**THE PREVALENCE OF ‘NOT OF STANDARD QUALITY’ MEDICINES IN AN INDIAN STATE - AN ANALYSIS.**

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**Abstract**

Medicines are vital and essential components of healthcare on whose quality is based the quality of care. Substandard medicines jeopardize the quality of healthcare services and there are frequent reports of substandard medicines in the market. The present study is aimed at examining the issue of ‘Not of Standard Quality’ (NSQ) medicines in the state of Kerala and assessing the measures undertaken by the state’s drug regulatory department in handling these. Reports of NSQ drugs obtained from various sources are also analyzed here and the data relevant to the period 2010-2013 are obtained from state’s drug control office and its official website. The NSQ data covers medicines’ samples acquired from the public health facilities, private hospitals, government-sponsored open market pharmacies, and the private pharmacies. Out of the 6890 samples tested during the three years specified above, 430 (6.25%) were NSQ drugs. There has been a gradual decrease in the percentage of NSQ drugs over the period of study: 14.37% (2010), 7.79 (2011), 4.07(2012), and 3.60 (2013) with only one case of counterfeit drugs being reported. Non-steroidal Anti-Inflammatory drugs (NSAID) and Gastro-Intestinal drugs were however, most frequently reported as substandard medicines. Nearly 34.42% NSQ samples failed in their assays and 30.25% failed the tests for dissolution. Interestingly, one product was found to have as high as 160% of labeled claim. The complete absence of NSQ medicines is essential to safeguard public health. Though the incidences of NSQ reports raise concerns, a gradual decrease in their incidence over the study period is deemed a promising sign. As Kerala is a state representing the highest consumption of medicines in the country, a strengthening of regulatory authorities and their vigilant functioning is expected to provide opportunities to bring down incidences further and initiate attempts to achieve zero NSQ medicines status.

**Key words:** Central Drugs Standard Control Organisation (CDSCO), Drug control department, Not of standard quality drugs (NSQ), Public health, Quality medicines.

**Introduction**

Medicines play an important role in healthcare and are essential components in saving lives, recuperating health, averting diseases, and containing epidemics. So, drugs must be safe, effective, of good quality, and used appropriately. The development, production, and supply chain management of medicines must be regulated to ensure compliance with their prescribed standards1. The quality of medicines is a complex subject and the quality of healthcare is directly related to the quality of medicines for use (2,3). The International Conference on Harmonisation (ICH) has defined drug quality, as “the ability of a product to satisfy stated needs, including identity, strength and purity, without undesired side effects”(3). Poor-quality medicines represent a serious threat to individual and public health, irrespective of whether they are sub-standard or counterfeit (4). The quality issue affects all medical products, such as, medicines, pharmaceutical ingredients, medical devices, and even diagnostics (5). Spurious medicine is a global issue and the problem is increasing day-by-day thereby, profoundly impacting not only the Lower-income Countries (LIC) and Lower Middle-income Countries (LMIC) but also the High-income Countries (HIC) (6).

**Different terminology used for Spurious / Counterfeit Drugs**

According to the Indian Drugs and Cosmetics Act (Amendment Act) of 1982. Section 17-B defines drugs estimated to be spurious as:- “ a*. If it is manufactured under a name which belongs to another drug; or b. if it is an imitation of, or is a substitute for, another drug or resembles another drug in a manner likely to deceive, or bears upon it or upon its label or container the name of another drug, unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other drug; or c. if the label or container bears the name of an individual or company purporting to be the manufacture of the drug, which individual or company is fictitious or does not exist; or d. if it has been substituted wholly or in part by another drug or substance; or e. if it purports to be the product of a manufacturer of whom it is not truly a product*.”(7)

The Food and Drug Administration, USA defines counterfeit drugs as:

“*A drug which, or the container of which, or labelling of which, without authorization, bears the trademark, trade name, other identifying mark, imprint or device or any likeness, there of a drug manufacturer, processor, packer, or distributor other than the person, or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by such other drug manufacturer, processor, packer, or distributor.*”(7)

According to the World Health Organization (WHO), “*a counterfeit medicine is one which, is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging*.”(7)

The word ‘counterfeit’ does not appear in the Indian terminology (Drugs and Cosmetic Act of India). But the above definitions of spurious drugs comprehensively cover counterfeit drugs as well. The Drugs and Cosmetics Act also defines a ‘Misbranded Drug’, under Section 17 and an ‘Adulterated Drug’, under Section 17A as “*A drug is considered “Not of standard Quality” or substandard if it fails to comply with any of the parameters of the overall standards laid down for it either in a recognized Pharmacopoeia or otherwise pre declared by the manufacturer.*”(7)

