QUALITY OF CEFTRIAXONE IN PAKISTAN: REALITY AND RESONANCE

OBAID ALI

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi

ABSTRACT

The quality of pharmaceuticals is a global concern, counterfeit/ poor quality/ substandard medicines can cause harms in various ways: In a number of developing countries including Pakistan there is reportedly a high incidence of the availability of substandard drugs. The majority of these reports do not contain quantitative data to support these claims, nor do they describe the methodology employed for the quality assessment. Quality of drugs available in Pakistan are being questioned and topic of discussion in local news paper, TV channels in general public including journalist and physicians due to disparity of price among same generics, lack of knowledge for such science and unknown reasons. Since, quality of drugs can neither be assessed by naked eye or by every one therefore, randomly selected, 96 samples of different strength of Injection Ceftriaxone Sodium and its generic, a widely used third generation cephalosporin in Pakistan since 1982 and 1994 till date respectively included in the said study to know the reality. 15.62% of Ceftriaxone Injection was found to be Out of Specification, however, not a single sample was found fake (spurious) out of 96 tested samples. Nevertheless, quality is a wide ranging concept covering all matters that individually or collectively influence the excellence of a product hence price and other related issues are also analyzed in the study.

Keywords: Quality, Ceftriaxone, generics, cGMP, standard, out of specification, counterfeit, spurious, substandard.

INTRODUCTION

Pakistan is a developing country with a population of about 160 million. The total estimated market of pharmaceuticals in Pakistan would be around 2 billion US dollar by 2010. It has ability to produce almost all types of drug products while biological and products having advanced drug delivery system up to a limited extent. The Pharmaceutical industries in Pakistan are capable and have enough capacity to fulfill the domestic requirements. Policies of the World Trade Organization and the Government of Pakistan do not prohibit the import of pharmaceuticals which is regulated and controlled under Drugs Act, 1976. Pakistan is importing raw materials intended for pharmaceutical use from other countries of the world due to its limited resources in terms of supply, intermediates and commercial viabilities from China, India, Europe and other related countries.

Pharmaceuticals and public health

The mainstay of public health is pharmaceutical sector in any country whether; it is developing or under developing nation (EC, TRTA for Pakistan, 2007).The pharmacy profession and society are complementary and dependant on each other for their development as a matter of fact (Vijay Kumar Sharma, 2008). Pharmaceutical preparations are the integral essential part of the health care system and best reward for the suffering people and society.

Quality expression of pharmaceuticals

Quality of drugs can neither be assessed by naked eye or by every one. Drug quality is assessed by compliance with its compendial specifications or approved specification in case of not included in Pharmacopeias. The development, manufacture, import, distribution, use of drugs and its regulation require special professional knowledge and skills. The issue of drug quality is in the interest of the following parties because each has a stake in them: a) consumers – cure and cost; b) prescribers – patient trust, future visits, future income; c) pharmaceutical companies – reputation, trust in their products, future profits; and d) governments protection of public health and prevention of increased public expenditure for drugs. Quality is a wide ranging concept covering all matters that individually or collectively influence the excellence of a product. Quality is monitored in four major areas: quality control, production, distribution, and inspections. The development of norms, standards and guidelines to promote quality is an integral activity that has been endorsed and supported through numerous Health Organizations e.g. WHO, International Convention of Harmonization (ICH), Pharmaceutical Inspectorate Corporation Scheme (PICS) European Directorate for Quality Medicines (EDQM), US-FDA (United States Food and Drugs Administration), Health Canada, Drugs Control Organization (Pakistan) etc. local regulatory authorities etc.

