

Investigations of the quality medicines distributed in Myanmar and Cambodia, through different surveys

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学位论文要旨

Medicines are the most essential things especially for human beings to survive in the world. But, it is increasing the amount of counterfeiting or substandard medicines in the markets and ultimately supply to the patient's day by day. Falsified or substandard medicines can present a health hazard to us. I have been attempting to clarify how often we might encounter such medicines and also to identify the specific features of defects to find clues for improvement. Despite of our results, much remains to be studied. Therefore, I reviewed the quality of medicines for lifestyle diseases in Cambodia for three years, and the quality of antimicrobial medicines in Cambodia for four years. In addition, I surveyed counterfeit or substandard medicines in Yangon, Myanmar survey in 2014 for collecting more data. I conducted a four-year and three-year study to evaluate the quality of selected antimicrobials and lifesaving medicines and to examine the prevalence of falsified or substandard antimicrobial and lifesaving medicines in Cambodia, aiming to promote efforts to improve the quality of medicines. I collected samples of clarithromycin, sulfamethoxazole/trimethoprim, ceftriaxone, cefuroxime, levofloxacin, gentamicin, ciprofloxacin, fluconazole, nalidixic acid, ofloxacin, phenoxymethyl penicillin and roxithromycin medicines as well as cimetidine, amlodipine, esomeprazole, rabeprazole, glibenclamide and metformin from pharmacies, Depot-A, Depot-B, wholesalers and non-licensed drug outlets in five provinces (rural areas) and Phnom Penh (an urban area), during 2011 to 2014 (antimicrobial) and 2011 to 2013 (lifesaving) Table 1& 2.

Table 1 Outline of samples (antimicrobial) collection

Year	Antibiotic	No. of samples	Types of area		Type of drug outlet				
			Urban area no. of sample%	Rural area no. of sample%	Pharmacy no. of sample%	Depot-A no. of sample%	Depot-B no. of sample%	Wholesaler no. of sample%	non-licensed no. of sample%
2011	Clarithromycin	50	28 (56%)	22(44%)	26 (52%)	5 (10%)	17 (34%)	2 (4%)	-
	Sulfamethoxazol e/ Trimethoprim	72	42 (58%)	30 (32%)	23 (32%)	15 (21%)	29 (40%)	4 (5%)	1 (2%)
2012	Ceftriaxone	61	32 (52%)	29 (48%)	26 (43%)	10 (16%)	19 (31%)	4 (7%)	2 (3%)
2013	Cefuroxime	53	37 (70%)	16 (30%)	34 (64%)	3 (6%)	10 (19%)	6 (11%)	-
	Levofloxacin	60	35 (58%)	25 (32%)	30 (50%)	6 (10%)	18 (30%)	6 (10%)	-
2014	Gentamicin	59	35 (59%)	24 (31%)	26 (44%)	11 (19%)	17 (29%)	5 (8%)	-
	Ciprofloxacin	56	36 (64%)	20 (36%)	40 (71%)	7 (13%)	5 (9%)	4 (7%)	-
	Fluconazole	57	35 (61%)	22 (29%)	36 (63%)	4 (7%)	9 (16%)	8 (14%)	-
	Nalidixic Acid	9	6 (66%)	3 (34%)	6 (66%)	2 (22%)	1 (2%)	-	-
	Ofloxacin	57	33 (58%)	24 (32%)	41 (72%)	6 (10%)	9 (16%)	1 (2%)	-
	Phenoxymethyl penicillin	56	33 (59%)	23 (31%)	42 (75%)	8 (15%)	3 (5%)	3 (5%)	-
	Roxithromycin	57	38 (66%)	19 (34%)	41 (72%)	9 (16%)	5 (9%)	2 (3%)	-
Total		647 (100%)	390 (60%)	257 (40%)	371 (57%)	86 (13%)	142 (22%)	45 (7%)	3 (1%)

Urban area: The capital of Cambodia (Phnom Penh)

Rural area: Other provinces (Battambang, Kandal, Kampong Speu and Takeo) which are located outsidess of capital city

Depot-A: Depot-A outlet by an assistant pharmacist (who received 3 years' pharmacy training)

Depot-B: Depot-B outlet by a doctor or retired nurse

The authenticity of the collected medicines was investigated, and the medicines were analyzed to determine whether they met the appropriate pharmacopeial standards. I collected 647 samples, produced by 179 manufacturers, from 353 outlets. Only 51 (15%) of the outlets were air-conditioned. I found different-coloured packaging of the same brand (different lots) of products from some manufacturers. The insert information of one sample was different from the package information.

