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Original Article

QUALITY AND AFFORDABILITY OF AMOXICILLIN GENERIC PRODUCTS: A PATIENT CONCERN

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ABSTRACT

Objective: Antibiotics save millions of lives from infectious diseases worldwide. Failing treatment, serious adverse effects, and antimicrobial resistance are constantly reported mainly from developing nations due to lack of quality of antibiotics medicines. In India quality of medicines remains a major regulatory challenge and patients concern. Thus, a pilot study to explore the quality of generic amoxicillin products and associated price along with their burden on patients was evaluated.

Methods: 46 amoxicillin trihydrate generic products with the label claim of 250 mg amoxicillin were procured from open market of Northern India without prescription. Identification and quantitative evaluations of these generic products were estimated using Indian Pharmacopoeia (IP) 2010 recommended High-Performance Liquid Chromatography (HPLC) method. And assay value was compared with the maximum retail price per unit dosage. Affordability was estimated in general for the population who daily live on less than Indian rupees Rs. 144 and `88.6.

Results: Out of 46 products, 28.26% were found to be out of IP specification, including 13.04% products which were of substandard quality. Fishers' exact test with p-value 0.87 showed products quality gaps were irrespective of their price. Ceiling price of Rs. 3.04 per unit dosage pose a high burden on the patients who are on amoxicillin treatment.

Conclusion: Situation demands the evidence of safety before approval and thereafter too. However, the situation may become worst if the price and quality could not be controlled. Thus Indian drug regulatory bodies need to be entreated to counter these critical issues.

Keywords: Amoxicillin, Generic, Substandard, Drug Quality, Affordability.

INTRODUCTION

"The dose makes the poison" as stipulated by Paracelsus. Consequently, the presence of active ingredient and its compliance to the pharmacopeia specifications considered as the most obvious paradigm for certifying the quality of drugs formulations [1]. From the majority of the developing countries; there are several reports of failing treatments, development of antimicrobial resistance and serious adverse drug reactions including death [2, 3]. In all probability, this is because of meager medications like spurious/ falsely-labeled/falsified/counterfeit (SFFC) medicines [2]. According to World Health Organization, "SFFC medicines include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient or too much active ingredient, or with fake packaging" [4]. Broadly poor quality medicines are divided into two categories viz. substandard and counterfeit [5]. From India, 12-25% of supplied medicines globally may be contaminated, substandard and counterfeit [6]. On one side the number of poor quality medicine decreasing year by year [7] and on another side without scientific evidence Indian media consider 30-40% availability of the poor quality drug in domestic market [8]. When a product is manufactured it is being utilized by the patients; and availability of good quality medicines strengthen the chances of better treatment for the individual patient which advances improved results for general well being by and large [9]. In developing countries this poor quality situation stresses the patients without the known extent [5]. Likely in developing nations; medicines account for 25-70% of total heath care expenses [10]. Thereupon in the case of India where 58.01% and 21.2% of the population has daily living cost of less than Rs. 144 and Rs. 88.6 respectively [11] then how could people afford the high price of medicines in addition to survival. Therefore Indian Government always emphasizes and promotes the affordable generic medicines for prescription and utilization [12]. The futile increase in the price of medicines is being wrangled on in the financial health care and public health domain, as it usually results in a reduced access of essential drugs [13]. Therefore to counteract the issue of spurious and substandard quality medicine in India there is an urgent demand for more research or routine analysis to document the magnitude of the problem.

Antibiotics are the life-saving medicines [14], thus, an ideal antibiotic therapy is a prerequisite to treat the systemic spread of the infection and to prevent their complications [15]. Prescribing antibiotics irrationally is a general trend in India [16]. However, antibiotic medicines are considered as the most poor quality class or counterfeit worldwide and observed as the major threat for patients especially children [17]. Penicillin antibiotics like amoxicillin is largely prescribed drugs [18] and it is used as broad spectrum antibiotics which is considered as susceptible to the β lactamase-negative strains and species like *Streptococcus pneumonia, Streptococcus species* (α-and β-hemolytic strains only) and *Haemophilus influenza* etc. [19]. In recent years no study has been done overall or for any individual drug to explore the situation leaving behind no clear documentation on the current extent of the problem. Hence, the purpose of this pilot study was to explore quality and affordability of amoxicillin products; and scope in creating awareness to public and attention to regulatory bodies to evaluate such products.