**The Indian Pharmaceutical Situation**

The pharmaceutical industry in India had modest beginnings with the establishment of the Bengal Chemical and Pharmaceutical Works at Kolkata in 1901(8).India produces more than 20% of the world’s generic products(9) and the annual turnover of the Indian Pharmaceutical Industry was estimated at about Rs. 1,04,944.351 Crores during 2010-11(10). The Indian Pharmaceutical Industry is one of the world’s largest, and ranks 3rd in terms of volume and 14th in terms of value, in the global pharmaceutical market. According to the Directory of Pharmaceutical Manufacturing Units in India (2007), there were 10563 pharmaceutical manufacturing units located across the country, from these, 8174 i.e., 77.4% of the firms were engaged in producing formulations and 2389 i.e., 22.6 % firms were manufacturing bulk drugs. These manufacturing units were responsible for 70% of India’s overall production of pharmaceuticals(11). Many Indian companies have acquired various international regulatory approvals -- from agencies like USFDA, MHRA-UK, TGA-Australia, MCC-South Africa etc. -- for their plants. India is the only country having the highest number of USFDA-approved plants for the manufacture of generic drugs outside the USA. It is one of the principal countries in the world to manufacture and supply medicines globally, to enable citizens to access quality medicines at affordable prices. Some of the leading Indian pharma companies derive 50% of their turnover from international businesses even though quality issues are still a problem, and many of the multinational companies are under USFDA scanners (10).

In India, both Spurious and Not of Standard Quality medicines have caused public outcries from patients’ groups and consumers due to several media reports and lack of prompt regulatory intervention, which has in turn created suspicion and distrust with regard to the existing supply chain in the country. The distribution system in the Indian pharma industry is highly fragmented, which leads to numerous ways for spurious drugs to enter the system. Mostly, the products are distributed through multiple layers (five or six or even more) by Clearing or Carrying and Forwarding (C&F) agents, depots, super stockists, wholesalers, stockists, sub-stockists etc. before they reach a retail pharmacy and finally, the patient. As predictable, this secondary market is predominantly exposed to considerable amounts of deceitful work by unethical traders and criminals. Through this secondary market, the illegally imported, pilfered, spurious or adulterated drugs gain easier access to the distribution system (12). Above all, the free availability of drugs without prescriptions has also contributed to the upsurge of spurious drugs(13). As per data acquired from the state drug controllers during the period 2003-2008, 6.3 to 7.5% of the samples tested were found to be of substandard quality and 0.16 to 0.35% were found to be spurious(14). According to the incident database of the Pharmaceutical Security Institute, Washington D.C, the largest share of counterfeits detected globally, were reported as coming from the countries in Asia. This is not only due to a negligent regulatory system, but also due to the extent of the production of counterfeits originating from China and the countries of South and Southeast Asia. Other leading manufacturers include Nigeria, Russia, Mexico, Brazil, and Latin America(2).

India has also endeavored to develop good manufacturing procedures for its production of medicines. Good Manufacturing Practices (GMP) are regulated by law, with suitable regulations published in “Schedule M”. In India, the regulation of medicines is decentralized, with particular State authorities reporting to the Drug Controller General of India (DCGI) in the Central Drugs Standard Control Organization (CDSCO). Obviously this system obscures the control of pharmaceutical production. Disappointingly, it has enforced some unreliable laws governing medicines, including the Quality Assurance and Good Manufacturing Practices (GMP), and has left unmonitored the unstable quality of medicines-testing in different States(9).

**The Central Drugs Standard Control Organization (CDSCO)**

The CDSCO is the Central Drug Authority of India discharging functions assigned to the Central Government under the Drugs and Cosmetics Act. The CDSCO has six zonal offices, four sub-zonal offices, eleven port offices, and six drug testing laboratories under their control.

Some of the major functions of the CDSCO are to enforce a regulatory control over the import of drugs, approving new drugs and clinical trials, conducting meetings of the Drugs Consultative Committee (DCC) and the Drugs Technical Advisory Board (DTAB), approving certain licenses as the Central License Approving Authority. This is exercised by the CDSCO headquarters along with the execution of joint inspections with the State Drugs Controllers under their jurisdiction. The CDSCO also has to ensure the quality of imported drugs coming into the country via the port offices and send and receive the drug samples test reports from drug testing laboratories (15).

**The Medicine situation in Kerala.**

# The usage of medicines -- both, modern medicine and herbal items -- is very high in Kerala. It is estimated that three percent of the Indian population living in the state of Kerala consumes about 11 to 13% of the modern medicines marketed in the country (16). This higher consumption average of drugs does impart its own deleterious impact on the health of the public. The numbers of modern medicine manufacturing units are insignificantly less in Kerala, that too only in the small scale sector. For pharmaceutical manufacturers, Kerala is considered a good market for the sale of their pharmaceutical products. Drugs worth `5000-6500 Crores a year was consumed by Kerala alone. Antibiotics, Non Steroidal Anti Inflammatory Drugs (NSAID), nutraceuticals, and tranquilizers were observed to be commonly used by the people in Kerala and this accounted for about 75% of the entire market share(16). Recently, the Health Ministry announced that of the 48,000 drug samples tested by all the State Drug Controllers across India between 2011 and 2012, nearly 5% failed the quality test, while almost one in three drugs (36%) were found to be “not of standard quality” in the country. States like Maharashtra (23%), Tamil Nadu (13%), and Kerala (9.2%) were found to have a huge issue of sub-standard drugs. Semi-urban and rural areas of all the states were seen to be facing a chronic issue in this regard(13).