Table 2 Outline of samples (lifestyle) collection

Year	Name of samples	No. of samples	Area		Type of drug outlet			
			Urban	Rural	Pharmacy	Depot-A	Depot-B	Wholesaler
2011	Cimetidine	86	57	29	30	19	34	3
2012	Amlodipine	79	45	34	33	12	27	7
	Esomeprazole	54	38	16	28	4	13	9
	Rabeprazole	11	10	1	8	0	2	1
2013	Glibenclamide	52	33	19	25	14	10	3
	Metformin	60	40	20	32	13	10	5
	Total	342	223	119	156	62	96	28

Twelve (1.9%) samples were not officially registered with DDF. In authenticity investigation, 43 of 179 manufacturers replied and confirmed the authenticity of 154 samples (out of 647); also, 18 out of 54 MRAs replied to enquiries about whether products were licensed or not (one was not). Among the samples, 424 (80.4%), 406 (86%) and 533(90.6%) passed in dissolution, content uniformity and quality tests, respectively (Table-3). Samples of cefuroxime and roxithromycin that failed were significantly cheaper than those that passed. Poor-quality antimicrobial medicines were found in Cambodian markets, though no falsified medicines were detected. Manufacturers should be encouraged to improve GMP implementation. Storage conditions in the distribution chain may also need to be improved. Continuous efforts by MRAs are needed to ensure that medicines are properly licensed.

Table 3 Summary of quality test of samples (antimicrobial)

Antibiotic	Total no. of samples	Dissolution	Content uniformity	Quantity	Identification	Sterility	Endotoxin	Microbial assay
Clarithromycin	50	36 (72%)	43 (86%)	49 (98%)	50 (100%)	-	-	-
Sulfamethoxazole / Trimethoprim	72	62 (86.1%)	70 (97.2%)	53 (73.6%)	72 (100%)	-	-	-
Ceftriaxone	61	-	46 (75.4%)	48 (78.7%)	61 (100%)	61 (100%)	61 (100%)	-
Cefuroxime	53	53 (100%)	43 (81.1%)	51 (96.2%)	53 (100%)	-	-	-
Levofloxacin	60	42 (72%)	-	57 (95%)	60 (100%)	-	-	-
Gentamicin	59	-	-	-	59 (100%)	59 (100%)	59 (100%)	59 (100%)
Ciprofloxacin	56	54 (96.4%)	56 (100%)	54 (96.4%)	56 (100%)	-	-	-
Fluconazole	57	29 (50.9%)	40 (70.2%)	54 (94.7%)	57 (100%)	-	-	-
Nalidixic Acid	9	3 (33.3%)	9 (100%)	9 (100%)	9 (100%)	-	-	-
Ofloxacin	57	49 (85.9%)	44 (77.2%)	46 (80.7%)	57 (100%)	-	-	-
Phenoxyethylpenicillin	56	56 (100%)	-	55 (98.2%)	56 (100%)	-	-	-
Roxithromycin	57	40 (70.2%)	55 (96.5%)	57 (100%)	57 (100%)	-	-	-
Total	647	424 (80.4%)	406 (86%)	533 (90.6%)	647 (100%)	120 (100%)	120 (100%)	59 (100%)

Number of pass samples are showing with percentage

In the case of three-year survey, we found 342 samples (223 from Phnom Penh) were collected from 263 outlets; among them, 32 (9.4%) had no inserts, and 14 (4.1%) were not registered with DDF. 38 (11.1%) were domestically produced. The containers of one amlodipine and three cimetidine samples were different from those of authentic samples. Nonstandard inserts were found in two samples (amlodipine and metformin). Only 21/81 manufacturers and 16/35 MRAs replied during authenticity investigation. In quality evaluation, 38 (11.1%), 52 (15.2%) and 48 (14%)

samples failed dissolution, content uniformity and quantity tests, respectively (Table-4). The failure rate in quality tests was significantly associated with the results of visual analysis of samples. Poor-quality medicines were prevalent in Cambodia in 2011-2013. Further surveys