MATERIALS AND METHODS

Chemicals and reagents

Amoxicillin, trihydrate reference standard, was directly purchased from Sigma-Aldrich. HPLC grade acetonitrile (Lichrosolv), potassium dihydrogen phosphate (LiChropur), potassium hydroxide GR grade were procured from Merck (India). The polytetrafluoroethylene (PTFE) filter of 0.45 µm and nylon filter of 0.20 µm pore size from Millipore system (Millipore Inc., USA) was used throughout the evaluation.

Instrument

A HPLC system (Waters, Milford, MA, USA) equipped with Alliance 2695 separations module with photodiode array detector was used

in this study. A reverse phase octadecylsilane bonded C-18 (250 mm×46 mm, 5 µm) column (Waters) was employed throughout the analysis. All samples for evaluation were weighed on high sensitive analytical balance TB-215D (Denver Instrument, Germany). Chromatograms were recorded and processed using Empower Pro Software (Waters).

Generic product collection

All amoxicillin generic products used in this study were purchased without prescription from the open market from different location of Northern India. In total 46 generic products were collected which comprise 43 different products of amoxicillin trihydrate (AMOX) capsules and two tablets having 250 mg dose. Among them, one capsule product was collected of two batches thus in total 46 products were collected.

Standard and sample preparation

For the identification and quantitative evaluation of amoxicillin in the finished pharmaceutical product, HPLC being highly sensitive and pharmacopeial established method was preferred. Thus in accordance to Indian Pharmacopoeia (IP) [20], 0.02M monobasic potassium phosphate buffer was prepared as a solvent mixture and adjusted to pH 5.0±0.05 using 4.5% potassium hydroxide (w/v) and finally filtered through 0.20 µm membrane nylon filter and degassed in an ultrasonic bath. An isocratic mobile phase of acetonitrile and solvent mixture in 4:96 v/v was used with a flow rate of 1.5 ml/min. Each analytical run was carried for 10 min with 10 µl injection volume, and data was acquired at 230 nm and processed. The solvent mixture was used as diluent in the preparation of analytical sample solutions. AMOX working reference standard (RS) solution of 1.2 mg/ml concentration was used as system suitability solution.

Test samples were prepared by mixing 250 mg equivalent to amoxicillin form content of ten capsules or tablets in diluent to prepare 1.2 mg/ml concentration. Samples were sonicated for 10 min and filtered using 0.45 µm PTFE. Each sample was prepared in triplicate and also injected in triplicate to ensure the precise assay result. Against the mean area of five injections of AMOX RS; assay of amoxicillin in the test sample was determined on percent label claim of the active pharmaceutical ingredient present in individual capsule or tablet. According to IP for ten capsules the assay requires to be within 89.5–110.6% of the label claim and for ten tablets assay requires to be within 89.4-110.8% of the label claim [21]. While according to the Central Drug Standard Control Organization (CDSCO) a product is said to be substandard quality only if assay found 5% below the IP limit [22].

RESULTS AND DISCUSSION

Our aim was not to expose any particular product or defame any company. Hence, product identity is not revealed. However the challenges involved in the collection and evaluation of substandard drugs in the market cannot be neglected; as all products were procured from the open market without prescription.

Due to listed in National List of Essential Medicines (NLEM) [23], its extensive production [24] and extensive utilization [25] AMOX was selected. The analytical techniques chosen need to be specific to every product; thus, amoxicillin capsule monograph was selected from IP 2010. However, the presence of excipients and another evaluation test like impurity profiling can determine the complete quality of the product.

In evaluating the generic product, it is necessary to face up the interaction of complex matrix of the product. Thus, an assumed placebo was prepared by blending microcrystalline cellulose, magnesium stearate, croscarmellose, sodium and colloidal silicon dioxide. And this placebo was spiked with the reference standard to confirm the interference. System suitability was demonstrated to be appropriate for routine analysis purpose, thus, AMOX RS peak was confirmed by theoretical plate count, tailing factor and maximum absorption at 230 nm wavelength. Peak purity was also checked with the higher purity threshold than purity angle. The observed retention time and peak area with system suitability are shown in fig. 1.