Quality of pharmaceuticals drug products and concern

Demonstration of products regarding its identity, purity, quality, efficacy and safety with predefined specification is considering Quality Products in broader sense. Any drugs found within specification can never be considered safe if cGMP (Current Good Manufacturing Practice) regulations are victimized during the manufacturing process. The quality of pharmaceuticals is a global

**Corresponding author:* oarohama@yahoo.com

concern and drugs comprise approximately 10% of the global medicine market (Robert Cokburn, 2005; Minzi, 2003; USP-DQA/GICM R-2004, Burns, 2006 and Newton 2001, 2002) and reported 5 to 8% by Gibson, 2004 in BMJ. Counterfeit medicines, a problem in both developed and undeveloped countries are becoming increasingly available worldwide (FDA Consumer, 2004). Recent several reports indicate the availability of substandard and counterfeit drugs has reached a disturbing proportion in many low-income countries (Wijesinghe *et al*., 2007). Lack of reliable drug quality assurance systems in many developing countries often contributes to the devastation of diseases. Quality, effectiveness, and safety should be demonstrated and verified prior to their rational use (Videau, 2001). These attributes are critical to the functioning of healthcare systems which require a sustainable supply of quality, efficacious, and safe essential medicines (Nishtar, 2006). Drugstores and drug outlets are the main sources of care for the majority (Yang *et al*., 2004).

Counterfeit/poor quality and substandard medicines can cause harms in various ways: the presence of toxic chemicals frequently causes injury or death, inappropriate delivery systems and/or, inadequate amounts of drugs from working effectively and, again, can lead to injury or death (Julian Morris and Philip Stevens, 2004). Use of substandard medicines is one of the causes of drugs resistant especially in antimicrobial and increased morbidity and mortality (Alubo, 1995 and O'Brien *et al*., 1998) which is considered the most commonly counterfeited drugs in developing countries (Wondemagegnehu, 1999). 11 countries including Pakistan are selected and data of chemical analysis of drugs sample of all countries except Pakistan were included in the report of USP- DQA/GICM R-2004. Said report and based on news paper statement of politician without any study declared 50% drugs are estimated fake in Pakistan (USP-DQA/GICM R-2004, Liza Gibson, 2004). In a number of developing countries there is reportedly a high incidence of the availability of substandard drugs. The majority of these reports do not contain quantitative data to support these claims, nor do they describe the methodology employed for the quality assessment. Many assume fake drug as the reason for the poor quality and in some cases this is not justified (Shakoor *et al*., 1997).

Quality of drugs available in Pakistan are being questioned and topic of discussion in local news paper, TV channels in general public including journalist and physicians due to disparity of price among same generics, lack of knowledge for such science and unknown reasons.

Poor/low quality or substandard and spurious (fake) drugs

Poor/low quality or substandard drugs are genuine products that do not conform to the pharmacopeial standards (strength, quality, purity, packaging, and/or labeling) set for them. Poor drug quality can be the result of poor manufacturing practices, or inappropriate drug storage in excessive heat, moisture, or light. (Kenyon *et al*., 1999; Ten Ham *et al* 1992, Pecoul *et al*., 1999 and Okeke *et al*., 1999). These drugs may be subpotent, lack active ingredients, contain harmful or cross-reactive impurities, lack or impede traceability, and be made or packed in unsuitable conditions (England, 2002). These of course may have potential to alter desired biological activity and safety profile. It may bear serious health implications such as treatment failure, adverse reactions, drug resistant and can erode public confidence resulting in reduced investment in the pharmaceutical industry (Shakoor *et al*., 1997 and Cuff, 1995) on Ministry of Health and waste scarce resources (Wondemagegnehu, 1999 and SEAM 2001).

Simply a drug is considered fake if does not contain labeled ingredient of therapeutic potential and legally comes under the meaning of Spurious Drugs in Pakistan Drugs Act 1976. The production of substandard and fake drugs is a vast and underreported problem, particularly affecting poorer countries. It is an important cause of unnecessary morbidity, mortality, and loss of public confidence in medicines and health structures (Robert Cockburn *et al*., 2005). Taylor et al., 2001 reported the quality of medicines available in some less-developed countries is inadequate in terms of content of active ingredient. Reasons for the poor quality of drugs include widespread counterfeiting of medicines in less-developed countries, excessive decomposition of active ingredient as a result of high temperature and humidity, and poor quality assurance during the manufacture of medicinal products (Taylor *et al*., 2001).