Table 4 Summary of quality test of samples (lifestyle)

Sample name	No. of samples	Dissolution		Content uniformity		Quantity	
		Pass	Fail	Pass	Fail	Pass	Fail
Cimetidine	86	79	7	65	21	71	15
Amlodipine	79	77	2	73	6	78	1
Esomeprazole	54*	31	22	32	22	33	21
Rabeprazole	11	11	0	11	0	11	0
Glibenclamide	52	47	5	49	3	46	6
Metformin	60	58	2	60	0	55	5
Total	342	303	38	290	52	294	48

should be conducted to monitor the situation. Measures are desirable to improve the quality of domestically manufactured products.

The availability of substandard or counterfeit medicines in Myanmar was examined by the WHO in 1999, but no further systematic survey on counterfeit medicines has been conducted in the country since then. Samples of oral medicines, cefuroxime axetil (CXM), donepezil hydrochloride (DN) and omeprazole (OM), and injections, ceftriaxone sodium (CTRX) and gentamicin sulfate (GM), were

Table 5 Outline of samples collection

collected from pharmacies, hospitals and wholesalers in Yangon, Myanmar in 2014 (Table 5).

Items	Government hospitals	Private hospitals	Community pharmacies	Clinical pharmacies	wholesalers
Ceftriaxone(49)	9	11	18	7	4
Cefuroxime(60)	14	12	22	9	3
Donepezil HCl(3)	-	-	2	-	1
Gentamicin(58)	11	7	31	6	3
Omeprazole(65)	13	12	30	6	4
Total (235)	47 (20%)	42(17.9%)	103 (43.8%)	28 (11.9%)	15(6.4%)

Authenticity and registration were verified. Quality tests of samples were performed according to the pharmacopeia indicated on the label. There were 221 (94%) foreign medicines among 235 samples collected from 75 locations. Five samples of GM and 1DN sample were not registered with Myanmar Food and Drug Administration (MFDA). In quality analysis, 36 samples out of 177 (20.3%) did not pass quantity tests, 27 samples out of 176 (15.3%) did not pass content uniformity

Table 6 Summary of quality test of samples

Items(n)	Assay test		Content uniformity test		Dissolution test		Endotoxin test		Sterility test		Identification		Microbial Assay	
	Pass	Fail	Pass	Fail	Pass	Fail	Pass	Fail	Pass	Fail	Pass	Fail	Pass	Fail
Ceftriaxone (49)	47	2	46	3	-	-	49	0	49	0	49	0	-	-
Cefuroxime (60*)	49	11	44	15	54	6	-	-	-	-	60	0	-	-
Donepezil HCl (3)	3	0	3	0	3	0	-	-	-	-	3	0	-	-
Gentamicin (58)	-	-	-	-	-	-	58	0	58	0	55	3	55	3
Omeprazole (65)	42	23	56	9	48	17	-	-	-	-	65	0	-	-
Total (235)	141	36	149	27	105	23	107	0	107	0	232	3	55	3

tests, and 23 out of 128 samples (18.0%) did not pass dissolution tests (Table-6). Three of the unregistered GM samples failed in both identification and microbial assay tests (Fig. 1, 2 & 3). Counterfeit GM is being sold in Yangon. Also, the quality of OM is a matter of concern, and requires

follow-up. Poor-quality medicines were frequently found among the products of a few manufacturers. Regular surveys to monitor counterfeit and substandard medicines in Myanmar are recommended.