**The Drug Control Department (DCD) of Kerala.**

The vision of the DCD is “health for all with minimal use of drugs” and their mission is to ensure the quality of drugs and cosmetics while making them available to the public at controlled prices by regulating and controlling their manufacture and sale.

The main functions of the DCD are: To control the manufacturers’ supply and sale of drugs including, homoeopathic drugs, Ayurvedic drugs, and cosmetics; To ensure the availability of all essential medicines; To identify spurious, adulterated and sub-standard drugs including, cosmetics and prevent its sale and distribution; To identify and prevent the manufacture and sale of banned drugs; To prevent sale of medicines and other cosmetics at prices other than that printed on the label; To spot and stop false and disingenuous advertisements of medicines for certain diseases and disorders; To verify that there is no pilferage of drugs from government hospitals and their stores; To control the sale and use of certain toxins; To identify all the Pain and Palliative Care Centres and ensure the accessibility of narcotic drugs therein; and finally, To allocate narcotic drugs to manufacturers, dealers, and health facilities(17).

The DCD has two wings that safeguard and implement these functions: the enforcement wing and the testing wing. The DCD is the authority for enforcing five laws: Drugs & Cosmetics Act 1940 & Rules 1945, The Drugs Price Control Order 2013 under the Essential Commodities Act, Drugs & Magic Remedies (Objectionable Advertisement) Act 1954 & Rules 1955, The Kerala Drugs & Other Stores (Unlawful possession Act 1971), and the Kerala Poison Rules 1996. The DCDs prime responsibility lies in implementing the provisions of these Acts and Rules and thereby safeguarding society(17).

This study aims at understanding the ‘Not of Standard Quality’ medicines (NSQ) in Kerala, India, identifying the manufacturers who supply more NSQ medicines there, Categorizing the NSQ medicines, identifying the reasons why they become NSQ, and comprehending the action the drug control authority will take against these substandard medicines and their manufacturers.

**Methodology**

The proposed research work is designed as a retrospective analytical study. Published articles and literature in various scientific and professional publications were reviewed based on the objectives of the present study. Retrospective data from January, 2010 to December, 2013 pertaining to the number of NSQ drugs and the number of officials involved in sampling, were collected from the official website as well as through personal interviews with the officials of the Drug Control Department. Different methods were used to collect data including, a survey, visual observations of processes, examination of records, and interaction with respondents. The main primary data gathering instrument for the survey was a structured questionnaire.

The questionnaire contained relevant questions which were designed with the objectives of the study in mind. There were both close-ended and open-ended questions. This was used to collect information from respondents. The data represented samples from the Public -- Government/ KMSCL / warehouse/ storage facilities, Hospital pharmacies (Primary, secondary and tertiary), Hospital storage facilities -- and the Private -- Hospital (Primary, Secondary, Tertiary) and their storage facilities.

The data collected was analyzed and the prevalence of the NSQ medicines was expressed in terms of percentages. A descriptive survey was considered because it was deemed non-experimental and it studied the relationship between the non-manipulated variables in a natural setting. It also enabled the collection of a large amount of data from a sizable population in a highly economical way. The data collected was primarily qualitative in nature. Additionally, the survey was also analytical because it was meant to assess the effect of the quality of medicines and its impact on public health and safety.

The primary data collected was initially edited to detect and correct any omissions and errors to ensure consistency and completeness. Again, the edited data was coded and analyzed. The analyzed data was presented in the form of descriptive statistics in frequency distribution, mainly tables, bar, and pie charts.

**Results**

A total of 6890 sample drugs were collected from the public and private healthcare facilities and pharmacies by the drug inspectors. Out of that 430 (6.25%) drugs were declared as NSQ, and the highest percentage of NSQ medicines was found in the year 2010 with 14.37%, results showing the number of NSQ drugs as decreasing from 14.37% to 3.60% in 2013. Table 1 shows the number of NSQ drugs and manufactures in India. Those drugs which are of the same batch and cosmetic preparations were excluded from the data.

The total number of NSQ drugs from government supplies (KMSCL) is compared with the essential drug list of Kerala by the KMSCL. During 2010, the percentage of NSQ drugs was found to be 8.37%, and then, it increased during 2012 with 13.34%. The, it declined in 2013 to 6%. So, while the quality of drug supplies regulated by the KMSCL was improving, still, after all the tender procedures and quality checks by the KMSCL, drugs were deemed NSQ by the Drug Control Department. This was a serious issue that raised the concerns of the KMSCL. Table 2 lists the drugs identified as NSQ by both, the government and the private sector.

From the study, it is clear that in the last four years, 216 manufacturing units supplied NSQ drugs into the Kerala market. A total of 93 manufacturing units were based in Kerala. From this number, about seven manufacturing units supplied NSQ drugs. Interestingly, we found out that the percentage of NSQ drugs supplied by the manufacturing units in Kerala increased from year to year i.e. from, 7.82% in 2010 to 17.56% in 2013. Table 3 shows the number of manufacturers in Kerala who supplied NSQ medicines.