Regulation of entire pharmaceutical operations

The quality of drug is a very complex issue. It cannot be assessed like other commodities by consumer; therefore, science based regulation of entire pharmaceutical operation and business right from manufacturing till Pharmacovigilance activities are observed almost throughout the world to protect public health from any potential risk. The business of pharmaceutical drug products possesses much risk potential and sometimes any minor mistake may cause horrible irreversible damages on masses of public. Compliance with current Good Manufacturing Practice and Good Storage Practice regulation plays an important role to ensure and preserve the quality of product. The level of control, monitoring and regulation is based on modern science and vary from country to country. To get access to developing countries like Europe, US, Japan etc. every pharmaceutical industry will have to comply with their regulations, which may certainly differ from each other. This difference faces a resistance in free trade even among the countries in question. An International Convention of Harmonization

(ICH) was being initiated to resolve the differences and try to harmonize the issues by developing Common Technical Document (CTD) accepted to all members including US, European Commission and Japan keeping WHO and Canada as observers. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme jointly referred to as PIC/S was constituted to lead the international development, implementation and maintenance of harmonized GMP standards and quality systems. PIC/S is two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP.

Price dilemma

In Pakistan Prices of drugs product are being controlled by Ministry of Health, Federal Government. The control over price of imported materials including Drugs Products is enjoying flexible approach of relevant authorities and regulatory bodies of Pakistan. From competitive to many fold difference in price of same molecules provide enough profit to bribe physician and exploit consumer. The same situations are observed in countries where price are not regulated. Price differentials between and brand products vary greatly among countries, as IMS 2003 revealed up to 80% and 90% lower price of same generic in USA and UK respectively. In Canada and France prices of generics are reported lower up to 50% and 35%. Prices of generics are lower less than 20% in countries like Belgium, Italy, and Spain etc. To increase access and affordability, promotion of generic medicines and improved availability of medicines in the public sector are required (Babar *et al*., 2006). The price of medicine is considered one of the most important obstacles to access (Videau, 2000 and WHO, 2003). Drug expenditures may amount to 50%-90% of non personnel costs is reported by Quick JD 1997 for developing countries.

Injection Ceftriaxone sodium

Ceftriaxone Sodium, a widely used third generation cephalosporin in Pakistan (IMS 2005) was approved and granted registration to a corporate group by Ministry of Health, Government of Pakistan in 1982 and generic players were allowed to come in market in 1994. 62 companies are registered to manufacture/market molecule containing Ceftriaxone Sodium in different strengths of parenteral dosage formulation approved by Ministry of Health, Government of Pakistan and available so far in local market (Pharma Guide, 2008).

MATERIAL AND METHOD

Specification reference

Ceftriaxone Sodium; approved specification and method for analysis of Injection Ceftriaxone Sodium of Ministry of Health, Government of Pakistan, 2005.

Code No. of the Brand Tested: T1…….T96 (table 5)

Specifications

Ceftriaxone for injection contains an amount of Ceftriaxone sodium equivalent to not less than 776 ug of Ceftriaxone ($C_{18}H_{18}N_8O_7S_3$) per mg, calculated on the anhydrous basis, and the equivalent of not less than 90% and not more than 115% of the labeled amount of Ceftriaxone ($C_{18}H_{18}N_8O_7S_3$).

Procedure for assay

HPLC technique as per USP method described below:

Chromatographic conditions

Instrument:	Shimadzu LC-10AVP
Analytical Column:	Stainless steel column (15cm×4.0 mm)
Stationery Phase:	L-1(Octadecyl silane chemically bonded to porous silica or ceramic micro particles, 5 um in diameter
Mobile Phase:	Acetonitrile containing 3.2g of tetraheptyl ammonium bromide: pH 7 buffer: pH 5 buffer: Water (400: 44: 4: 552)
Flow rate:	2.0 ml/min
Injection volume:	20u liter
Detector:	UV at 270 nm

Precautions

Calibration period and theoretical plate of the column was taken under precaution.

