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Surveillance of Quality of Medicines Available in the Nepalese Market: A Study from Kathmandu Valley

Gyanwali P,[1] Humagain BR,[2] Aryal KK,[1] Pandit A,[1] Acharya T,[1] Bista B,[1] Dhimal M,[1] Karki KB[1]

[1]Nepal Health Research Council (NHRC), Ramshah Path, Kathmandu, Nepal, [2]Nepal Pharmacy Council (NPC), Bijulibazar, Kathmandu, Nepal

ABSTRACT

Background: Many countries are having problem of substandard and counterfeit drugs which results in life threatening issues, financial loss of consumers and loss in trust on health system. This study is concerned with the assessment of drugs quality available in the Nepalese market.

Methods: A cross sectional survey was carried out in Kathmandu valley. Five different brands from each eight molecules of drugs (Paracetamol tablet, Cloxacillin capsule, Amlodipine tablet, Metformin tablet, Losartan tablet, Cefixime tablet, Ofloxacin tablet, Carbamazepine tablet) were purposively selected. Registration compliance was verified from Department of Drug Administration (DDA) and laboratorial analysis was done in two different laboratories.

Results: Out of 40 drug samples, 90% did not comply with the existing regulatory requirement on labeling and 42.5% brands did not mention about the pharmacopoeial standard. There was no uniformity in mentioning the self-life. Similarly, large variation was seen on price of same generic drugs. Laboratory analysis showed that 40% samples failed to meet the standard among domestic companies and 28% among imported brands. Altogether 32.5% samples were found to be of substandard quality. Only the result of one sample matched with both laboratories. This indicates that there was variation in the selected two laboratories.

Conclusions: The result of this survey indicates that, substandard medicines are available in Nepalese market. Moreover, there is weak regulation and no uniformity in similar pharmaceutical products. A larger study is required to access the quality of pharmaceutical products in the Nepalese market with testing of products in more than two independent laboratories.

Keywords: Counterfeit medicine; substandard medicine; quality of drugs.

INTRODUCTION

Drugs play a crucial role in saving lives, restoring health and preventing diseases and epidemics but when it is counterfeit (deliberately and fraudulently mislabeled with respect to identity and/or source) or substandard (not complying with the standard specification as per the related pharmacopoeia or not complying with the specification of the manufacturer or the requirement of the drug regulatory authority.) , it results in life threatening issues, financial loss of consumers and loss in trust on health system.[1] Counterfeiting is a serious worldwide issue involving networks of manufacture and distribution that are integral part of industrialized organized crime.[2] Up to 10% of all medicines sold worldwide are counterfeit, with higher prevalence in regions where drug regulatory and enforcement systems are weakest.[3] According to WHO, 60% of counterfeit drug cases take place in less-developed countries.[4] The quality of some pharmaceutical products that are exported to the least developed countries do not even meet basic quality standards.[5]

Correspondence: Babu Ram Humagain, Nepal Pharmacy Council, Bijulibazar, Kathmandu, Nepal. e-mail: brhumagain@yahoo.com.

This study is concerned with the assessment of drugs quality available in the Nepalese market. This study aims to find a baseline to approximate the situation of quality of limited generics of different brands.

METHODS

A descriptive cross-sectional study design was adopted to find baseline information to approximate the situation of quality of limited generics of different brands of drugs available in Nepalese Pharmaceutical Market. Prior to the sample collection, ethical approval was sought from the independent Ethical Review Board (ERB) of Nepal Health Research Council.

Eight molecules of drugs (Paracetamol tablet, Cloxacillin capsule, Amlodipine tablet, Metformin tablet, Losartan tablet, Cefixime tablet, Ofloxacin tablet, Carbamazepine tablet) were purposively selected for this study. Selection of drugs was based on the frequency of prescription and therapeutic category. Post market surveillance of selected drugs was done using various parameters (compliance to registration status, compliance to the regulatory requirements on labeling, compliance to the quality control parameter (physical standard, identification, assay, disintegration, dissolution) as per their standard as appropriate).

Five different brands of drugs which have same batch number were concurrently purchased from different location of Kathmandu valley. Selected brands of drugs were collected from periphery through central of valley. The collected brands of drugs were dispatched for analysis for quality to two different pharmaceutical analytical laboratories of Nepal which are recognized by Department of Drug Administration (DDA) for testing and analysis of drugs. One to two strips of each sample were kept as reference. The obtained report results from the laboratories were entered into MS-Excel and necessary analysis was made to produce comparable results.

RESULTS

Out of total 40 brands of drugs, 25 (62.5%) were manufactured by domestic manufacturers and 15 (37.5%) were manufactured by Indian pharmaceutical companies. Three generic/molecules were among antimicrobials, two antihypertensive whereas one each from NSAID, antidiabetic and anticonvulsant.

