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Not Of Standard Quality Drugs:: A Case Study On Identification, Dissolution Test And Assay Failures

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Abstract

Poor quality medicines reach the consumer through sub-standard production of drugs and due to inadequate quality control processes during their manufacture. Substandard drugs pose a serious threat to health care resulting in total loss of faith in allopathy. Availability of quality drugs is important from the perspective of health of the patients.The manufacture and sale of drugs in India is a licensed activity under the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945.Proper and effective enforcement of the Act is mandatory for curbing the sale, storage distribution and consumption of spurious and not of standard quality medicines in any country, thereby safeguarding the public health. In this paper, we have presented a study on quality of more than 6600 drug samplesfor the period from January, 2015 to June, 2018.It was indentified that, in the year 2015 highest number of samples failed to meet identification test and hence were spurious.In subsequent period of sampling highest failures were with respect to dissolution test and assay for active ingredients. The reasons for failure of drug samples in these test parameters was highlighted. Proper and effective enforcement of legislation is necessary at all levels to curb the manufacture and sale of substandard drugs and to see that safe drugs are available to public.

Keywords: Public Health, Spurious drug, Not of Standard Quality drug, D&C Act 1940, Andhra Pradesh

1. Introduction

Indian pharmaceutical industry accounts for about 3.1% to 3.6% of global pharmaceutical industry in terms of value and 10% in terms of volume and is expected to grow up to 100 billion U.S. dollars by 2025. India contributes to 2nd largest share of pharmaceutical market in the world. In 2018, the Indian pharmaceutical

market grew at 9.5% with sale of Rs. 10,029crores. The Indian pharmaceutical market witnessed growth at a CAGR (compounded annual growth rate) of 5.64% during financial years 2011-2016, with market increasing from 20.95 billion USD in the year 2011 to 57 billion USD in the year 2016.Growing domestic consumption and medicine spending in India is expected to increase at 9-12 per cent CAGR between 2018-22 and increase the market to US$ 26-30 billion, driven by increasing consumer spending, rapid urbanisation, and rising healthcare insurance among others.

Drug regulation is a public policy response to the demands of public health and the changing needs of pharmaceutical industry [1]. Thus, the objective of regulatory control is a question of achieving a 'balance' between protecting and promoting public health and facilitating the industry *vis-à-vis* compliance with regulatory standards.

In the Indian context, the architecture of drug regulation is designed as a classic command and- control system in which the legislation and act prescribes standards, regulator distributes licences and then undertakes inspection to check for compliance. This has a number of positive attributes including clarity in regulatory standards, which makes it easier to apply and to spot instances of non-compliance [2].

The existence of not of standard quality (NSQ) /Spurious Drugs is a global phenomenon. Trade in NSQ/ Spurious Drugs affects both developing and developed countries and India is no exception. The NSQ/Spurious Drugs adversely impact on human safety and it could sometimes cause a grievous injury and even death due to failure of therapeutic intervention. The impact of poor-quality medicines is most clearly evident if they contain harmful impurities, incorrect active ingredients or improperly formulated products since, patients may suffer from adverse/lethal effects.

As per the Government of India health ministry survey [3], about 10% drugs in the government supply chain were found to be of not of standard quality (NSQ) and 0.059% were spurious. The estimated percentage of NSQ drugs from private retail outlets was 3% while 0.023% were found to be spurious.

The manufacture and sale of drugs in India is licensed under Drugs & Cosmetics Act, 1940. The primary objective of this Act is to ensure safe and effective medicines are available to public. This act has elaborate provisions to prevent the production of spurious and substandard drugs in the country. Drug products may be substandard because of low quality manufacturing or deliberately counterfeited or falsified in some way. Such medicines are threat to patients and may result in treatment failure or may lead to development of antibiotic resistance.

Several quality indicating tests are to be performed on finished dosage forms as per pharmacopoeias or in house test procedure before letting it out into distribution chain. Tests like description, identification for active pharmaceutical ingredient(s), dissolution or disintegration test, assay for active ingredient are some of the essential tests recommended by Indian pharmacopoeia. Tablet or capsule dissolution is a regular method to measure the rate of release of drug from a product [4]. There could be various reasons for the failure of drugs quality in different test parameters as prescribed by various pharmacopoeias. This article focuses on certain technical reasons for the drugs failed in identification test (spurious drugs), assay and dissolution test etc.

