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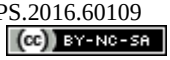
ISSN 2231-3354 

Evaluation of the Pharmaceutical Quality of Different Brands of Ranitidine Tablets Manufactured in Bangladesh: A Pharmaceutical and Public Health Prospective

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ABSTRACT

Drug counterfeiting and production of substandard drug is a global problem. Substandard or counterfeit drugs are threat for the effective treatment of diseases and highly worsen the quality of life of patients. This study was aimed to assess the pharmaceutical quality of ranitidine hydrochloride tablets manufactured in Bangladesh. Tablets were collected from different parts of Bangladesh and quality parameters were evaluated according to the United States Pharmacopoeia and the British Pharmacopoeial methods. The potency of tablets was measured spectrophotometrically. Weight variation and disintegration time were performed according to pharmaceutical monographs. Among 43 brands tested, 8 failed to comply with the USP specification (active ingredient: 90±10%) due to containing of less amount of ranitidine of which 6 brands were spurious and 2 were substandard in nature. Two brands did not comply with the specification for weight variation of tablets whereas all brands passed disintegration time test. The findings clearly demonstrate the production of substandard ranitidine tablets in Bangladesh. The drug control authority of Bangladesh should take effective steps to prevent the production of substandard drugs to secure public health.

INTRODUCTION

The problems of substandard/spurious/adulterated/ counterfeit drugs are now global issue. No country is safe from the threat of drugs counterfeiting, even the United States of America which has the strictest drug regulation has to face this problem. The World Health Organization (WHO) has listed the recent incidents of spurious/falsely-labelled/falsified/counterfeit (SFFC) drugs which include anticancer drug Avastin in USA in 2012, erectile dysfunction drugs Viagra and Cialis in United Kingdom (UK) in 2012, Truvada and Viread drugs for the treatment of HIV/AID in UK in 2011, Anti-HIV drug Zidolam-N in Kenya in 2011, Weight-loss medicine Allii in USA in 2010, Anti-diabetic traditional medicine in China in 2009 and Anti-malarial drug Metakelfin in Tanzania in 2009 (WHO, 2012). It is a matter of great regret that even the life-saving anticancer drugs are frequently counterfeiting and it represented the eighth most commonly counterfeited medicine all over the world in 2011 (Whalen and Faucon, 2012). Drugs counterfeiting is high in developing countries as they have very weakest policy, regulatory and enforcement systems for medicine (WHO, 2012; Siva, 2010). In average, it is traditionally accepted that about 10% of the drugs in the world are counterfeit (Cohen, 2010). According to the estimation of WHO, 25% of all medicines in least developed countries are substandard or counterfeit (WHO, 2010).

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The spurious/counterfeit/substandard drugs not only increase the financial burden of treatment but also increase the sufferings and endanger the quality of life and unnecessary morbidity and mortality of patients at any age (Shill and Das, 2011; Cockburn *et al.*, 2005). Like other developing countries, the history of the production of substandard/counterfeit medicines in Bangladesh is not new. During the last few decades, the practice of the production and trafficking of substandard/counterfeit/spurious drugs has been reduced but not eradicated (Shill and Das, 2011; NDP, 2005). A number of small- and mid-level companies are still involved with the production of substandard drugs and the pharmaceutical market of Bangladesh becomes flooded with smuggling of counterfeit/fake/unapproved drugs from India and China (Roy, 1994; Zahur, 2011; The New Nation, 2013).

Ranitidine is a histamine H_2-receptor antagonist which is effective for the treatment of gastric and peptic ulcers (Rang *et al.*, 2007; Yeomans *et al.*, 2006), uncomplicated gastroesophageal reflux disease (GERD) (Hoogerwerf and Paricha, 2006) and erosive esophagitis (McCarty-Dawson *et al*., 1996) by reducing gastric acidity and esophageal acid exposure (Varannes *at al.*, 1998). In Bangladesh, ranitidine, an over-the-counter (OTC) drug, is extensively consumed by the people through prescription or by self- medication. The food habit of people (too spicy, oily, and fried foods; open and dirty foods from the roadside) and food adulteration play significant role for the huge consumption of anti-ulcerants including ranitidine. The annual sales of ranitidine is US$ 31.41026 million which shares 20.30% of total sales of antiulcerant drugs (sales per year US$ 155.0769 million) (IMS, 2012). Ranitidine is currently manufactured and marketed by 108 pharmaceutical companies in Bangladesh (IMS, 2012; DGDA, 2014). Quality evaluation of marketed drugs is very important to know the actual status of medicines patients receiving, to create awareness among the people, to stop and take immediate action against the criminals by the law enforcing authority. The quality evaluation reports of marketed drugs tested by drug testing laboratories under the licensing authority have not usually been published; instead the authority keeps the report confidential for official purposes. Therefore, the actual status of the availability of substandard and counterfeit drugs in Bangladesh is unknown. The quality evaluation by the individual researcher or research organization, academic and research institutes followed by publication of the results in scientific journals and other print and electronic media may play significant role to create awareness to the people. As ranitidine is a widely consumed drug and no report has been published on the quality of ranitidine tablets in the last 10 years, we aimed to investigate the pharmaceutical quality of different brands of ranitidine tablets manufactured and marketed in Bangladesh.