By an analysis of the NSQ medicines list over four years (2010-2013), we identified that the NSAIDs, such as, Paracetamol, Diclofenac, Ibuprofen etc. were found to be the most common NSQ medicines (23.48%), followed by Gastro-intestinal medicines, such as, Rabeprazole, Omeprazole, Pantaprazole (16.28%), and the Cardiovascular drugs, especially anti-hypertensives, such as, Enlapril, Atenolol, Amolodipine, and Statins (12.80%). This was followed by the antibiotics, such as, Amoxycillin and Ciprofloxacin (11.17%). Figure 1 and Table 4 represent the percentage of the sub-standard drug category.

Manufacturers who repeatedly supplied NSQ medicines over the four years studied, were analyzed in the NSQ list. Forty-two manufactures supplied NSQ medicines repeatedly across two years, eight manufacturers supplied NSQ medicines repeatedly over three years, and three manufacturers supplied NSQ medicines in all the four years and among these, two were government-owned companies.

On assessing the reasons for such prevalence of these NSQ medicines, we found that most of the medicines failed the assay test 148 (34.42%), followed by the dissolution test 130 (30.25%), and 36 (8.37%) failed both, the assay and the dissolution tests. Paracetamol, Ibuprofen, Rabepraxole, Omeprazole, and Enalapril were frequently found to be failing in the assay test, and were therefore, declared NSQ. Eighty-five (19.76% ) drugs failed other tests, such as, those for physical appearance, the pH test, test for purity, sterility test etc. Figure 2 shows the percentage of drug samples which failed the quality control test.

**Discussion**

According to the World Health Organisation (WHO), 65% of India’s population does not have access to quality healthcare, but affordable healthcare and quality medication is our fundamental right(18). So, the factor that hinders the access to quality medicines is the overwhelming presence of spurious and substandard medicines. Through this study, we have analyzed the presence of the Not of Standard Quality (NSQ) medicines in Kerala. Analyzing the four years’ list on NSQ drugs shows a decrease from 14.37% to 3.60% over the period of study. This decrease can be taken in two ways: first, the DCD became more effective as the number of drug inspectors increased in the state (from eight to 57) and through their active efforts and media hype, the number of substandard drugs began to decrease compared to the previous years. Second, poor storage facilities, climatic conditions (high humidity in Kerala), transportation, poor manufacturing practices, and insufficient regulatory system in the state could also be the reasons attributed for the presence of NSQ drugs in the state.

The presence of banned drugs in the state was equally crucial a factor. Vitamins and Analgesic combinations banned by the Government of India (GOI) in 1983 were pointed out as being present in the market in September, 2011 and one of the medicines available was the drug Septidase-D. This was however, banned by the DCD in October 2011. The medicine Gatifloxacin which was banned by the government in March, 2011 was detected in the market in May 2011. These incidents show that the DCD was not effective in banning the drugs completely from the market. There was also no procedure in place to ensure that all banned drugs were dispatched to the manufacturer by the retailers. In June 2012, the government announced that there would be a standard operating procedure in place to check the actions taken by these agencies(19).

There is no foolproof surveillance mechanism to watch the status of every licensed manufacturer and pharmacy or even check the renewal of their licenses(19). There is no authenticated data regarding the drugs available in the market (more than 15,000 brands of medicines are available in the state today). Currently, the state does not have any mechanism to create a database of the medicines used/ marketed within its broders. Drugs with the same and similar trade/brand names are available in the hospitals and community pharmacies with entirely different, active ingredients. Some agencies supply medicines to the state and vanish from the scene which makes it difficult to trace them especially since they do not have any offices or premises anywhere. These add to the DCDs helplessness.

In order to solve such issues and establish a system in the state, a computerized medicine registry is required, established by the Drugs Control department and the Pharmacy Council. The services of the pharmacy colleges having PG courses in Pharmacy practice and Doctor of Pharmacy (PharmD) may be utilized for its fucntioning. A Vigilance and Ethical wing with the objective of identifying illegal and unethical practices in dispensing and distributing medicines needs to be established in an effective manner.

Substandard medicine will have a disgraceful impact in the form of increased mortality and morbidity rates, drug resistance and failure of medicines’ efficacy, and adverse effects from the inaccurate drug ingredients -- on society. Patients will lose their trust in the health system and health workers, and this may result in financial losses for the patients, their families, and the available healthcare facilities.

Considering the government supply of medicines to the public, one of the factors that merits appreciation is the decrease in the percentage of NSQ medicines. This was possible through the stringent rules laid down by the Kerala Medical Services Corporation (KMSCL) -- a government-owned company -- for the procurement of quality medicines which they made freely available to the public. Even though stringent rules were implemented, the presence of substandard medicines in that supply proved annoying. The government institutions making bulk purchases through the tender system and settling for the lowest bids were particularly prone to being affected by the presence of these drugs (21).The KMSCL took action against those manufacturers who supplied the NSQ medicines. Manufacturers who supplied the NSQ medicines to the retailers -- more than three times -- were subsequently blacklisted and this was made public through the official website and newspapers. Once these steps were undertaken, the blacklisted manufacturers were not allowed to supply their medicines to the medical service corporations of other states either. When the period for which they were blacklisted ended, they were allowed to participate in the tender procedures of the KMSCL and that for the other states too. If a manufacturer was frequently blacklisted, he was prohibited from supplying medicines to the KMSCL. Between 2008 and 2011, the KMSCL blacklisted four manufacturing units for not participating in the tender system and other activities of the KMSCL(22) .