2. Materials and Methods

2.1 Drug samples for analysis:

Under section22.1.b (i) & (ii) of the Drugs and Cosmetics Act, 1940 (D&C Act) of India 6612 drug samples falling into different therapeutic categories were lifted by Drugs Inspectors of 13 districts of Andhra Pradesh state and were received in the Government notified Drugs Control Laboratory (DCL), Vijayawada, India.

2.2 Period of Sampling:

The period of sampling in the present study is January, 2015 to August, 2018.

2.3 Area of sampling: The Drugs Inspectors lifted the drug samples from Government hospitals and private retail market shops of Andhra Pradesh state.

2.4 Analysis of received drugs samples: The samples received in DCL were assigned a unique number and analyzed as per the established monographs in standard pharmacopoeias like IP, (Indian Pharmacopeia) BP (British Pharmacopeia), USP (United States Pharmacopeia) etc. In case of non-pharmacopeial patent and proprietary formulations, Standard Test Procedures were adopted for the analysis of such samples.

2.5 Reporting of Analytical Results: After the completion of the analysis of drug samples, the report was generated in Form-13 as prescribed in D& C Act, 1940 and the opinion was declared as Standard Quality (SQ) or Not of Standard Quality (NSQ) sample by the Government Analyst as per the powers delegated to him under section 20 of the D& C Act, 1940 and Rules there under, 1945.

3. Results:

3.1 Drug Samples:

From January, 2015 to June, 2018, about 6612 samples were received in DCL, Vijayawada belonging to 23 different therapeutic categories as a part of enforcement activity under Drugs and Cosmetics Act in the state of Andhra Pradesh in post market surveillance (Table 1).

3.2 Analysis of drug samples:

During the period of 42 months the analysis of received samples revealed that in the year 2015 out of 2408 samples analyzed 2317 samples were found to be of standard quality and 91 samples were declared as NSQs. Out of 91 NSQs reported, 77 samples were identified as 'Spurious' due to the absence of active pharmaceutical ingredients as per the label claim of the manufacturer (Table 1 & 2).

Totally, 3154 samples were analyzed in 2016 out of which 3113 were SQ samples and 41 were NSQ samples. Among 41 NSQs samples, 14 were identified as '*Spurious'* (Table 1& 2).

Similarly, in the year 2017, about 2281 samples were received and analyzed and 2195 samples were marked as SQ samples and 86 were found to be NSQ samples. The number of spurious samples was only 4 this year. In case of the year 2018 up to June, 891 samples were analysed of which 858 were of standard quality and 33 were NSQs (Table 1 & 2).

3.3 Classification of NSQs and Test Parameters:

The sampling details were provided for a period of total 42 months (i.e. from January 2015 to June 2018).It was found that, of the total 8734 samples analysed 8483 samples were of standard quality and 251 were NSQs. Further, based on guidelines issued by Central Drugs Standard Control Organisation, New Delhi [5] all the NSQs were broadly classified into five categories (Table 3 and Fig 1).

The percentage of spurious samples were about 38% among the total number of NSQs. Further, the samples that failed in minor test parameters like description, uniformity of content, pH etc were 28% of total NSQs. Samples failed in dissolution test were 15% and dissolution test assay were 8.7%. Samples that failed in assay of active ingredient were 10% of total NSQs reported during the 42 months period (Fig 1)

As per the categorisation, highest NSQs were under category-B and next highest were classified under Category-A and lowest samples were under category-C (Fig 2).

4. Discussion:

Poor-quality medicines can reach the market through substandard production and due to inadequate quality-control processes during manufacture, as well as by greed driver deliberate fraudulent practices. The relative contribution of the two sources is unknown; however, genuine but low-quality drugs are likely to account for the majority of cases [6].

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consuming and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products [7].

Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications [8]. In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging.