It was found that most of the products did not comply with the existing regulatory requirement on labeling. 90% of the non-compliance was felt under the provision of mentioning class of drug (Schedule) and system of medicine as per Regulation on Standards of Drugs, 2043 B.S.[6]

While evaluating the pharmacopoeial standard of the samples, it was found that 17 (42.5%) brands did not mention about the pharmacopoeial standard they are following. A total 22 (55%) brands claimed that they are IP (Indian Pharmacopoeia) standard, 1 (2.5%) brand was BP (British Pharmacopoeia) standard and 3 (7.5%) from USP (United States Pharmacopoeia) standard.

Looking at shelf-life, it was seen that there was no uniformity in mentioning the self-life. Interestingly, the self-life of similar formulation was found to be varied (Table 1).

Table 1. Self-life (Expiry) duration

Generic	1.5yrs	2yrs	2yrs 3mnts	2.5yrs	3yrs	4yrs
Ofloxacin 400mg tab		2			2	1
Cloxacillin 500mg cap	1	2	1	1		
Cefixime 200mg tab		3		1	1	
Losartan 50mg tab		3			2	
Metformin 1g SR tab	1	3		1		
Amlodipine 5mg tab		2			3	
Carbamazepine CR/Plain 200mg tab		3			2	
Paracetamol 500mg tab		1			4	
Total	2(5%)	19(47.5%)	1(2.5%)	3(7.5%)	14(35%)	1(2.5%)

Large variation was seen on analyzing the price of same generic drugs. However, the price of Paracetamol was seen to be same in all brands. Maximum of almost 114% variation was found in Cefixime tablets (Table 2).

Out of 40 brands analyzed, it was found that 6 (40%) failed to meet the standard among the domestic companies and 7 (28%) among the imported brands. Altogether 13 (32.5%) samples were found to be of substandard quality (Table 3). Among 40 samples sent to Laboratory I, 10 (25%) failed to meet the standard

Table 2. Analysis of price of drugs

Generic	Max	Min	Mean	Max Variation %
Ofloxacin 400mg tab	18.52	15.00	16.20	23.47
Cloxacillin 500mg cap	12.00	10.00	10.40	20.00
Cefixime 200mg tab	27.00	12.64	22.93	113.61
Losartan 50mg tab	11.00	7.68	8.97	43.23
Metformin 1g SR tab	7.28	5.50	6.27	32.36
Amlodipine 5mg tab	3.00	6.00	4.70	100.00
Carbamazepine CR/Plain 200mg tab	1.89	3.32	2.77	75.6 6
Paracetamol 500mg tab	1.00	1.00	1.00	0.00

Table 3. Analysis Result by Generic and by testing laboratories

Drugs			Substandard			
	Domestic	Imported	Total (n=40)	Lab I (n=40)	Lab II (n=35)	Total
Paracetamol 500mg tab	1	0	**1**	0	1	**1**
Cloxacillin 500mg cap*	1	0	**1**	1	1	**2**
Amlodipine 5mg tab	0	0	**0**	0	0	**0**
Metformin 1g SR tab	1	3	**4**	4	0	**4**
Losartan 50mg tab	1	0	**1**	1	0	**1**
Cefixime 200mg tab	2	1	**3**	2	1	**3**
Ofloxacin 400mg tab	1	0	**1**	0	1	**1**
Carbamazepine CR/Plain 200mg tab	0	2	**2**	2	NA	**2**
Total (%)	**7(28%)**	**6(40%)**	**13(32.5%)**	**10(25%)**	**4(11.43%)**	**13(32.5%)**

Table 4. Result of analysis by tests (Cefixime 200mg tablet)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	F	P	P	P	F	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	383.73	384.95	498.59	502.94	692.98	692.08	412.17	413.38	458.44	456.24
Assay (content)	1.33%	94.21%	97.49%	99.78%	102.65%	105.81%	97.64%	98.38%	92.35%	90.12%
Disinteg-ration time	-	-	27 to 29 sec	-		1min 37 sec	-	-	-	-
Dissolution %	-	86.19 to 93.53	-	-	-	-	-	96.14 to 97.95	-	84.13 to 90.29

(Here, L=Lab, P=Pass, F=Fail/ Does not comply and + indicates positive)

Table 5. Result of analysis by tests (Paracetamol 500mg tablet)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	621.39	617.95	606.45	608.33	584.67	588.69	583.87	577.62	573.66	572.45
Assay (content)	96.73%	98.80%	96.33%	98.58%	97.45%	100.16%	97.68%	97.99%	97.88%	99.06%
Disintegration time	6 min		2.5 min		2.5 min		3 min		2.5 min	
Dissolution %	86.93 to 94.56	81.79 to 88.76	98.93 to 104.25	96.88 to 99.48	97.12 to 99.88	97.94 to 102.98	92.63 to 102.67	71.98 to 96.20	97.09 to 100.84	98.66 to 100.97