MATERIALS AND METHODS

Collection of sample and reference standards

Different brands of ranitidine tablets were collected from retail and wholesale medicine shops located at different locations of Bangladesh including Dhaka, Gazipur, Rangpur, Tangail, etc. The samples were identified by the name of the company, manufacturing license number, DAR (Drug Administration Registration) no., Batch no., manufacturing date and expiry date. The samples were then coded as RANT-01 to RANT-43. The USP reference standard of ranitidine was collected as a donation from the Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh.

Measurement of weight variation of tablets

Twenty tablets from a batch were selected randomly and accurately weighed individually by an electrical weighing balance (Shimadzu Corporation, Japan; Type AY 220) and the average weight of tablets was calculated. Weight variation was then calculated by using the following formula:

$$\text{Weight variation (\%)} = \frac{(\text{Individual weight of tablets} - \text{Average weight of tablets})}{\text{Average weight of tablets}} \times 100$$

According to the United States Pharmacopoeia (USP) 2007, the weight variation range is ±7.5% if the average weight of tablets is 130-324 mg, whereas weight variation range is ± 5% for the average tablets weight > 324 mg. The tablets are said to comply with the specification if not more than 2 tablets out of 20 cross the weight variation range (USP, 2007).

Determination of disintegration time (DT) of tablets

Disintegration time of ranitidine (film-coated) tablets was determined according to the United States Pharmacopoeia (USP) (USP, 2007) by using USP tablet disintegration test apparatus-double unit (Scientica, India). Briefly, a single tablet was placed in each of the six tubes of the basket. The basket is immersed in a bath of distilled water at 37±2 °C in a 1L beaker. A disc was added into each tube, the apparatus was operated to record the time required to disintegrate all the tablets. According to the USP specification, the tablets pass the test if all of the 6 tablets have disintegrated within 30 minutes.

Preparation of sample solution

Twenty tablets were weighed and crushed into powder by mortar and pestle. One hundred and seventy (170) mg of tablet powder was taken into a 100-mL volumetric flask. Seventy five (75) mL of de-mineralized and distilled water was added into the flask and shook it well by a mechanical shaker for 20 minutes to dissolve the powder. Additional purified water was added to the flask to make the volume 100 mL and shook again. The solution was then filtered through Whitman filter paper. 2 mL of filtrated solution was transferred into another volumetric flask and purified water was added into the flask to make the final volume 100 mL.

Preparation of standard solution

Thirty four (34) mg of USP ranitidine hydrochloride reference standard (potency 99.1% as is basis) was taken in a 100-mL volumetric flask and 75 mL of de-mineralized and distilled

water was added to it. Shaking the flask by a mechanical shaker for 20 minutes, purified water was again added to the volumetric flask to make the final volume 100 mL and mixed it homogenously. The solution was then filtrated through Whitman filter paper. Five (5) mL of filtrated solution was diluted with de-mineralized water to make the final volume 100 mL.

Measurement of absorbance, potency and amount of active ingredient in the tablets

The absorbance of standard and sample solutions were measured at 314 nm in a UV-VIS spectrophotometer with UV-probes 2.21 (Shimadzu Corporation, Japan) using purified water as blank. Each sample was run in duplicate and average result was considered. The amount of ranitidine in each tablet or its potency was calculated by using the following formula:

$$\text{Quantity of ranitidine/tablet} = \frac{A_{sam}}{A_{std}} x \frac{W_{std} \times 5}{100 \times 100} + \frac{100 \times 100}{W_{sam} \times 2} \times Ps \times Ave.wt.of\ tablet \times 0.896$$

Where,

A_{sam} = Absorbance of sample preparation
A_{sam} = Absorbance of Sample solution
A_{std} = Absorbance of standard preparation
W_{sam} = Weight of sample as powder/granules (mg)
W_{std} = Weight of reference standard (mg)

Ave. wt. of tablet = Average weight of intact tablets
0.896 = Conversion factor of ranitidine HCl to ranitidine
Ps = Potency of reference standard in % as is basis
All the experiments were conducted in the Biopharmaceutics laboratory of the department of Pharmacy in Primeasia University, Banani, Dhaka, Bangladesh.