Reagents

Acetonitrile HPLC Grade
Tetraheptyl ammonium bromide
Dibasic potassium phosphate
Monobasic potassium phosphate
Sodium citrate
Citric acid solution (1 in 5)
Phosphoric acid 85 %
Potassium hydroxide
De-ionized double distilled water

Buffer preparation

pH 7 buffer

13.6g of dibasic potassium phosphate and 4g of monobasic potassium phosphate was dissolved in water to obtain 1000 ml of solution. The pH of the solution was adjusted to 7.0 ± 0.1 with phosphoric acid or 10N potassium hydroxide.

pH 5.0 buffer

25.8g of sodium citrate was dissolved in 500ml of water. The pH was adjusted to 5.0 ± 0.1 with citric acid solution (1 in 5), and diluted with water to a volume of 1000 ml.

Preparation of mobile phase

3.2g of Tetraheptyl ammonium bromide was dissolved in 400ml of Acetonitrile; 44ml of pH 7.0 buffer and 4ml of

Table 1: Assay profile of Ceftriaxone Sodium as Ceftriaxone base of 96 samples aseptically filled by 33 Pharmaceutical Manufacturing Units (PMU). Specification 90-115 (USP 2006)

Sample No	Mfg Identity	Strength mg	Assay (%)	Sample No	Mfg Identity	Strength mg	Assay (%)	Sample No	Mfg Identity	Strength mg	Assay (%)
1	T23	250	98.34	33	T32	250	106.15	65	T3	250	100.52
2	T23	1000	100.61	34	T13	250	108.30	66	T19	500	99.25
3	T3	1000	106.20	35	T9	250	101.83	67	T2	250	90.05
4	T3	500	100.28	36	T24	1000	103.99	68	T24	250	106.35
5	T12	1000	106.43	37	T16	250	106.23	69	T17	250	113.21
6	T3	250	101.90	38	T16	500	92.12	70	T26	500	100.36
7	T12	500	104.99	39	T16	1000	90.11	71	T3	500	99.93
8	T12	250	103.29	40	T26	500	109.22	72	T3	500	103.62
9	T15	1000	126.22	41	T22	500	113.65	73	T9	500	133.96
10	T12	1000	109.23	42	T30	1000	101.86	74	T26	1000	113.79
11	T8	250	115.12	43	T17	500	83.44	75	T14	1000	105.85
12	T8	500	102.41	44	T17	1000	95.01	76	T10	250	107.80
13	T12	500	105.18	45	T14	250	105.37	77	T14	250	107.98
14	T15	1000	119.57	46	T13	1000	107.62	78	T26	250	114.70
15	T7	500	95.19	47	T4	1000	100.16	79	T31	1000	103.71
16	T15	250	92.41	48	T3	250	102.26	80	T10	500	104.86
17	T33	1000	88.95	49	T24	500	106.80	81	T10	500	107.38
18	T18	1000	90.43	50	T3	250	108.12	82	T3	250	112.12
19	T21	1000	104.76	51	T3	250	113.75	83	T22	1000	126.78
20	T20	1000	103.54	52	T3	500	99.65	84	T2	500	89.22
21	T6	250	55.16	53	T3	500	110.26	85	T25	500	76.33
22	T33	250	84.91	54	T24	250	104.84	86	T25	250	113.82
23	T19	250	119.15	55	T4	250	105.47	87	T14	500	100.27
24	T29	500	101.89	56	T3	250	92.94	88	T11	250	93.90
25	T21	500	106.71	57	T4	1000	106.13	89	T27	250	100.45
26	T21	250	125.42	58	T3	500	101.66	90	T5	250	103.47
27	T6	250	104.43	59	T24	1000	107.37	91	T4	250	94.82
28	T33	1000	72.63	60	T15	250	105.33	92	T1	1000	100.70
29	T15	1000	101.81	61	T28	1000	106.28	93	T26	1000	103.89
30	T18	1000	88.63	62	T28	250	99.19	94	T4	250	101.95
31	T33	250	116.77	63	T28	500	95.94	95	T10	250	105.12
32	T13	500	102.95	64	T18	500	106.84	96	T19	1000	96.59

pH 5.0 buffer was added. Water was added to make 1000ml, filtered through a membrane filter of 0.5um or finer porosity, and degassed.

Standard solution

40 mg accurately weighed quantity of USP Ceftriaxone sodium RS was dissolved in a 200 ml volumetric flask with mobile phase to obtain a solution having a known concentration of about 0.2mg/ml. This solution was used promptly after preparation.