**Procedures taken by Drug Control Department after finding a drug as NSQ**

If a drug is found to be NSQ by the Drug Control Department, the officials inform all the retail pharmacy shops and hospitals to cease the prescribing and dispensing of that particular drug. They inform the manufacturer and the corresponding state drug control officials to stop the sales and dispensation of that NSQ medicine, and ask them to conduct inspections at the manufacturing units. After proper action is taken by the drug control officials, the file is closed. If the manufacturer challenges the issue regarding substandard drugs, the DCD sends the sample and other details to the CDSCO and their laboratory unit. If their report also substantiates the DCD’s findings, the manufacturer is bound to face legal action. The Health Ministry has been planning to revise the present guidelines for taking action on the basis of the samples of drugs declared spurious or NSQ in the absence of a uniform pattern following the implementation of the Drugs and Cosmetics (Amendment) Act 2008 which had enhanced the penalty provisions.

According to our study, out of 216 manufacturers, seven are from Kerala -- the Small Scale Industries (SSI) segment to be precise. Results show that the numbers of NSQ medicines in four years from these manufacturers have been on the rise. During the study, we also noticed that there were decreases in the supply of the medicines to the KMSCL by the manufacturers in the Kerala. This could be due to the strict pre-qualification criteria laid down by the KMSCL in procuring drugs.

When comparing the drug category, the common therapeutic category of medicines found to be NSQ are NSAID, Anti-biotics, Anti-diabetics, Gastro-intestinal medicines and Cardio- vascular drugs. The NSAIDs showed a decrease from 22.60% in 2010 to 14.86% in 2013, but all the other categories of drugs showed a drastic increase especially in the case of cardiovascular drugs which jumped from 4.34% in 2010 to 14.87% in 2013. The medicines which were commonly used, such as, Paracetamol, Ibuprofen, Enlapril, Glimepride, were found to be NSQ recurrently. Medicaments like Ranitidine and Rabeprazole are hygroscopic and water soluble in nature, hence its stability is very poor . These could be one of the reasons for the medicines becoming NSQ. It is therefore, required that proper packing material be chosen to suit these products and protect them from moisture. Proper storage and transportation is necessary to ensure the label claim of such hygroscopic products. The primary, secondary, and tertiary packing of most of the drugs often does not meet the standard storage conditions needed for the drug and thus, this affects the stability of the medicament.

Analyzing the details regarding the manufacturers who supplied NSQ drugs in the four years under study, we know that three manufacturing companies, such as, the Kerala State Drugs and Pharmaceutical Ltd (KSDP), Indian Drugs and Pharmaceutical Ltd., and Nandani Medical Labs, Indore, supplied NSQ medicines all the four years, and eight manufacturing units supplied medicines for three years consecutively (ie, 2010-2012). The KSDP, a government-owned company was functioning without renewing its license since January 2007. On inspection by the DCD officials, it was found that the company was not functioning in accordance with the good manufacturing practices, such as, maintenance of the building, production and process control, quality control, water system etc. Due to the request of the KSDP that they were under renovation by the govt. with a grant of 17 cores. DCD officials did not cancel the license (19). But from the study, it was clear that the KSDP inspite of what it pleaded was still supplying NSQ medicines. According to the KMSCL, in November 2012, the KSDP was a major supplier of medicines to the government hospitals. Out of a total of 1.03 lakh medicines purchased from the KSDP during 2010-2012, 0.23 lakhs of medicines were deemed NSQ. The DCD filed 206 cases in court during 2010-11 and out of this, 53 cases were judged culminating in 38 convictions and 15 acquittals. Those who were set free were charged in the supply of NSQ medicines and keeping expired stock. But due to the failure of the department in terms of a delay in depatching samples, testing and the change of statements by the witnesses, there were acquittals in some cases (19). The Health Ministry in planning to revise the present guidelines for taking action on those samples that were declared spurious, or not of standard quality (NSQ), in the absence of a uniform pattern, took recourse to the Drugs and Cosmetics (Amendment) Act of 2008 which had enhanced the penalty provisions.

**Case report on supply of spurious drug in Kerala.**

According to information from the DCD officials, the issue occurred at a cooperative medical store at Nilambur in the Malappuram district of Kerala. The product was manufactured by Ultra Drugs Private Ltd., Solan in Himachal Pradesh and marketed by Laennec Pharmaceuticals, Thrissur. After thorough verification conducted on the route of drug lines, it was found that the expiry date and batch number had been manipulated. The label of Lactum SB injection (combination of Ceftriaxone and Salbactam) was affixed on the vials of the expired Zonactum-SB injection (combination of cefoperazone and sulbactam) by the supplier. On comparing with the retail prices of well-known companies, Lennac Pharmaceutical’s prices were found to be 20% higher. For example, Ranbaxy priced the Ceftriaxone Salbactum injection at Rs 129 (US$ 2.06), whereas Lactum SB injection was Rs 135 (US$ 2.15), Cefixime was Rs 67.80 (US$ 1.08) for Intas Biopharmaceuticals, and Rs 200 (US$ 3.19) for Lennac Pharmaceuticals. The inspecting team seized all the available stocks of the products from the medical shops and produced this before the court. They also registered cases against the shops for the engaging in the sale of spurious and illegal drugs. The department has prohibited the sale of the drug in the state till further orders(23).