RESULTS

Weight variation of tablets

We observed in Table 1 that 2 brands of tablets (RANT-17 and RANT-20) did not comply with the weight variation range according to its official pharmacopoeia (USP specification: weight variation range ± 7.5% if the average weight of tablets is 130-324 mg, ± 5% if average weight of tablets is >324 mg). The weight variation in tablets may result from the improper mixing of the active ingredient(s) with excipients or errors in the flow properties of the granules or filling-error in the dies during compression of tablets.

This is also an indicator of poor or absence of the practice of the guidelines of good manufacturing practice (GMP) by the respective pharmaceutical companies.

Disintegration time of tablets

The disintegration time (DT) of ranitidine tablets was determined according to the USP as described in the Materials and Methods section. It was observed in table 2 that all the tested brands complied with the USP specification (all the 6 tested tablets should disintegrate within 30 minutes). Ranitidine is readily soluble in water. Therefore, it was generally expected that ranitidine tablets would meet its specification for disintegration time and we found that in our study.

Quantity and potency of ranitidine in marketed brands of ranitidine tablets

According to the USP specification, the potency of ranitidine as active ingredient in tablet should be 100 ±10%. We observed that 8 brands (RANT-10, RANT-14, RANT-18, RANT-20, RANT-31, RANT-32, RANT-38 and RANT-43) out of 43 did not comply with the USP specification due to containing of lower amount of ranitidine (active chemical) in the tablets (Table 3 and Figure 1).

The above brands contained ranitidine 87.31, 82.58, 2.06, 43.01, 54.77, 42.40, 15.82 and 29.98%, respectively. WHO defines substandard drugs as "Each pharmaceutical product that a manufacturer produces has to comply with quality standards and specifications at release and throughout the product shelf-life required by the territory of use. Normally, these standards and specifications are reviewed, assessed and approved by the applicable National Medicines Regulatory Authority before the product is authorized for marketing. Substandard medicines are pharmaceutical products that do not meet its quality standards and specifications" (WHO, 2010).

Therefore, we can clearly state that the above-mentioned 8 brands, non-complied with the USP specification, were "substandard".

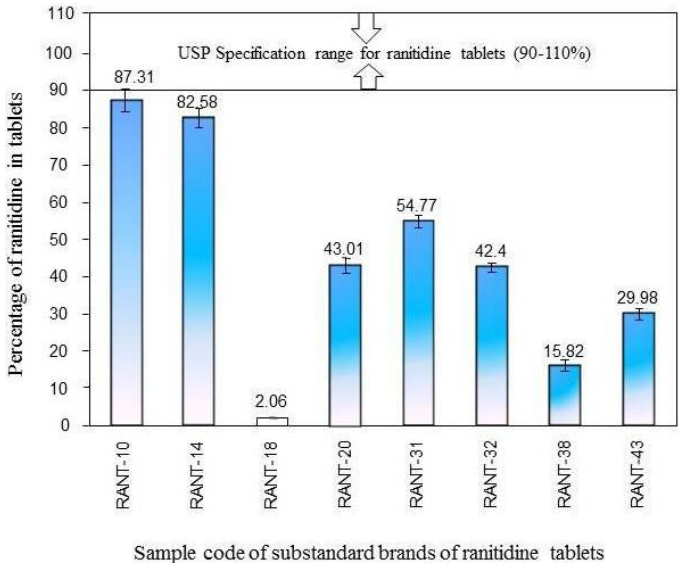

Fig. 1: The potency of substandard brands of ranitidine tablets marketed in Bangladesh. The amount of ranitidine in film-coated tablets collected from different medicine shops in Bangladesh were determined by spectrophotometric analysis. The results are expressed as % of the content of ranitidine in tablets and compared with the USP specification for containing of active ingredient in the product (USP specification: ranitidine content should be 90-100%). The data are expressed as the means of ± S.D. of three different observations.