System suitability test

5 consecutive injections of standard solution were repeatedly injected and the peak response was recorded prior to injection of sample solution and after completion of work to observe the consistency of performance of system.

Criteria for acceptability

- The Relative Standard Deviation (RSD) less than 2% for 5 replicate injections of standard solution was also the criteria to qualify the system suitability test.
- Tailing factor for cefotaxime is not more than 2 that has been derived from the equation given below:

$T = W_{0.05} / 2f$

Where:

T = tailing factor

$W_{0.05}$ = width of peak at 5% height

f = distance from the peak maximum to the leading edge of the peak, the distance being measured at a point 5% of the peak height from the baseline.

Qualification of total performance of HPLC system

Standard solution of equal volume that is 20 u liters was introduced twice at the end of analytical work and the correspondent Peak Area Response of the chromatograms was measured.

Acceptance criteria

Tolerance limit of 3% ratio between both injections (5 consecutive injections of system suitability and 2 consecutive injections of standard solution at the end of analytical work) was the pre-requisite to safely conclude and incorporate the result in study based on following formula:

Table 2: Distribution profiling of 96 samples of different strengths of Injection Ceftriaxone sodium calculated as Ceftriaxone base aseptically filled in 33 various Pharmaceutical Manufacturing Units (PMU).

Compliance range in %	250 mg		500 mg		1000 mg	
	Number	%	Number	%	Number	%
Less than 75	1	2.56	0	0.00	1	3.45
75-85	1	2.56	2	7.14	0	0.00
85-90	1	2.56	1	3.57	2	6.90
90-95	4	10.26	1	3.57	2	6.90
95-100	2	5.13	5	17.86	2	6.90
100-105	10	25.64	10	35.71	10	34.48
105-110	11	28.21	6	21.43	8	27.59
110-115	5	12.82	2	7.14	1	3.45
115-125	3	7.69	0	0.00	1	3.45
More than 125	1	2.56	1	3.57	2	6.90
Total	39		28		29	

Table 3: Explores dose compliance with label claim in samples of injection Ceftriaxone sodium (n= 96)

Mfg. ID	No of Samples	250 mg	500 mg	1000 mg	Mfd ID	No of Samples	250 mg	500 mg	1000 mg
TI	1	×	×	√	T18	3	×	√	√ ‡
T2	2	√	‡	×	T19	3	†	√	√
T3	14	√√√√√√√	√√√√√√	√	T20	1	×	×	√
T4	5	√√√	×	√√	T21	3	†	√	√
T5	1	√	×	×	T22	2	×	√	†
T6	2	‡ √	×	×	T23	2	√	×	√
T7	1	×	√	×	T24	5	√√	√	√√
T8	2	√	√	×	T25	2	√	‡	×
T9	2	√	†	×	T26	5	√	√√	√√
T10	4	√√	√√	×	T27	1	√	×	×
T11	1	√	×	×	T28	3	√	√	√
T12	5	√	√√	√√	T29	1	×	√	×
T13	3	√	√	√	T30	1	×	×	√
T14	4	√√	√	√	T31	1	×	×	√
T15	5	√√	×	† √ †	T32	1	√	×	×
T16	3	√	√	√	T33	4	†	‡ ×	‡‡
T17	3	√	‡	√					

√: within specification, †; Above than specification, †: Substandard

Formula

Ratio of both injections (5 consecutive injections of system suitability and 2 consecutive injections of standard solution at the end of analytical work)

$$= \frac{\text{Max. Peak area} \;\; \text{Min. peak area}}{\text{Max. Peak area}} \times 100$$

Tolerance = ± 3%

Sample solution

Accurately measured volume of solvent as specified on the label was added to constitute Ceftriaxone injection in a subjected single dose container. All withdrawable contents were taken out by a syringe containing a suitable hypodermic needle and diluted with mobile phase to obtain a solution having a final concentration of 0.2mg/ml Ceftriaxone sodium and used promptly after preparation for chromatography.