**Case report on adverse drug reaction.**

A 39 year old male who was a chronic asthma patient was admitted to the Neyyattinkara taluk hospital in the Trivandrum district of Kerala. He had undergone treatment for severe chest infection and pneumonia-like symptoms. He was being treated with the medicine, Ceftazidime (brand name Spazi), a third-generation Cephalosporin antibiotic since his admission. However, the next day, soon after being injected with the Ceftazidime at 4:30 pm, the patient expired. Another patient suffered fits after being injected with the same drug leading to him being referred to the Medical College Hospital. Doctors suspected adverse drug reaction(24).

On further analysis about the medicine, the Injection Ceftazidime (Spazi) was found to cost Rs 208 (US$ 3.32) in Neyyatinkara Town, whereas at another location—Karamana, in Trivandrum district the same medicine was being sold by the agent for Rs 35 rupees (0.56$). The innovator company GlaxoSmith Kline engaged in bringing this drug into the market was selling this medicine at Rs 202.2 (US$ 3.23). Other branded companies like Lupin (Tizime) were pricing it at Rs 159.36 (US$ 2.54). This reveals that the medicine Spazi was costlier than those the branded companies were selling, but was not present in CIMS (Current Index of Medical Specialities) or in Google search. This medicine was manufactured by a company in Himachal Pradesh and was sold only at Neyyatinkara and Karamana -- two places in Kerala. Even when the KMSCL had the supply of the same medicine, the hospital authorities did not give indent to them and took the medicine from external source. This shows that unauthorized medicine supplied by fake suppliers influenced doctors and pharmacy owners in unethical ways.

At present, the Drug Control Department has only one drug testing laboratory situated at Thiruvananthapuram with a capability for testing 4,000 samples in a year. Lack of new facilities and shortage of technical staff, is known to delay results by a year. During 2008-2011, 84 samples were returned untested. By that time, all the substandard or expired drugs would probably have been sold out in the market resulting in the enhanced consumption of NSQ medicines(19). An increase in the drug testing laboratories in the state could reduce the NSQ drugs in market ensuring thereby effectively, the quality of the drugs(19).

Several methods have been used to detect substandard medications -- inspection, dissolution assays, chromatography techniques, such as HPLC, TLC, Mini-lab and Mass spectrometry , Visual control, Colorimetric methods and Dissociating tests or Simple colour reaction tests -- which reveal only very rough forgeries(25). Here, in DCD, detection of substandard medicines were carried out through the test and assay of drugs requiring the use of animals, microbiological tests and assays, identification tests, physical tests, assays, polymorph tests etc. On analyzing the data regarding the failure of NSQ over the past four years, 34.42% of drug samples were seen to have failed the assay test and 30.25%, the dissolution test which meant that the drugs were not effective and potentially unsafe. For example, some prominent drugs which showed the least and the highest active ingredients have been shown in Table 5. The reason for the failures could be the instability of the medicines given inadequate storage conditions in the Tropics -- in warehouses and in some wholesale pharmacies, hospitals, etc. where reliability of drug products would be hard to ensure. Moreover, interactions could possibly occur when products were stored at high temperatures and humidity’s, consequently decreasing the dissolution rate (25).

There were 22,000 medical shops in the state of Kerala, but the number of drug inspectors were as low as 57 during the year 2013. The actual requirement of inspectors stands at 110, which may have been another major issue faced by the DCD (26).

According to Mashelkar Committee Report, it was concluded that the problems in the regulatory system in the country were mainly due to inadequate or weak drug control infrastructure at the State and Central levels, insufficient testing facilities, lack of drug inspectors, non-uniformity of enforcement, lack of specially trained officers for specific regulatory areas, non-existence of data store, and the nonavailability of accurate information(7). This study also tries to show that, factors including a lack of regulatory infrastructure, corruption and a weak judiciary system favored the production and marketing of spurious and NSQ medicines in India.

In summary, the data we reviewed, suggests that the negative aspect of substandard medicines had a huge direct and indirect impact on public health. These drawbacks could be overcome by spreading awareness among consumers about the medicines they often bought. The role of the pharmacist was deemed to be critical at this stage and there was found to be a need to educate consumers about this. If any manufacturer was found to have committed mistakes during the course of regular operations, it was deemed that governmental response -- suspension or termination of licenses – would be an effective punitive action for the violation of the provisions of the Drug and Cosmetics Act and the rules. The study necessitates the fact that the provisions of the Drugs and Cosmetics Act and the Rules should be strictly implemented to discourage the purchase of spurious drugs by wholesalers/retailers and the movement of spurious drugs in the marketplace be controlled. Promotion of public health and protecting the public from substandard and spurious drugs are the main principles of drug regulation as formulated by the DCD. These drug regulations – it is stated -- should strictly cover all the activities related to the manufacture, distribution, storaging, dispensing, and promotion of drugs.