DISCUSSION

The present study evaluated the pharmaceutical quality of 43 brands of ranitidine tablets manufactured and marketed in Bangladesh by measuring the quantity of active ingredient (ranitidine), weight variation and disintegration test of each tablet brand. We observed that 2 brands failed to comply with the specification of weight variation of tablets (Table 1) and 8 brands were substandard due to containing less amount of ranitidine in the product (Table 3 and Figure 1).

Table 1: Weight variation test result of different brands of ranitidine tablets.

Sample code	No. of tablets taken	Average weight of tablets (mg)	USP Specification	No. of tablets within USP specification	No. of tablets out of USP specification
RANT-01	20	317.10	Weight variation range ± 7.5% (average weight of tablets 130-324 mg) Weight variation range ± 5% (average weight of tablets >324 mg)	19	**1**
RANT-02	20	298.95		20	0
RANT-03	20	254.20		20	0
RANT-04	20	269.00		20	0
RANT-05	20	354.65		20	0
RANT-06	20	257.30		20	0
RANT-07	20	349.15		20	0
RANT-08	20	248.55		20	0
RANT-09	20	256.70		20	0
RANT-10	20	366.05		19	**1**
RANT-11	20	246.55		20	0
RANT-12	20	324.95		20	0
RANT-13	20	302.60		20	0
RANT-14	20	258.75		20	0
RANT-15	20	308.05		20	0
RANT-16	20	259.85		20	0
RANT-17	20	315.40		15	**5**
RANT-18	20	246.25		20	0
RANT-19	20	350.50		20	0
RANT-20	20	229.10		14	**6**
RANT-21	20	246.90		20	0
RANT-22	20	297.40		20	0
RANT-23	20	274.80		20	0
RANT-24	20	274.80		20	0
RANT-25	20	239.90		20	0
RANT-26	20	290.70		18	**2**
RANT-27	20	260.00		20	0
RANT-28	20	313.50		20	0
RANT-29	20	253.00		20	0
RANT-30	20	280.17		20	0
RANT-31	20	322.83		20	0
RANT-32	20	234.33		20	0
RANT-33	20	466.80		20	0
RANT-34	20	224.30		20	0
RANT-35	20	239.80		20	0
RANT-36	20	264.17		20	0
RANT-37	20	349.00		20	0
RANT-38	20	213.50		20	0
RANT-39	20	324.00		20	0
RANT-40	20	215.60		20	0
RANT-41	20	276.60		20	0
RANT-42	20	239.90		20	0
RANT-43	20	207.00		18	**2**

Weight variation may result in the variation of pharmacological effect of drugs, the higher tablet weight with high amount of active ingredient may contribute to the toxicity and lower weight tablet having less active ingredient may not elicit the therapeutic response to the patients. Among 8 defective brands, the amounts of active ingredient in 2 brands (RANT-10 and RANT-14) were just below the lower limit of the specification (87.31 and 82.58%, respectively) and, therefore, they may be classified as substandard brands. Six tablet brands (RANT-18, RANT-20, RANT-31, RANT-32, RANT-38 and RANT-43) were spurious due to containing of a negligible amount of active ingredient (2.06, 43.01, 54.77, 42.40, 15.82 and 29.98%, respectively). Substandard medicines resulted from a small deviation of drug quality from the standard specification may result from poor formulation and preparation techniques, weighing errors and incorrect storage of ingredients but substantial quantitative variation of active ingredient is considered as intentionally-created problem.

Table 2: Disintegration time (DT) test result of different brands of ranitidine tablets.

Sample code	Average DT (min)	USP Specification
RANT-01	10	Tablets should disintegrate within 30 minutes in water medium at 37±2 °C temperature
RANT-02	13	
RANT-03	11	
RANT-04	14	
RANT-05	16	
RANT-06	9	
RANT-07	17	
RANT-08	13	
RANT-09	10	
RANT-10	21	
RANT-11	13	
RANT-12	11	
RANT-13	12	
RANT-14	20	
RANT-15	14	
RANT-16	13	
RANT-17	11	
RANT-18	24	
RANT-19	15	
RANT-20	23	
RANT-21	13	
RANT-22	12	
RANT-23	17	
RANT-24	15	
RANT-25	12	
RANT-26	18	
RANT-27	16	
RANT-28	14	
RANT-29	13	
RANT-30	17	
RANT-31	22	
RANT-32	20	
RANT-33	15	
RANT-34	13	
RANT-35	12	
RANT-36	16	
RANT-37	11	
RANT-38	9	
RANT-39	11	
RANT-40	12	
RANT-41	16	
RANT-42	13	
RANT-43	19	