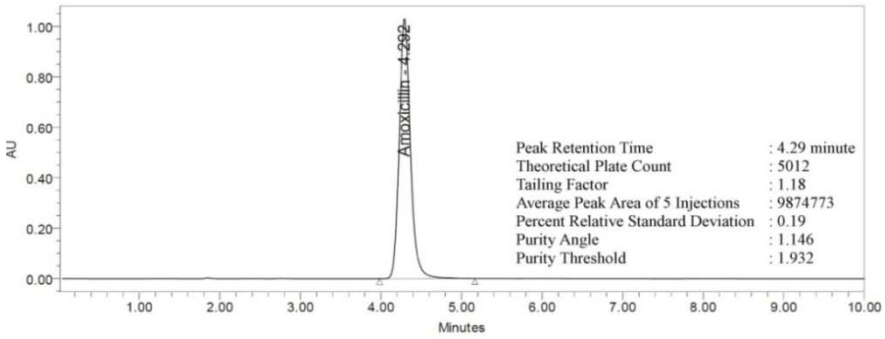

Fig. 1: Full-scale typical chromatogram of amoxicillin trihydrate reference standard

In order to compare the quality of AMOX capsules or tablets, we identified its presence and calculated the amoxicillin quantity with respect to label claim. Out of 46 products the percentage content of 13 products were not matched with the label claim. As shown in table 1, 13 products were failed to follow the IP specification. And among them, six products were failed according to the specified limit by CDSCO. Thus, 28.26% products were out of IP specification, and 13.04% products were of substandard quality, high demand for antibiotics which are often prescribed in developing countries and is a very profitable market for the manufacturers who deliberately manufactured such products.

India has to ensure the continuity of the generic competition in order to respect, protect and fulfill the right to health of its people [26]. Thus additionally, we raise quibble over the consideration of price to be one of the controlling parameters influencing the access of medicines in India. Under article 21 of the Indian constitution; the right to health includes availability and accessibility to affordable drugs. While substandard product such as Amox Rs.14 and out of pharmacopeia specification products like Amox-05, Amox-21, Amox-09 and Amox-41 were available in the market at high prices, range between `5.43-6.50 as shown in fig. 2. However, recently National Pharmaceutical Pricing Authority (NPPA) of India has revised the price of several essential medicines. Current revised ceiling price of amoxicillin 250 mg capsule is `3.04 [27]. For instance, in the treatment of helicobacter pylori infection, one gram orally two to three times a day administration [28] of AMOX capsule only; would cost 16.88-25.33% and 27.63-41.45% of total daily living cost of 58.01% and 21.25% Indian population respectively out of their daily living cost and this burden will continue for 14 d till completion of treatment. Other medicine in combination would cost extra. In the same way for mild pneumonia to adult 500 mg three times a day administration [28] of AMOX capsule only; would cost 12.66% and 20.58% to the 58.01% and 21.25% population respectively out of their daily living cost and this burden will continue from seven to ten days. It is an alarming state where people are suffering, and the burdens of health care cost are increasing continuously. And on above all when treatment fails; situation become grievous with no treatment benefits and high financial burden. In addition, such quality also has a big contribution in antimicrobial resistance and unfortunately for one decade there is no antibiotic in the pipeline of the invention.

