard:</b> Poor content uniformity
<b>AMX2</b>	Amoxicillin capsules	North China Pharmaceutical Group Corporation, China	Capsule, #090502	Amoxicillin trihydrate, 500mg	passes	103	passes	103.8 <sup>c</sup> ( <b>95-111.3</b> )	-	No response	<b>Substandard:</b> Poor content uniformity
<b>AMX3</b>	Amoxicillin capsules	Unknown, repacked product	Capsule	<b>Not stated</b> , 500mg	passes	<b>113</b>	passes	<b>113 (105.4-116.7)</b>	API, dispensing date, storage not stated	-	<b>Substandard,</b> inappropriate labeling, fails assay, poor content uniformity
<b>AMX4</b>	Amoxicillin capsules	Unknown, repacked product	Capsule	<b>Not stated</b> , 500mg	passes	<b>116</b>	passes	<b>116.14 (114.4-117.4)</b>	API, dispensing date, storage not stated	-	<b>Substandard,</b> inappropriate labeling, fails assay, poor content uniformity
<b>AMX5</b>	Amoxicillin tablets	Alkem Laboratories Ltd, India	Tablet, #9160353	Amoxicillin trihydrate, 250mg	passes	98	passes	98.2 ( <b>54.15-108.2</b> )	-	No response	<b>Substandard/counterfeit:</b> poor content uniformity <b>Counterfeit</b>
<b>AMX6</b>	Amoxyceare 500	Bodiam International Pty Ltd., Australia	Capsule, #S3939002	Amoxicillin trihydrate, 500mg	passes	<b>88</b>	passes	<b>88.3 (48.06-103.7)</b>	-	<b>Non-existent distributor</b>	
<b>AMX7</b>	Moks 500 capsules	Pharmawealth laboratories Inc, Philippines, repacked	Capsule, #36J838	Amoxicillin trihydrate, 500mg	passes	<b>119</b>	passes	<b>119.1 (113.7-143.1)</b>	One empty capsule found in the blister, dispensing dt. and storage not stated	No response	<b>Substandard:</b> fails assay, poor content uniformity, inappropriate labeling, empty capsule

(Continued)

Table 2. Continued.

Product Code	Name of the product	Source according to label	Dosage form, batch no	Claimed active ingredient, strength	Weight variation	Assay% <sup>a,b</sup>	TLC	Content Uniformity <sup>a</sup> Mean % (min-max)	Visual Inspection	Product authenticity check response	Product quality assessment
<b>AMX8</b>	Amoxicillin 250mg	Unknown, repackaged product	Capsule	<b>Not stated</b> , 250mg	passes	<b>115</b>	passes	<b>115.51 (107.8-140.9)</b>	Capsule shells were brittle and contents were sticky, dispensing dt. and storage not stated	–	<b>Substandard:</b> poor content uniformity, inappropriate labeling and packaging
<b>ADQ1</b>	Amodiaquine tablets	Zhongnou Pharmaceutical Co. Ltd. China	Tablets, #070702	Amodiaquine hyclate, 100mg	passes	<b>108</b>	passes	<b>108 (103.6-109.7)</b>	API mislabelled as hyclate instead of hydrochloride salt.	No response	<b>Substandard:</b> poor content uniformity, fails assay, inappropriate labeling
<b>ADQ2</b>	Amodiaquine hydrochloride chewable tablets	North China Pharmaceutical Corporation, China	Tablets, #081010	Amodiaquine hydrochloride, 100mg	passes	<b>91</b>	passes	<b>91.8 (86.2-93.1)</b>	Address of the manufacturer missing	No response	<b>Substandard/possibly counterfeit:</b> fails assay, inappropriate labeling
<b>ADQ3</b>	Amodiaquine hydrochloride, 100mg USP	North China Pharmaceutical Group Corporation, China	Tablets, #080802	Amodiaquine hydrochloride, 100mg	passes	101	passes	100.81 (92-104.3)	Address of the manufacturer missing	No response	<b>Substandard:</b> poor content uniformity, inappropriate labeling
<b>ADQ4</b>	Infant Camoquin Tablets	Unknown, repackaged product	Tablets	Amodiaquine hydrochloride, 0.1g	passes	<b>109</b>	passes	<b>109.5 (108.5-111)</b>	Dispensing dt, storage not stated.	–	<b>Substandard:</b> poor content uniformity, fails assay, inappropriate labeling
<b>ADQ5</b>	Infant Camoquin Tablets	Bodiam international Pty. Ltd. Australia	Tablets, #PT-103	Amodiaquine, 100mg	fails	<b>0.7</b>	fails	<b>0.703 (0.56-1.07)</b>	API not mentioned. Presence of foreign contamination and surface spots.	<b>Non-existent distributor</b>	<b>Counterfeit</b>
<b>ADQ6</b>	Infant Camoquin Tablets	Unknown, repackaged product	Tablets	Amodiaquine hydrochloride, 0.1g	passes	<b>3.9</b>	<b>fails</b>	<b>3.98 (3.91-4.09)</b>	Dispensing dt., storage not stated, mottling of tablets	–	<b>Counterfeit</b>