Table 4: Explores dose compliance with label claim in samples of injection Ceftriaxone sodium (n= 96) describes % distribution of result within different corridor observed in 250 500 and 1000 mg of samples of injection Ceftriaxone sodium (n= 96)

Results (%)	250 mg (n= 39)	500 mg (n= 28)	1000 mg (29)
Above than specified limit (more than 115%)	7.7	3.6	10.3
Within specifications (90 to 115%)	87.1	85.7	79.3
Substandard below specification (less than 90%)	5.1	10.8	10.3

Table 5: Shows maximum retail prices in Pak Rupees of different brands of Ceftriaxone injections aseptically filled by various Pharmaceutical Manufacturing Units (PMU) available in Pakistan

Sample No	Mfg Identity	Strength mg	Price	Sample No	Mfg Identity	Strength mg	Price	Sample No	Mfg Identity	Strength mg	Price
1	T23	250	75	33	T32	250	70	65	T3	250	54
2	T23	1000	200	34	T13	250	59	66	T19	500	95
3	T3	1000	180	35	T9	250	42	67	T2	250	114
4	T3	500	95	36	T24	1000	478	68	T24	250	141
5	T12	1000	147	37	T16	250	55	69	T17	250	60
6	T3	250	54	38	T16	500	85	70	T26	500	95
7	T12	500	90	39	T16	1000	155	71	T3	500	95
8	T12	250	53	40	T26	500	95	72	T3	500	95
9	T15	1000	291	41	T22	500	140	73	T9	500	72
10	T12	1000	147	42	T30	1000	300	74	T26	1000	180
11	T8	250	65	43	T17	500	110	75	T14	1000	291
12	T8	500	110	44	T17	1000	185	76	T10	250	123
13	T12	500	90	45	T14	250	120	77	T14	250	120
14	T15	1000	291	46	T13	1000	150	78	T26	250	54
15	T7	500	88	47	T4	1000	200	79	T31	1000	321
16	T15	250	120	48	T3	250	54	80	T10	500	220
17	T33	1000	162	49	T24	500	243	81	T10	500	220
18	T18	1000	321	50	T3	250	54	82	T3	250	54
19	T21	1000	150	51	T3	250	54	83	T22	1000	280
20	T20	1000	280	52	T3	500	95	84	T2	500	195
21	T6	250	75	53	T3	500	95	85	T25	500	100
22	T33	250	54	54	T24	250	141	86	T25	250	58
23	T19	250	54	55	T4	250	75	87	T14	500	170
24	T29	500	95	56	T3	250	54	88	T11	250	125
25	T21	500	99	57	T4	1000	200	89	T27	250	50
26	T21	250	59	58	T3	500	95	90	T5	250	65
27	T6	250	75	59	T24	1000	478	91	T4	250	75
28	T33	1000	162	60	T15	250	120	92	T1	1000	200
29	T15	1000	291	61	T28	1000	200	93	T26	1000	180
30	T18	1000	321	62	T28	250	75	94	T4	250	75
31	T33	250	54	63	T28	500	125	95	T10	250	123
32	T13	500	100	64	T18	500	170	96	T19	1000	180

Calculation for estimation of Ceftriaxone sodium

The quantity, in ug, of ceftriaxone per mg of the ceftriaxone for injection was calculated by the following formula:

$$200(CP/W)\ (r_u/ r_s)$$

Where:

C = the concentration, in mg per ml, of USP Ceftriaxone Sodium RS in the standard preparation;

P = the designated potency, in ug, of ceftriaxone per mg of USP Ceftriaxone Sodium RS;

W= the quantity, in mg, of ceftriaxone for injection taken;

r_u = the ceftriaxone peak responses obtained from Assay preparation

r_s = the ceftriaxone peak responses obtained from standard preparation

RESULTS

Randomly selected Ninety Six (96) different samples of injection Ceftriaxone Sodium bearing different batch numbers, aseptically filled (manufactured) by thirty three (33) various Pharmaceutical Manufacturing Units (PMU) in 3 regularly available strengths (250, 500 and 1000 mg) were analyzed to determine the actual concentration of drug in filled vials as shown in table 1 and fig. 1.