Table 1: Amoxicillin trihydrate generic products assay and price

Sample code	Assay I (%) (Mean of triplicate injections)	Assay II (%) (Mean of triplicate injections)	Assay III (%) (Mean of triplicate injections)	Mean Assay (%)	Standard Deviation (%)	Relative Standard Deviation (%)	Maximum Retail Price per Capsule or Tablet Rs.
AMOX-01A	98.80	99.37	101.36	99.84	1.34	1.34	5.90
AMOX-01B	99.69	101.30	100.82	100.60	0.83	0.83	2.90
AMOX-02	90.49	89.58	89.21	89.76	0.66	0.74	4.80
AMOX-03	95.75	93.59	93.26	94.20	1.35	1.43	5.07
AMOX-04	92.55	93.56	94.05	93.39	0.76	0.81	3.50
AMOX-05	85.54	86.66	86.22	86.14	0.56	0.65	5.75
AMOX-06	85.66	85.32	85.30	85.43	0.20	0.23	3.25
AMOX-07	89.06	90.39	89.47	89.64	0.68	0.76	2.90
AMOX-08	95.72	95.00	94.63	95.12	0.55	0.58	3.96
AMOX-09	88.95	90.11	89.17	89.41	0.62	0.69	5.50
AMOX-10	100.22	100.53	100.71	100.49	0.25	0.25	3.00
AMOX-11	89.86	91.48	90.96	90.77	0.83	0.91	3.60
AMOX-12	90.57	91.31	91.30	91.06	0.42	0.46	3.40
AMOX-13	93.05	89.72	90.98	91.25	1.68	1.84	1.50
AMOX-14	81.92	83.72	83.47	83.04	0.98	1.18	6.50
AMOX-15	22.41	22.40	22.17	22.33	0.14	0.63	4.50
AMOX-16	92.23	92.34	92.10	92.22	0.12	0.13	2.90
AMOX-17	97.89	99.18	99.08	98.72	0.72	0.73	4.70
AMOX-18	99.08	99.65	99.79	99.51	0.38	0.38	3.90
AMOX-19	90.12	91.48	90.53	90.71	0.70	0.77	3.80
AMOX-20	100.21	99.88	101.08	100.39	0.62	0.62	4.70
AMOX-21	87.08	89.12	88.77	88.32	1.09	1.23	5.50
AMOX-22	89.13	90.83	90.58	90.18	0.92	1.02	4.10
AMOX-23	94.52	95.89	95.16	95.19	0.69	0.72	4.10
AMOX-24	93.52	94.27	94.39	94.06	0.47	0.50	5.75
AMOX-25	90.47	90.72	91.20	90.80	0.37	0.41	3.20
AMOX-26	95.39	95.62	96.15	95.72	0.39	0.41	5.25
AMOX-27	96.14	96.00	95.86	96.00	0.14	0.15	1.40
AMOX-28	91.23	91.98	90.00	91.07	1.00	1.10	5.63
AMOX-29	91.09	91.52	91.22	91.28	0.22	0.24	6.50
AMOX-30	83.21	84.46	83.71	83.79	0.63	0.75	3.95
AMOX-31	91.88	91.01	91.94	91.61	0.52	0.57	3.60
AMOX-32	92.24	93.67	93.64	93.18	0.82	0.88	3.83
AMOX-33	86.89	86.60	86.76	86.75	0.15	0.17	3.25
AMOX-34	91.52	92.92	92.82	92.42	0.78	0.84	4.07
AMOX-35	83.26	85.36	84.09	84.24	1.06	1.26	3.50
AMOX-36	89.77	90.23	90.44	90.15	0.34	0.38	6.20
AMOX-37	87.26	88.99	88.87	88.37	0.97	1.10	5.00
AMOX-38	91.20	89.28	90.39	90.29	0.96	1.06	3.40
AMOX-39	27.94	27.61	27.54	27.70	0.21	0.76	3.20
AMOX-40*	105.92	106.12	105.76	105.93	0.18	0.17	4.00
AMOX-41*	86.95	84.85	85.55	85.78	1.07	1.25	5.43
AMOX-42	90.75	93.28	91.82	91.95	1.27	1.38	5.87
AMOX-43	79.95	81.31	81.24	80.83	0.77	0.95	2.90
AMOX-44	90.87	91.80	91.46	91.38	0.47	0.51	2.50
AMOX-45	98.80	98.45	98.55	98.60	0.18	0.18	3.97

*Tablets, Total number of samples N=46

Patient demand affordable and quality generic products like Amox-13 and Amox-27, which are manufactured by the companies who may have no motive to more profit but are more patient-centric. Raising competition with expanding the drug production ultimately lowers the price, improve the access and verify public benefits.

Fisher's exact test with two-tailed p-value 0.87 showed no significant difference between assay and price of the evaluated products. Based on Indian pharmaceutical generic scope and affordability; Indian Government promotes the generic medicines and recommend to prescribe them by the medical practitioners; but the practitioners must be aware of the sources, quality and all possible benefits and risk of the prescribed medication so as to educate the patients. Moreover, pharmacist's involvement in switching the branded medicines to generic medicines may be a good intention only if pharmacists know the quality of medicines besides the trade brokerage.