The present study showed that, most of the not of standard quality drugs fell under the category that they failed to possess the active pharmaceutical ingredient (API) i.e. in identification test or dissolution test and assay for active ingredient. The gross reasons for failure of samples in identification test could be intentional manufacture of spurious drugs by unlicensed manufacturer or any other anti-social elements. Further, it could be presumed that, the API be replaced with a cheaper substance such as starch and hence the formulation fails in identification test and could be called spurious [9]. The movement of spurious drugs in the retail distribution chain poses severe threat to public health and therefore could be sometimes risky for human health. It can also lead to death in case certain antibiotics and when life saving drugs turn out to be spurious (Table 2 and Fig 1, 2). The percentage of NSQ drugs in the state of AP during 2014 to 2016 was 3.95% which was around national average [10].

Tablets or capsules (oral dosage forms) are one of the most effective ways of current treatment. The efficacy of such dosage forms is dependent on the dissolution profile of the drug in the gastrointestinal fluids prior to absorption into the systemic circulation; therefore, the rate of dissolution of the tablet or capsule is critical. Further, in the current study it is observed that, the reason for failure of samples in dissolution test could be due to the various lapses in manufacturing process like, quantity of lubricating agent used and lubrication time, blending time, qualitative and quantitative changes in binder materials and compression force during compression of tablets (Table 2). Other factors like the dissolution medium and pH environment etc can influence the dissolution performance of a drug product [11]. Further, in view of the importance of dissolution test it is now also extended to other dosage forms including trans-dermal systems and suppositories [12]. The storage conditions from time & place of manufacture to time & place of lifting the sample is not being recorded anywhere and it is not ensured that the products are stored as per the labelled conditions and the storage condition is the major factor to ensure the product stability.

One of the major obstacles that both the industry and regulators face is related to the definition and interpretation of quality standards of the manufacturing process. It is further understood that, drug manufacturers have to follow stringent (Good manufactory practices) GMP guidelines and develop elaborate dosage forms so that they are stable till their expiry period is attained. This ultimately will result in reduction in number of NSQs and take care of the supply chain management for storage of drugs for further supply to the consumers in the form it intended to be. Government drugs procurement agencies must also get checked the medicines procured by them for meeting the standards. Also better drug regulation through stringent law enforcement through state and central regulators as part of post market surveillance is also an effective step to curb the movement of spurious and sub-standard drugs in the market.

The relative contribution of the two sources is unknown; however, genuine but low-quality drugs are likely to account for the majority of cases [6].

5. Conclusion:

The issues of quality and the efficacy of manufactured medicines are of utmost importance for a consumer and plays a pivotal role in disease treatment. The movement of spurious drugs is a matter of grave concern which could be hazardous for human health leading to increased mortality and morbidity, drug resistance, economic loss to patients and adverse affects from incorrect active ingredients. In the absence of effective medicines regulation, increased globalization of the pharmaceutical trade can lead to the proliferation

of harmful, ineffective, substandard and counterfeit medicines in national and international markets. With the current study it is evident that, the highest number of NSQs that were identified were spurious due to lack of active ingredient and those which failed in assay and dissolution test. The reason for spurious drugs as mentioned under Drugs and Cosmetics Act, 1940 could be due to unscientific manufacturing processes adopted. Further, the failure in case of dissolution test and/ or assay could be due to various lapses in manufacturing of drugs. In order to curb the movement of such sub-standard medicines further effective legislations are required at the field level to ensure that, safe medicines are made available to general public in the interest of the humanity. Secure I.T. based trace and track mechanisms, permitting only authorised players i.e. doctors, pharmacists, nurses, chemists in the field of manufacturing, dispensing, storage, prescription & supply chain will go a long way in keeping out NSQ drugs and improving the overall efficacy of the health system of the country. Onus of failure in identification can be attributed to loop holes in the chain& forting from 1) Industry 2) Storage 3) Retailers.