# Conclusion

# The NSQ and spurious medicines were proving to be an enormous problem and the prevalence of NSQ medicines in Kerala in particular, though on the decline, was annoying. The government-owned manufacturing companies were seen as the frequent suppliers of NSQ medicines. Non Steroidal Anti-inflammatory Drugs (NSAID) was recurrently falling in the NSQ category. Inadequate amounts of active ingredients were considered the main reason for a drub being categorized as an NSQ medicine. Each case of NSQs or spurious drugs was reported to the Drug Control General of India (DCGI) in the CDSCO. Corresponding medicines were seized and the authorities were asked to withdraw the medicine from the market.

Through this study we have found that drug regulation measures initiated by the Drug Control Department in Kerala were effective and transparent. But the regulations omitted certain areas regarding the availability of medicines in the market, product registration, and lack of human resources which created a gap, as a result of which they could only provide partial protection to the unsuspecting consumers. Such regulatory gaps, it was felt, could only be addressed by modifying or extending existing regulation.

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**Competing interest**

No competing interest are declared by Lekshmi.S, G.P.Mohanta and P.K.Manna

**References.**

1. Ratanawijitrasin S , Wondemagegnehu E . Effective drug regulation: A multi country study, World Health Organization, 2002.
2. Jain SK. Chapter – 9 The Spurious Drug Menance & Remedy, *Health Administrator*. 2006; 19 (1): 29-40.
3. ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: chemical substances. Available from http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf
4. Ravinetto R . Access to Quality Medicines in Developing Countries, An informal selection of scientific literature, Quamed Quality medicines for all, 0807/2013. Available from :http://www.quamed.org/media/27423/130708\_quamed\_factsheet\_on\_quality.pdf
5. Finlay BD .Counterfeit Drugs and National Security, 2011.p 1-6, Available from: http://imuna.org/sites/default/files/Counterfeit%20Drugs%20National%20Security.pdf
6. Almuzaini T, Choonara I, Sammons H .Substandard and counterfeit medicines: A systematic review of the literature, *BMJ Open* .2013; 3:e002923. Doi: 10.1136/bmjopen-2013-002923.
7. Report of the Expert Committee on A Comprehensive Examination of Drug Regulatory Issues, Including The Problem Of Spurious Drugs, Ministry Of Health And Family Welfare, Government Of India, November 2003.
8. Sarkar PK .A rational drug policy. *Indian J Med Ethics*.2004; 1(1):11-2.
9. Van Zyl AJ, Zweygarth M, SummersRS . Making Medicines Better, International and national trends with a focus on WHO ,PIC/S , China and India, Pharmacy Training and Development Project, Department of Pharmacy, University of Limpopo, Medunsa Campus.2007 .p. 9- 38.
10. Annual Report 2011-12,Government of India, Ministry of Chemicals & Fertilizers Department of Pharmaceuticals, 8-20. Available from: http://pharmaceuticals.gov.in/annualreport2012.pdf
11. Akhtar G . Indian Pharmaceutical Industry: An overview. *IOSR-JHSS*. 2013; 13(3): 51-66.
12. Proposed Methodology to Conduct a Study on the Extent of Spurious Drugs in the Supply Chain of Indian Market: By [www.Safemedicinesindia](http://www.Safemedicinesindia) . Building International Co operation to Protect patients, 2011.
13. Pooja K, Hasan S. A Database of the incidences of Counterfeit Medicines in the SEA Region, South East Asian FIP- WHO forum of Pharmaceutical Association.2011-12.
14. Report on country wide survey on spurious drugs, CDSCO, Directorate general of health services, Ministry of Health and Family welfare, Govt. of India, 2009. p.3-5.
15. Functions of CDSCO, <http://www.cdsco.nic.in/> , Assessed on December 10, 2013.
16. Thomas P .The New Indian Express, Trivandrum edition, Keralites take to medicines in a big way, Published Date: Oct 19, 2013; Available from: <http://epaper.newindianexpress.com/>. [Assessed on December 20].
17. Drugs Control Department Kerala State Citizen’s Charter 2009 .www.dc.kerala.gov.in.
18. Emerging Trends in Healthcare, A Journey from Bench to Bedside, 17 Feb. 2011.<http://www.kpmg.com/IN/en/IssuesAndInsights/ThoughtLeadership/Emrging_trends_in_healthcare.pdf>
19. Chapter III, Audit of Transactions, Health and Family Welfare Department, Government of Kerala, 81-87, Audit report (General and Social Sector) for the year ended 31 March 2012.
20. Paul Newton N, Michael Green D , Ferna´ndez F M. Impact of poor-quality medicines in the ‘developing’ World, *Trends Pharmacol Sci*. 2010; 31( 3) : 99-101.
21. Patil DD, Pandit VS, Pore SM, Fighting Counterfeit and Substandard Drugs at Periphery: The Utility Of Basic Quality Control Test. *IJCP*. 2012; 3 (3):1-3.
22. Kerala Medical Services Corporation Ltd, List of firms Blacklisted. <http://kmscl.kerala.gov.in/> . [Assessed on December 16, 2013].
23. Peethambaran K. Kerala Drug Control Officials seize expiry date altered antibiotic drugs, Pharmabiz, Oct 25,2012, <http://www.pharmabiz.com/>. [Assessed on November 29,2013].
24. Special Correspondent, Panel to Probe Patients death in Neyyatinkara taluk hospital, The Hindu,Thiruvananthapuram edition, January 18, 2014, <http://www.thehindu.com/news/cities/Thiruvananthapuram>. [Assessed on January 20,2014].
25. Kelesidis T, Kelesidis I, Rafailidis P I , Falagas M E. Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence, *J Antimicrob Chemother* . 2007;60 (2): 214–236.
26. Thomas P. Testing times for drug testing laboratories in Kerala, The New Indian Express, 08th April 2013, <http://epaper.newindianexpress.com/>. [Assessed on 10th November 2013].