(Here, L=Lab, P=Pass and + indicates positive)

Table 6. Result of analysis by tests (Ofloxacin 400mg tablet)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	606.78	606.34	626.68	622.50	642.02	641.36	566.10	565.80	728.45	725.29
Assay (content)	102.97%	102.24%	96.63%	97.49%	102.09%	97.19%	100.45%	96.76%	99.75%	94.80%
Dissolution %	88.46 to 92.23	58.06 to 73.79	92.44 to 96.22	80.35 to 92.02	96.91 to 98.93	84.14 to 94.57	97.48 to 101.51	92.82 to 94.02	94.92 to 98.20	86.91 to 88.94

(Here, L=Lab, P=Pass and + indicates positive)

Table 7. Result of analysis by tests (Amlodipine 5mg tablet)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	136.21	135.39	189.66	189.20	99.63	100.09	134.33	134.30	171.69	171.69
Assay (content)	95.54%	91.00%	107.42%	106.00%	102.96%	101.60%	102.04%	99.40%	99.26%	101.80%
Dissolution %	95.63 to 103.40	94.73 to 101.03	92.77 to 98.49	110.58 to 115.63	100.13 to 105.44	89.72 to 98.78	96.27 to 105.32	100.16 to 104.51	104.37 to 107.27	101.16 to 108.40

(Here, L=Lab, P=Pass and + indicates positive)

Table 8. Result of analysis by tests (Losartan 50mg tablet)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	166.425	165.090	185.750	184.220	155.680	156.410	140.265	139.880	210.320	209.920
Assay	101.270	102.320	99.818	101.760	98.170	101.380	101.000	106.180	97.956	104.240
Dissolution %	76.29 to 96. 44	-	99. 21 to 100.95	-	101. 47 to 105.70	-	101. 04 to 104.61	-	95. 97 to 101. 57	-

(Here, L=Lab, P=Pass and + indicates positive)

Table 9. Result of analysis by tests (Cloxacillin 500mg capsule)

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	580.435	566.080	594.825	591.560	561.690	574.250	579.350	576.16	626.900	627.650
Assay (content)	88.156	94.450	104.666	106.048	102.179	101.508	104.829	102.738	104.217	104.196
Dissolution %	-	88. 23 to 90. 25	-	102. 01 to 104. 30	-	99. 6 to 104. 71	-	94. 53 to 102. 88	-	96. 54 to 106. 05

(Here, L=Lab, P=Pass and + indicates positive)

Table 10. Result of analysis by tests (Carbamazepine tablet)

(Carbamazepine 200mg tablet)			(Carbamazepine CR 200mg tablet)		
Parameters	**Lab 1**	**Lab 1**	**Lab 1**	**Lab 1**	**Lab 1**
Physical description	Pass	Pass	Pass	Pass	Pass
Identification	+ve	+ve	+ve	+ve	+ve
Average weight	300.525	445.425	303.300	463.235	321.800
Assay	98.269	100.574	96.259	100.738	104.322
Dissolution %	102.89-107.09	85.52-94.94			
Acid Medium	-	-	50.43-56.93	28.68-35.54	5.22-5.91
Buffer Medium	-	-	83.62 - 90.41	81.29 - 89.95	87.46 - 93.46

Table 11. Result of analysis of Metformin SR 1g (1000mg) tablet

Result of analysis by tests-General

Sample	A		B		C		D		E	
Parameter	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**	**L1**	**L2**
Physical description	P	P	P	P	P	P	P	P	P	P
Identification	+	+	+	+	+	+	+	+	+	+
Average weight	133 5.64	133 5.36	140 7.34	140 3.86	134 7.33	134 8.26	122 2.52	121 9.20	134 4.66	134 1.40
Assay (content)	100. 65%	97. 30%	99. 22%	96. 76%	94. 43%	95. 26%	92. 10%	95. 08%	101. 12%	97. 88%

Result of analysis by tests-Dissolution

Sample	A	B	C	D	E
Acid Medium	45.36 to 47.42	43.62 to 47.22	41.85 to 45.52	59.76 to 61.67	-
Buffer Medium	63.66 to 65.95	66.67 to 72.33	63.60 to 69.09	93.6 to 98.78	-
1st hour	41.9 to 42.27	29.36 to 30.11	31.08 to 31.86	37.90 to 38.52	30.33 to 33.94
3rd hour	65.08 to 66.63	55.27 to 56.85	55.67 to 59.85	65.61 to 66.62	51.93 to 59.65
6th hour					72.22to77.99
10th hour	92.23 to 94.74	90.67 to 92.52	89.01 to 94.69	92.19 to 93.26	87.38 to 3.16

(Here, L=Lab, P=Pass and + indicates positive)

whereas among 35 samples sent to Laboratory II, only 4 (11.43%) samples failed to meet the standard. Only the result of one sample matched with both laboratories. This indicates that there was variation in the selected two laboratories (Table 3).