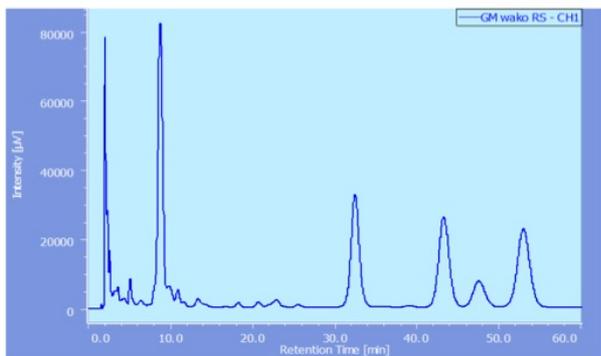


Figure 1 Chromatogram of GM standard

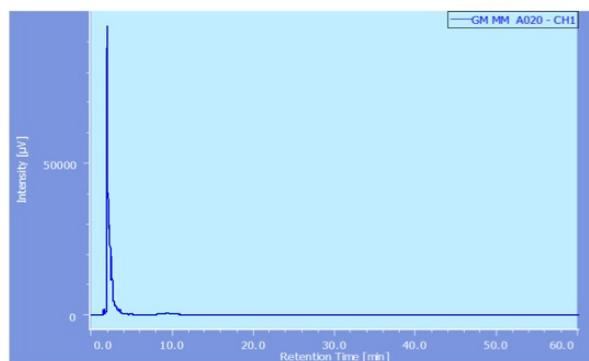
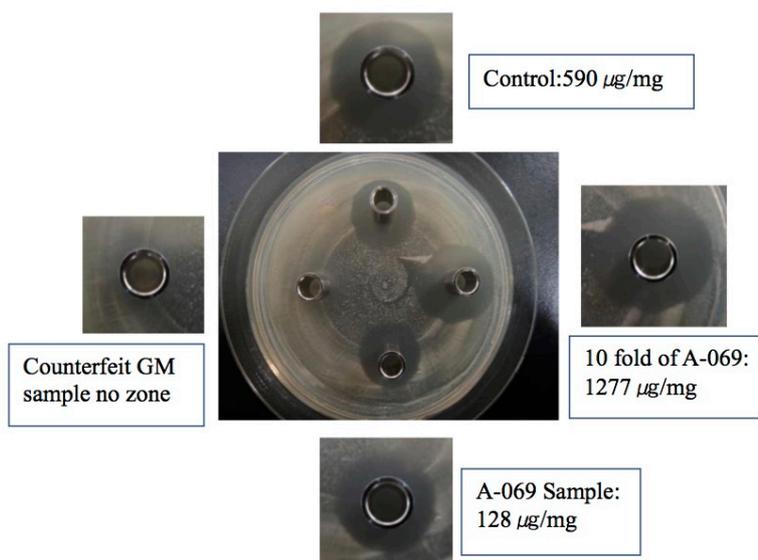


Figure 2 Chromatogram of counterfeit GM samples

I found that poor-quality medicines are the urgent problems in Cambodia and Myanmar, even though the medicines were not counterfeit. Serious dissolution failure is the dominant problem in these countries. It is necessary to collect more information of such medicines, and to analyze the characteristics of the data for preventing health hazards caused by falsified or substandard medicine.

Figure 3 Zone of inhibition (microbial assay) are showing between standard concentration and counterfeit GM samples



審査結果の要旨

Islam 氏は 2011-2014 年にカンボジアとミャンマーで行った流通医薬品 23 種類、1224 サンプルの品質と真正性について、その一部は自ら分析するとともに、全体を解析し、次のような特徴を把握した。1) 無登録薬が、少数 (3-4%) ながら存在し、これらは偽造薬、不良薬であった 2) 医薬品の多くを輸入に頼っていた。甚だしく品質の悪いもの (基準値の 50%) は国産 (カンボジア) にも輸入品にもみられた。また、不合格を出す製造者は医薬品ごとに限定された 3) 局方試験の合格率が 74.0-80.0% に留まった。特に、溶出試験については国産、輸入品とも、また、薬効分類に拘わらず、非常に溶出率が低いものが散見された 4) 品質不合格品の価格は合格品よりも安く、偽造品は真正品よりも安かった 5) 薬局の空調設備の普及率は 11% (Cambodia)、39% (ミャンマー) と低い。一方、品質は空調設備のある薬局の方が不合格率が低い。以上より、i) 無登録薬の流通をなくすこと ii) 甚だしい溶出性不良の原因を明らかにし iii) 品質不良品を出した特定の製造者の GMP 遵守を徹底させること iv) 安い製品には品質不良や偽造品が混在している可能性があり、仕入れや調剤時には価格も考慮すること v) 空調設備の整備を図ること、これらがカンボジア、ミャンマーの流通薬の品質改善に必要であることを明らかにした。

以上、今後のカンボジア、ミャンマーで代表される発展途上国の医薬品品質の改善に必要な事項を 1000 以上のサンプルの解析から明らかにしたもので、本審査委員会は、審査員全員一致で、Md. Rafiqul Islam 氏に対して博士 (学術) の学位を授与することが適当であると判断した。