<sup>a</sup> USP limits for drug content for amodiaquine tablets is 93-107%.<sup>b</sup> BP limits for drug content for amoxicillin capsules is 92.5-110%.<sup>c</sup> Std.deviation outside pharmacopoeial limits.**Bold** face indicate that the products failed the test.



**Figure 3.** Graph showing content uniformity in amodiaquine hydrochloride tablet samples. None of the samples complied with the USP specifications.

revealed that the tablets had a mottled appearance, suggestive of decomposition and/or foreign contamination.

ADQ6, the second repacked amodiaquine product, showed similar aberrations in the labeling as found in ADQ4. Additionally, physical inspection of the tablet revealed mottling, thus leading to suspicion about the quality of the product. Quality control tests indicated the drug content to be less than 4%, in agreement with the absence of the API spot during TLC test. Consequently, the product was categorized as a counterfeit according to the WHO guidelines.

Products AMX1 and AMX2 were identical products but with different batch numbers. AMX1 capsules failed to comply with the BP specifications for assay and content uniformity. The container could be opened without breaking the “tamper proof” seal, thus indicating poor quality packaging. The product was hence classified as substandard.

In the case of AMX2, although the drug content of the capsules fell within pharmacopoeial limits, they showed a standard deviation greater than the 6% permitted by the specifications. Even though uniformity of content is not a prerequisite test for amoxicillin capsules, it helped to demonstrate the nonuniformity of drug content within the batch. As experienced with the amodiaquine products, no response was obtained from the manufacturer as to the legitimacy of AMX1 and AMX2.

Samples AMX3 and AMX4, two of the repacked products, showed several errors in labeling. Basic information such as the name of the active ingredient, date of dispensing, and storage conditions was missing. Assay tests showed drug concentrations greater than the permissible 110%. The product was deemed to be substandard as it failed to comply with the phar-

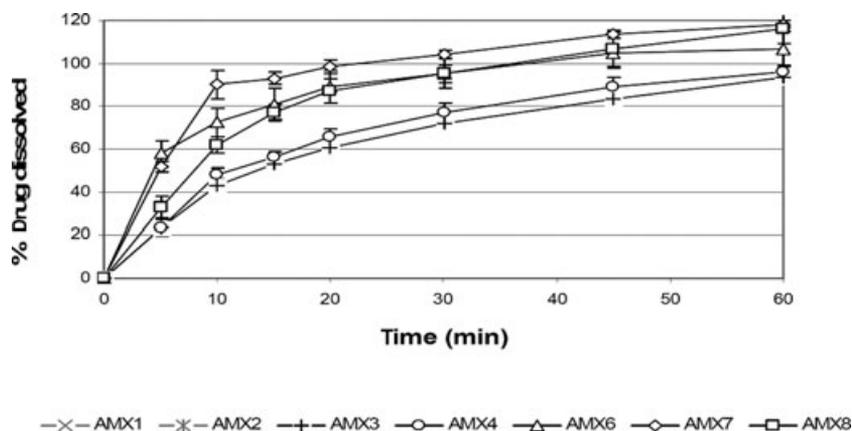
macopoeial specifications and the product label was not in accordance with the FIP checklist.<sup>11</sup>

AMX5 was chewable amoxicillin tablet marketed by Alkem Laboratories Ltd., a company registered with the Indian FDA and which manufactures generic products with marketing authorization in the US. The product passed all the tests except uniformity of content, in which the minimum content of amoxicillin detected was around 54% and thus of substandard quality. Because of lack of response from the manufacturer, it was difficult to distinguish if the product was a substandard product from a legitimate source or a low-quality counterfeit.

Sample AMX6 was a clear case of a counterfeited, poor quality product. AMX6 contained 88% of labeled amoxicillin content, lower than the permissible BP limit of 92.5%–110% for amoxicillin capsules/tablets. The content uniformity test on this sample revealed capsules containing drug content as low as 48%. An authenticity check on the product distributor, Bodiam International Pty Ltd., Sydney, Australia, revealed that a company by this name had been liquidated in 2007 as per the information in the Australian business gazette.<sup>19</sup> Samples ADQ5 and AMX6, purportedly distributed by this company, had manufacturing dates of 2008 and 2009, respectively.