**TABLES AND FIGURES**

**Table 1: Number of NSQ Drugs and Manufactures in each year.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **No of drug samples collected** | **No of NSQ Drugs** | **%** | **No of Manufactures** |
| 2010 | 800 | 115 | 14.37 | 78 |
| 2011 | 1680 | 131 | 7.79 | 81 |
| 2012 | 2700 | 110 | 4.07 | 78 |
| 2013 | 1710 | 74 | 3.60 | 49 |
| Total | 6890 | 430 | 6.25 | 216\* |

\*Manufacturers who supplied drugs in one year will be supplying in next year also, so without repeating the number of manufactures in four years

**Table 2: Drug Supplied By KMSCL (Government) & Private Health Facilities Listed as NSQ**

|  |  |  |  |
| --- | --- | --- | --- |
| **Year** | **No of Manufacturing unit in Kerala** | **No of NSQ drugs supplied by Manufacturing units in Kerala** | **Percentage** |
| 2010 | 3 | 9 | 7.82 |
| 2011 | 2 | 6 | 4.58 |
| 2012 | 4 | 12 | 10.90 |
| 2013 | 4 | 13 | 17.56 |
| Total | 7\* | 40 | 9.30 |

**Table 3: No of NSQ Supplied by Manufacturing Units in Kerala**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **No of NSQ drugs from Gov. Facilities** | **No of drugs in Essential drug list Kerala** | **Percentage** | **No of NSQ drugs from private pharmacies and health facilities** |
| 2010 | 24 | 287 | 8.37 | 91 |
| 2011 | 17 | 287 | 5.93 | 114 |
| 2012 | 40 | 300 | 13.34 | 70 |
| 2013 | 18 | 300 | 6.00 | 56 |
| Total | 99 |  |  | 331 |

**Table 4: Classification of Substandard Drugs in Each Year**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sl.no** | **Drug Category** | **2010** | **%** | **2011** | **%** | **2012** | **%** | **2013** | **%** | **Total** | **%** |
| 1 | NSAID | 26 | 22.60 | 36 | 27.48 | 28 | 25.45 | 11 | 14.86 | 101 | 23.48 |
| 2 | Antibiotics | 15 | 13.04 | 15 | 11.45 | 8 | 7.28 | 10 | 13.51 | 48 | 11.17 |
| 3 | Anti Diabetics & Hormones | 5 | 4.34 | 3 | 2.29 | 4 | 3.64 | 7 | 9.45 | 19 | 4.42 |
| 4 | GIT Drugs | 15 | 13.04 | 26 | 19.84 | 16 | 14.55 | 13 | 17.57 | 70 | 16.28 |
| 5 | Cardiovascular Drugs | 5 | 4.34 | 19 | 14.50 | 20 | 18.19 | 11 | 14.87 | 55 | 12.80 |
| 6 | Dermatological drugs | 19 | 16.52 | 5 | 3.81 | 9 | 8.19 | nil | nil | 33 | 7.67 |
| 7 | Sutures and Consumables | 13 | 11.30 | 3 | 2.29 | 7 | 6.36 | 2 | 2.70 | 25 | 5.82 |
| 8 | Vitamin & Minerals | 7 | 6.08 | 8 | 6.10 | 2 | 1.80 | nil | nil | 17 | 3.95 |
| 9 | Others | 10 | 8.69 | 16 | 12.21 | 16 | 14.54 | 20 | 27.02 | 62 | 14.41 |

**Table 5: Prominent Drugs Which Fail In Assay**

|  |  |  |
| --- | --- | --- |
| **Sl. No** | **Drug Name** | **% of Active ingredient** |
| 1 | Rabeprazole Tab | 0.5247 |
| 2 | Diclofenac Sodium Tab | 122.52 |
| 3 | Domperidone Tab | 160.6 |
| 4 | Amoxycillin Cap | 21.8 |
| 5 | Theophylline Tab | 11.52 |
| 6 | Enlapril Tab | 18.38 |

**Fig1: Percentage of Drug Category Falling Under NSQ in Each Year**

**Fig 2: Percentage of drug samples failing in the Quality test in each year**