On analysis of Cefixime tablet, two brands were reported to be non-compliant to the physical specification as per the report issued by Lab I but Lab II reported as compliant. There was little variation in the average weight of the tablet, which is also unlikely since the batch number was same. There was variation in the assay too. However, except one brand all were within the pharmacopoeial limit. Among two brands tested for disintegration of dispersible tablet; one had little higher value. Lab II passed the test result for dissolution for three brands (Table 4).

On analysis of Paracetamol tablet, brand D was reported not meeting the standard for dissolution test by Lab II. Though Lab II showed the pass result, literature suggests that the result below 85% is taken as substandard (Table 5).

Similarly, brand A of Ofloxacin tablet, was reported not meeting the standard for dissolution test by Lab II. There were variations in the results in both labs (Table 6).

On the analysis of Amlodipine tablet, it was found that all the tested parameters were within the limit hence comply with the standard. However, variation was seen in the results of two different laboratories (Table 7).

Sample A of Losartan tablet, did not comply with the standard as per result produced by Lab I on the dissolution parameters. There was variation in the result of other samples (Table 8).

Similarly, sample A of Cloxacillin capsule was found to be of substandard quality. There was no uniformity in the result produced by both laboratories (Table 9).

Carbamazepine tablet was analyzed by laboratory I only. Out of three samples, two samples of Carbamazepine CR (Controlled release) tablet did not comply with the specification for their release pattern while following Indian Pharmacopoeia (Table 10).

All the Metformin 1g (1000mg) SR (Sustained release)

tablets were found to be within the range for its content but sample A, B, C & D did not pass for their release pattern upon analysis from Lab-I. All five samples were found within the range as per the report produced by Lab-II. Lab-I claimed that the manufacturing specification were not provided so the samples were analyzed using Indian Pharmacopoeia (Table 11).

DISCUSSION

It was found that most of the products did not comply with the existing regulatory requirement on labeling system of medicine as per Regulation on Standards of Drugs, 2043 B.S.[6] While evaluating the pharmacopoeial standard of the samples, it was found that 42.5% brands did not mention about the pharmacopoeial standard they are following. There was no uniformity in mentioning the self-life. Similarly, large variation was seen on price of same generic drugs. A similar study carried out in Kathmandu valley found that out of 34 generics studied, 25 of them had more than 50% price variation.[7] Similarly, according to another study carried out in India, variation in prices of all the drugs ranged from 2.8% to 3406%.[8]

On laboratory analysis, it was found that, 40% samples failed to meet the standard among domestic companies and 28% among imported brands. Altogether 32.5% samples were found to be of substandard quality. Only the result of one sample matched with both laboratories. This also indicates that there was variation in the selected two laboratories.

The survey indicates that, substandard medicines are abundant in Nepalese market. Low income countries are particularly exposed to poor-quality medicines, including falsified products (manufactured without regulatory approval and with the criminal intent to mislead), sub-standard products and products degraded due to inappropriate storage/transport conditions.[9] Estimates suggest that counterfeit drugs can account for over 30% of all drugs in parts of Africa, Asia and the Middle East, in contrast to less than 1% in the US and Western Europe.[3]

According to Drug Bulletin of Nepal, out of 687 samples tested in National Medicine Laboratory, 14.4% samples were found substandard. But 41.9% (57 out of 136) samples failed to meet standard which were received from its branch offices and inspection division.[10] In 2008, a pilot study performed in two major cities of India, Delhi and Chennai to explore the extent of substandard and counterfeit drugs available in market, under which it was estimated that 12 and 5% samples from Delhi and Chennai, respectively, were of substandard quality.[11]

Drug's quality problem imparts wide range of impact that ranges from individual level to national level, health impact to systematic impact. The surveillance made by National Medicine Laboratory (NML) is inadequate. Major effort is made to assess the quality of drugs before the permission for marketing which does not reflect the situation of the marketed drugs.

CONCLUSIONS

The result of this survey indicates that, substandard medicines are abundant in Nepalese market. Moreover, there is weak regulation and no uniformity in similar pharmaceutical products. The study has suggested that, larger study is required to access the quality of pharmaceutical products in the Nepalese market with testing of products in more than two independent laboratories.

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