Another concern is selling the 'Schedule H' drug without prescription. As products were purchased directly from the retailer and wholesalers, and they didn't ask for any prescription or the buyer identity. Maybe they consider medicines as a commodity. Thus, in short Drug and Cosmetic Act 1940 and Rules 1945 are improperly followed. Therefore good pharmacy practice guidelines [29] has to be followed for the safety of patients. Inversely due to patient's lack of knowledge, unawareness of adverse effects and seller ignorance during trade may increase morbidity and mortality.

It can be concluded that several products available in the market are of substandard quality. The high extremity of this situation, as shown by the results is not significantly related to low cost only as show in table 2. Precisely there is no single step to restrain the issue of quality medicine, however; the interventions adopted by regulatory authorities must be more practicable and durable to uproot the cause of the problem. As a part of interventions, education and providing information to the public may enhance awareness. Other feasible strategies have been increasing the number of testing laboratories, and use a fast and efficient method like near infrared spectroscopy or capillary electrophoresis for monitoring the poor quality medicines trade.

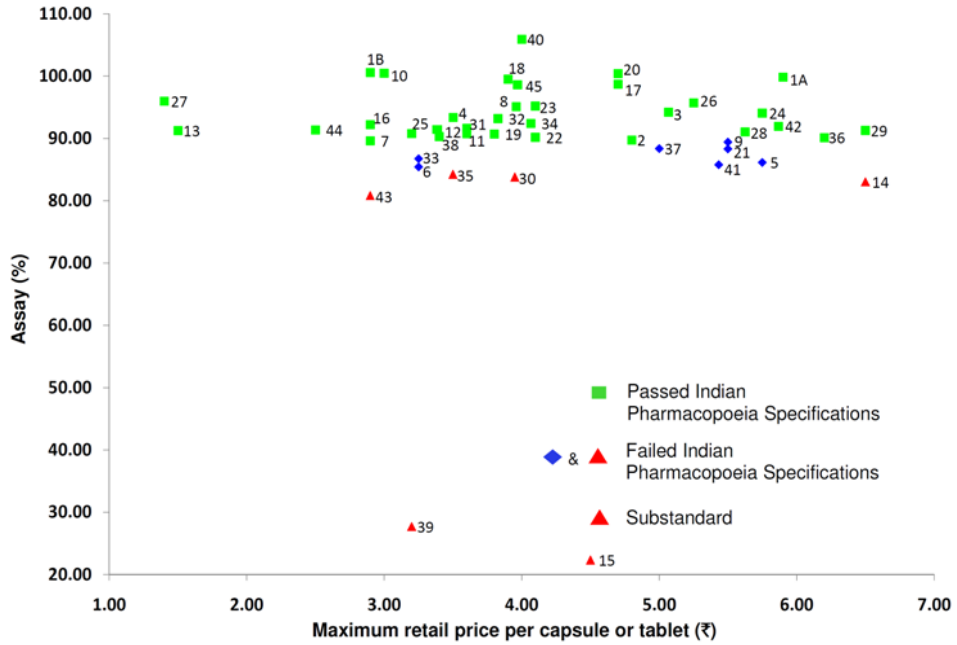

Fig. 2: Maximum retail price versus assay plot showing generic amoxicillin products (N=46) quality

Table 2: Price wise distribution of passed and failed AMOX products

Maximum retail price per capsule/tablet Rs.	No. of products failed	No. of products passed
1-2	-	2
>2-3	1	5
>3-4	6	11
>4-5	2	5
>5-6	4	6
>6-7	1	2

CONCLUSION

When people in developing countries don't have access to quality medicine at an affordable price, improving regulatory system should be the first challenge that has to take care off. As many substandard products are available in the market and ready to use by the patients for their treatment. These results would create awareness among the public and drug regulatory authorities about a brief extent of the problem. The patient can compromise with price but patients' health cannot be compromised with poor quality. Therefore, situation demands the evidence of safety before approval and thereafter too. Improved quality of antibiotics and inclusion of additional parameters for their effective supply and strategies may further eliminate the antibiotic resistance. Study determine the requirement for further investigation into how this substandard product are available in the market and explore other quality compromised medicines in order to protect the public health and promote the health system.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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