Samples AMX7 and AMX8 were repacked by the pharmacies into labeled, resealable polythene bags. However, AMX7 consisted of 10 capsule blister packs as the primary pack, whereas AMX8 contained loose capsules directly filled into the bag.

AMX7 failed assay, showed poor content uniformity, with the amoxicillin content (in some capsules) as high as 143%, and lacked the name of the active ingredient, dispensing date, and storage conditions on the



**Figure 4.** Graph showing dissolution profiles of amoxicillin samples AMX1–AMX8 in water. All the seven samples complied with the USP specifications of 80% drug release in 60 min.

label. In addition, an empty capsule was found in one of the blisters. As a result, the product was classified to be substandard.

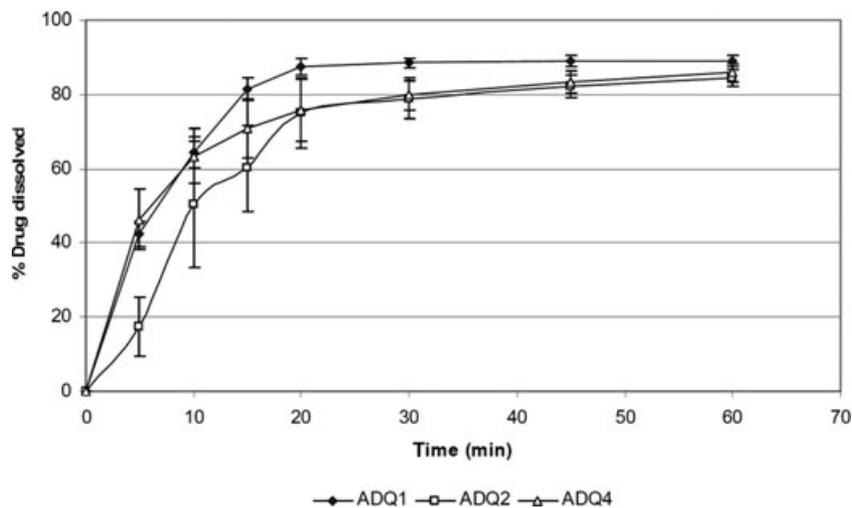
Like AMX7, AMX8 failed assay and showed inappropriate labeling. Physical examination of the capsules showed the capsule shells to be brittle, with sticky capsule contents. This could be attributed either to poor quality manufacture or improper dispensing of the product by the pharmacy. As capsules containing more than 140% amoxicillin were detected in the test of content uniformity, the product was concluded to be of substandard quality.

Samples AMX5, ADQ2, ADQ5, and ADQ6 were not subjected to dissolution testing as AMX5 and ADQ2 were chewable tablet formulations and ADQ5 and ADQ6 had no detectable API content in the tablets. The rest of the formulations (ten in all) passed the dissolution test prescribed by the individual monographs in USP (Figure 4 and 5).

To summarize the results, 3/14 products were found to be counterfeits, 9/14 were found to be substandard, and 2/14 were found to be substandard products and additionally suspected to be counterfeits.

## DISCUSSION

There has been disparity in the terms and definitions used by countries to describe counterfeit and substandard drug products. In the absence of a consensus over a common definition for counterfeit and substandard drugs, for the purpose of this manuscript, the products were classified according to the WHO definitions. The WHO defines counterfeit medicines as those which are deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can occur with both branded and generic products. Products without active ingredients, with incorrect quantities of active ingredients, with wrong



**Figure 5.** Graph showing dissolution profiles of amodiaquine samples ADQ1, ADQ2, and ADQ4 in water. All the three samples complied with the USP specification of 75% drug release in 30 min.

active ingredients, with correct quantities of active ingredients but with fake packaging, copies of the original product, and with high levels of impurities and contaminants are the categories into which counterfeit products can be broadly classified.<sup>3</sup>

In addition to counterfeit medicines, substandard medicines produced by legitimate manufacturers also pose a threat to therapeutic efficacy. Substandard products are defined as those that are manufactured or repacked by legitimate manufacturers but do not meet the pharmacopoeial specifications.<sup>2</sup> Additionally, if good quality products are repacked in poor quality packaging by the pharmacist or not stored correctly at some point in the shelf life, this can result in a substandard medicine at the time of use by the patient.