Table-1: Total number of samples received, analysed and number of NSQs declared for both hospital and market picked samples

Year	2015			2016			2017			2018		
	H	R	Total	H	R	Total	H	R	Total	H	R	Total
Number of Samples Received	284	1586	1870	289	1197	1486	575	1607	2182	276	798	1074
Number of Samples Analysed	526	1882	2408	548	2606	3154	546	1735	2281	201	690	891
Number of NSQs Declared	02	89	91	12	29	41	25	61	86	21	12	33
Percentage	0.38	4.72	3.77	2.19	1.11	1.30	4.58	3.52	3.77	10.45	1.74	3.70

***H**= Hospital Samples; **R**= Retail market picked samples*

Total number of samples analysed in columns are including the samples carry forwarded from previous years

Table-2: Year wise and parameter wise total number of NSQs reported

S.No.	Test Parameter	Year				
		2015	2016	2017	2018	Total
1	Identification	77	14	4	-	94
2	Dissolution Test	2	2	23	10	37
3	Description & General Requirements	6	4	14	4	28
4	Assay for Active Ingredient(s)	2	5	14	5	26
5	Dissolution Test & Assay	-	1	16	5	22
6	Particulate Matter	-	1	8	1	10
7	Uniformity of Weight	2	1	1	-	4
8	Uniformity of Content	-	-	-	2	2
9	Disintegration Test	-	4	1	1	6
10	Appearance of Solution	-	4	-	-	4

11	Disintegration Test & Assay	1	-	-	-	1
12	pH & Assay	1	-	-	-	1
13	Description & Assay	-	1	1	-	2
14	Identification & Assay	-	1	2	1	4
15	Uniformity of Weight & Dissolution Test	-	-	2	1	3
16	Identification & Disintegration Test	-	-	1	-	1
17	Uniformity of Content & Assay	-	-	-	2	2
18	pH Test	-	-	-	1	1
	Total	**91**	**38**	**86**	**33**	**248**

Table-3: Major categorization of NSQ drugs as per CDSCO (Central Drugs Standard Control Organization)

Category	**Description of Tests in which Samples fail**
Category-A (Spurious & Adulterated Drugs)	The product may or may not contain the active ingredients.
Category-B (Grossly Sub-standard Drugs)	(i) Active ingredient contents below 70% (for thermo labile products) and below 5 % of the permitted limits for thermo stable products. (ii) Tablets/Capsules failing in disintegration tests (iii) Tablets/Capsules failing in dissolution test (iv) Liquid preparations showing presence of fungus. (v) Parental preparations failing in sterility, pyrogen/endotoxin test. (vi) Vaccines failing in potency, sterility, toxicity or moisture content. (vii) Presence of any adulterant which renders the product injurious to health.
Category-C (Minor Defects)	(i) Broken or chipped tablets. (ii) Presence of spot/discolouration/uneven coating. (iii) Cracking of emulsions. (iv) Clear liquid preparations showing sedimentation. (v) Change in colour of the formulation. (vi) Slight variation in net content. (vii) Formulations failing in weight variation. (viii) Formulations failing to respond to the colour test. (ix) Isolated cases of presences of foreign matter. (x) Labelling error including nomenclature mistake, Rx, NRx, XRx, Red Line, Schedule H. Caution, Colour etc.