The observed low-potency of ranitidine tablets in our study might be due to the addition of less amount of active ingredient deliberately at the time of manufacturing. Similar observations were reported previous by several investigators. Sarket *et al.* (2006) analyzed the quality of 15 brands of

Ciprofloxacin tablets marketed in Bangladesh (13 local and 2 foreign brands). Seven brands (6 local and 1 foreign brands) were substandard due to containing of lower level of active ingredient (Ciprofloxacin HCl) (USP specification: 90-110%) (Sarker *et al.*, 2006).

Table 3: Result of potency of different brands of ranitidine tablets obtained by Spectrophotometric analysis.

Sample code	Mfg. date	Expiry date	Claimed value of Ranitidine per tablet (mg)	Observed value of Ranitidine per tablet (average value in mg)	Potency (% w/w)	Comment
RANT-01	May 13	May 15	150	160.75	107.17	CS
RANT-02	April 13	Oct 15	150	148.97	99.32	CS
RANT-03	May 12	May 14	150	145.68	97.12	CS
RANT-04	May 12	May 15	150	140.44	93.63	CS
RANT-05	Jan 13	Jan 15	150	143.63	95.75	CS
RANT-06	Dec 12	Dec 14	150	141.86	94.57	CS
RANT-07	April 13	April 16	150	143.30	95.53	CS
RANT-08	Mar 13	Feb 16	150	142.06	94.70	CS
RANT-09	May 13	May 15	150	141.43	94.28	CS
RANT-10	Mar 13	Mar 15	150	130.96	87.31	NCS
RANT-11	May 13	May 15	150	142.75	95.17	CS
RANT-12	Mar 13	Mar 15	150	141.99	94.66	CS
RANT-13	Aug 12	Aug 15	150	143.02	95.35	CS
RANT-14	July 13	July 15	150	123.87	82.58	NCS
RANT-15	Feb 13	Jan 15	150	157.38	104.92	CS
RANT-16	Mar 13	Mar 15	150	140.01	93.34	CS
RANT-17	May 13	April 16	150	152.94	101.96	CS
RANT-18	Sep 12	Mar 15	150	3.09	2.06	NCS
RANT-19	Nov 13	Nov 14	150	138.52	92.35	
RANT-20	Oct 12	Oct 15	150	64.51	43.01	NCS
RANT-21	Nov 12	Oct 14	150	155.90	103.94	CS
RANT-22	Apr 12	Oct 14	150	154.29	102.86	CS
RANT-23	Aug 12	Aug 14	150	145.85	97.23	CS
RANT-24	Dec 12	Dec 13	150	154.59	103.06	CS
RANT-25	April 11	April 14	150	150.73	100.49	CS
RANT-26	Sep 12	Sep 14	150	144.00	96.00	CS
RANT-27	Dec 12	Dec 15	150	139.88	93.25	CS
RANT-28	Dec 12	Dec 14	150	149.33	99.56	CS
RANT-29	May 13	Nov 14	150	156.74	104.50	CS
RANT-30	Jul 13	Jul 15	150	147.23	98.15	CS
RANT-31	May 13	Apr 16	150	82.16	54.77	NCS
RANT-32	Apr 13	Apr 15	150	63.59	42.40	NCS
RANT-33	May 13	May 16	150	150.61	100.41	CS
RANT-34	Jun 13	Jun 15	150	149.17	99.45	CS
RANT-35	Aug 12	Jul 14	150	150.85	100.56	CS
RANT-36	May 13	May 15	150	156.10	104.07	CS
RANT-37	Jun 13	Jun 15	150	163.74	109.16	CS
RANT-38	Jun 12	Jun 14	150	23.73	15.82	NCS
RANT-39	Jul 13	Jul 15	150	153.20	102.14	CS
RANT-40	Nov 12	Oct 14	150	138.01	92.01	CS
RANT-41	Jul 12	Jul 14	150	146.29	97.53	CS
RANT-42	May 12	May 14	150	137.48	91.66	CS
RANT-43	Jun 13	Jun 15	150	44.97	29.98	NCS

USP specification: The potency of active ingredients should be 100 ±10%
CS = Complied with USP specification, NCS = Not Complied with USP specification

Several other investigators reported the existence of substandard drugs marketed in Bangladesh, such as, metronidazole tablets and suspensions (Ahmed *et al.*, 2003), Nifedipine tablets (Rafiquzzaman and Das, 2001) Paracetamol tablets, suspensions, syrups and elixir (Roy *et al.*, 1993), and Amoxicillin trihydrate dry powder for suspension (Sultana *et al.*, 2003).