None of the 14 formulations collected from registered pharmacies in Port Moresby were able to comply with the criteria for all three aspects of the quality evaluation: visual evaluation, quality control specifications, and product authenticity. Five of the products are or may be counterfeits. Even though two of the remaining nine products passed the assay, content uniformity testing revealed that a few units in these samples had drug contents higher than the specified limit. These results demonstrate that both counterfeit and substandard products are in circulation in pharmacies in Port Moresby. Pharmacies represent the best available quality distribution chain for drugs in PNG; other sources, such as open markets selling groceries and other wares (a commonplace practice in PNG), are likely to deviate even more from required quality standards. The findings, even though obtained from a small sample size, indicate that the prevalence of counterfeit/substandard drug products in this study area outweighs products with acceptable quality. This is especially alarming in view of the importance of communicable diseases as a cause of morbidity and mortality in PNG.

Incorrect labeling and packaging of repacked products by the pharmacies indicate a lack of awareness about product dispensing by the pharmacists. Sample AMX8 was repacked in a resealable polythene bag, which provided little or no protection for the product against light, moisture, and damage during transportation and normal use by patients. Not surprisingly, some of the capsule shells in this sample were found to be brittle and the capsule contents had formed a lump. Such improper repacking not only affects product integrity but also fails to hinder drug degradation. Adequate and periodic training of pharmacists, indicating the significance of proper labeling and dispensing of products, would facilitate maintenance of the product integrity during therapy and administration of the right dose.

The unresponsiveness from the pharmaceutical manufacturers that was encountered during the

course of this study exposes another hurdle that authorities or pharmacists face when tracking or verifying the source of pharmaceutical products. These obstacles can be best tackled by mutual cooperation between the manufacturer, pharmacists, consumers, and the regulatory authorities.

Although the precise extent of prevalence of counterfeit/substandard drug in PNG cannot be estimated due to the small sample size, the present study clearly indicates that counterfeit and substandard anti-infective drug products are present in Port Moresby and easily finding their way into the distribution chain in PNG. The presence of poor quality products not only defeats the very aim of the National Health Policy but also poses risks to the well-intentioned changes introduced by the health professionals to treat, control, and confine the spread of these deadly diseases.

Malaria and pneumonia, the two leading causes of illness and death in PNG, are specifically addressed in the Child Health Policy Plan<sup>7</sup> and the new National Health Plan.<sup>20,21</sup> However, at the moment, inadequate legislation and enforcement, absence of licensing and registration of imported drugs, illiteracy, and lack of public awareness make PNG a haven for counterfeiters and manufacturers of substandard drug products.

It is therefore suggested that proper and immediate measures be taken in PNG to assure that good quality drug products are available to patients. Drug regulation needs to be expanded by introducing product licensing since free circulation of unregistered medicines raises the chances for entry of counterfeit and substandard products into the country. Mechanisms need to be put in place to enforce the existing as well as new regulations. A crucial step in this regard would be to establish government-run quality control laboratories with adequately trained personnel. Setting up well-equipped laboratories, where the products are periodically evaluated, will assist in detection of these kinds of products, and also serve as a deterrent for defaulters. Also essential for enforcement are appropriate legal instruments to facilitate collaboration between National Department of Health and the police.

On a global level, a central administration should be established, where collaborating countries can report and exchange information on counterfeit/substandard medicines and which would also provide an accessible database of implicated cases for interested countries. At present, PNG is not part of the either the WHO (<http://www.counterfeitmedalert.info/>) or USP (<https://secure.usp.org/worldwide/medQualityDatabase/terms.html>) database for counterfeits. Specifically, for PNG, cooperation with regulatory authorities in neighboring countries such as Malaysia and Australia would help PNG make faster

progress toward the goals of its National Health Plan.

In order to evaluate the impact of the new legislation in PNG, a study similar to this one in 2–3 years, but with a larger sample size and across a wider area in PNG, is suggested.

## CONCLUSION

This study detected counterfeit and substandard anti-infective drugs in the distribution chain in Port Moresby, PNG. Of the 14 samples of amoxicillin and amodiaquine tested, two samples contained the API at levels below the detection limit. Of the remaining 12, nine failed the assay and all failed to comply with the content uniformity test specified by the pharmacopoeia. Even though the sample size used in this study was small, it is a clear indicator of the magnitude of the problem faced by PNG in ensuring a high quality in drugs reaching the patients. It is to be hoped that through the National Health Plan and new legislation, stronger drug regulation, stricter control on quality of pharmaceutical products, better training of pharmacists, raising public awareness, and a reduction in the prevalence of substandard and fraudulent anti-infective products can be achieved.

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