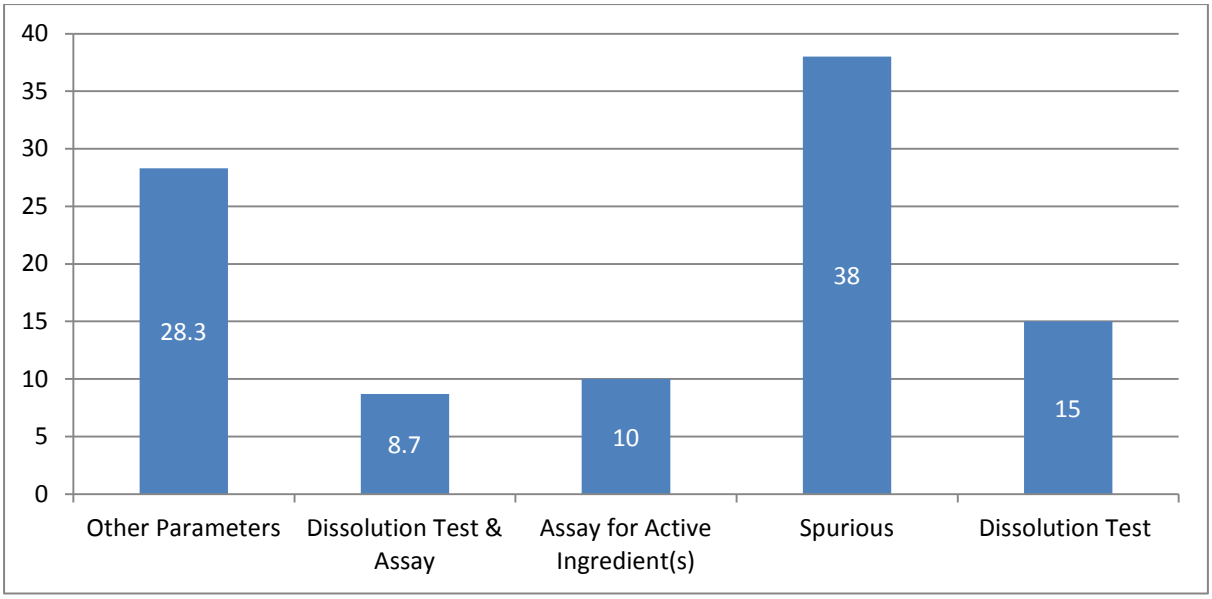

Fig 1: Percentage of samples failed in different parameters in 4 years period

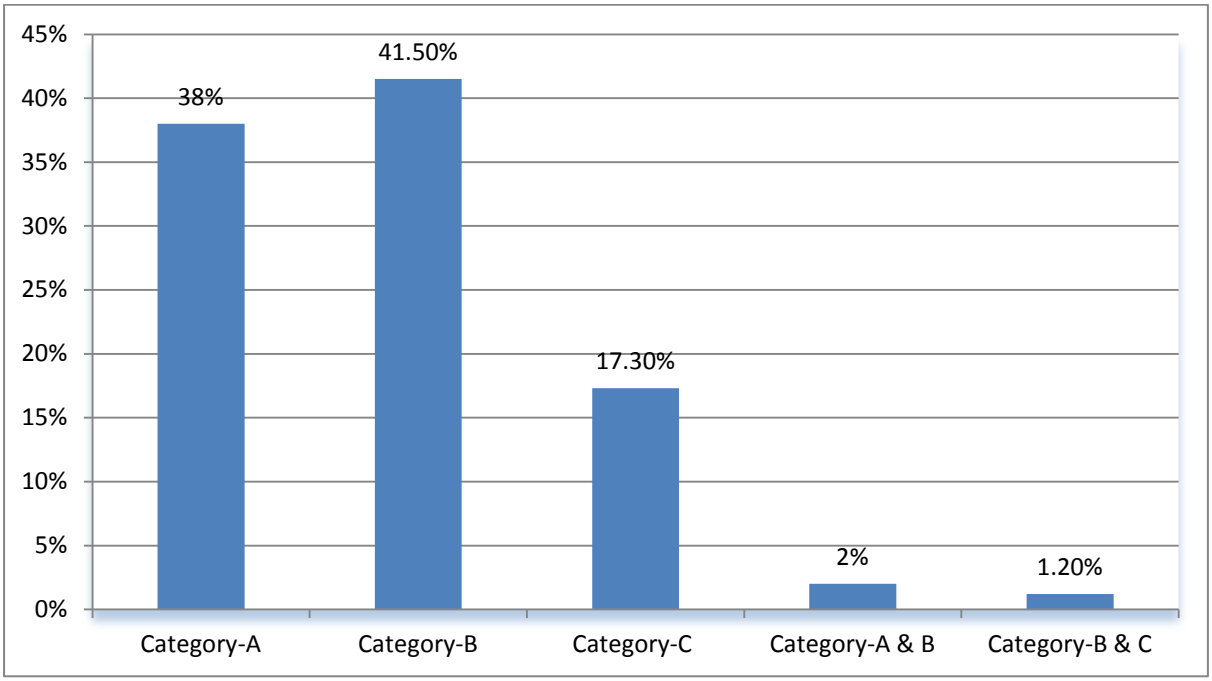

Fig 2: Categorization of not of standard quality of current study drugs in terms of CDSCO classification

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