In a study of WHO on 325 substandard drug products, it was found that 60% of the products contained no active ingredients, 17% and 16% had incorrect amount and incorrect ingredients, respectively (Rago, 2002). This means the major part of substandard drugs is due to containing less amount or no active ingredients, which is also similar with this finding.

Substandard and counterfeit medicines may cause critical clinical and public health problems because lack of active drug may misguide the effective treatment or the presence of unwanted toxic chemicals may lead to death of the patients (Caudron *et al.*, 2008). For example, paracetamol syrup, adulterated with diethylene glycol in the formulation, manufactured by small-scale pharmaceutical companies killed 339 children in 1992 and 27 children in 2009 in Bangladesh (The Guandian, 2009; The Daily Star, 2009; Hanif *et al.*, 2005). Besides, under dosing of drugs may cause drug-resistance (Caudron *et al.*, 2008; Taylor et al., 2001). Patients may lose faith on the physicians, pharmacists and modern medicines. It hampers pharmaceutical international business, economic implications, pharmaceutical manufacturers who produce quality drugs, the government losses its revenue.

Medicines should be manufactured following the strict guidelines of good manufacturing practice (GMP) (WHO, 1996). Unfortunately, most of the medium-and small-scale pharmaceutical companies in Bangladesh do not strictly follow any GMP guidelines in the manufacturing and quality control of medicine due to lack of technical, financial and human resources required or because of their poor attention to the necessity of it. The main reasons of the availability of substandard drugs in Bangladesh include the production of medicines providing lower amounts of active ingredients deliberately instead of technical error, poor controlling activity and ability of licensing authority (DGDA) on the production, marketing, distribution and dispensing of medicines.

Corruption and conflict of interest among the people of licensing authority who are mostly managed with bribe, lack of enforcement and penalty with existing laws against criminals, too many wholesale and retail outlets, and under evaluation of the value of human life in the country can also be mentioned.

It is noteworthy that the medicines of some suspended companies are still available in the market. We also analyzed few of such brands which were found to be spurious in nature containing negligible amount of active ingredient. Hundreds of people in the world die silently each year (Jha *et al.*, 2010) due to the consumption of substandard and counterfeit drugs as the immediate identification and protection of those drugs have not yet been possible, and its actual estimation is also not known.

CONCLUSION

The present investigation clearly demonstrated the evidence of the production and marketing of substandard ranitidine tablets in Bangladesh. The question is why substandard drugs are

available in Bangladesh and who are responsible for this? Several factors are associated which are directly or indirectly responsible for or promote or shelter the business of substandard and counterfeit drugs. First blame goes to the accused pharmaceutical companies. Few small pharmaceutical companies who have purchased manufacturing license only for economic benefit by cheating the people with substandard/counterfeit medicines. Such companies do not have minimum drug manufacturing hygienic environment in the factory, let alone follow the cGMP guidelines. They wholesale their substandard medicines with substantial lower price compared to the usual price of the drug. These drugs are mainly consumed in remote areas through unregistered and unlicensed pharmacy shops and promoted by quack prescribers who mainly practice in the villages.

Who is next? Qualified experts involved with the manufacturing of the drugs cannot avoid their liabilities. The weakness of drug control authority having less manpower, corruption and reluctant in imposing penalty or harder punishment against criminals has to bear the large share of the liabilities. Ministry of health, pharmacies all over the country, and physicians may also play significant role against substandard and counterfeit drugs.

The present report is a message to the Drug Control Authority of Bangladesh (DGDA) about the quality of marketed ranitidine tablets produced in Bangladesh and to the common people for their awareness. The government of Bangladesh should immediately establish a well-equipped good laboratory with sufficient skilled and technical staffs to evaluate the quality of marketed drugs manufactured locally and imported or donated from abroad as there is no well-equipped up-to-date drug testing laboratory in Bangladesh.

The law and enforcing authority should amend the existing law to impose stronger punishment such as, life-time custody or death penalty for medicine crime and should ascertain the implementation of that law. The government should consider scientific reports with importance and should take immediate actions against the accused.

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