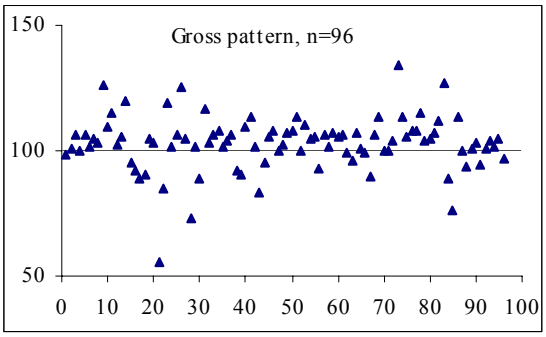

Fig. 1: Assay profile of Ceftriaxone sodium as Ceftriaxone base of 96 samples aseptically filled by 33 Pharmaceutical Manufacturing Units (PMU). Specification 90-115 (USP 2006)

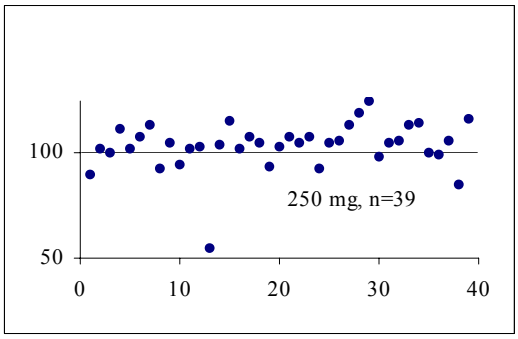

Fig. 2: Distribution profiling of assay of injection Ceftriaxone Sodium calculated as Ceftriaxone base 250 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

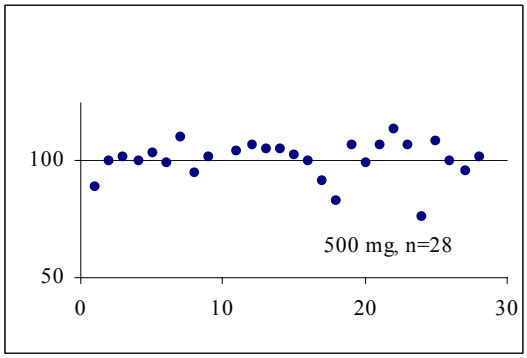

Fig. 3: Distribution profiling of assay of injection Ceftriaxone sodium calculated as Ceftriaxone base 500 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

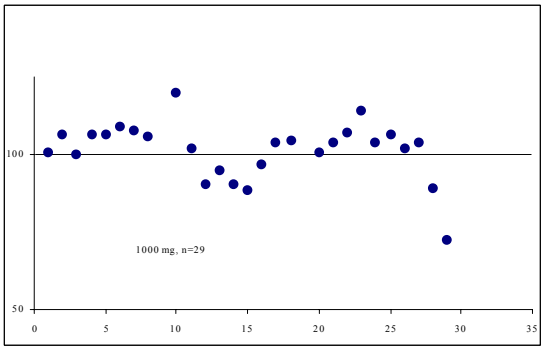

Fig. 4: Distribution profiling of assay of injection Ceftriaxone sodium calculated as Ceftriaxone base 1000 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

Injection Ceftriaxone sodium

Results of Chemical Analysis of 250, 500 and 1000 mg revealed that 85.42% (n=82) samples were well within range of pharmacopeial specification that is 90% to 115% while 7.29% (n=7) found out of scale of upper limit from 116to 133% and like wise 7.29% (n=7) samples could not reach up to lower limits from 55 to 89%. 41.15% (n=6) samples from out of specification were very close (88 to 119%) to the prescribed limit as shown in tables 1, 2 and figs. 1 to 9.

Injection Ceftriaxone 250 mg

Individual results of Chemical Analysis of 250 mg revealed that 81.74% (n=35) samples were well within range of pharmacopeial specification that is 90% to 115% while 7.69% (n=3) found out of scale of upper limit from 116% to 125% and like wise 2.56% (n=1) samples could not reach up to lower limits that is 55%. 50% (n=2) samples from out of specification were very close (116 to 119%) to the prescribed limit as shown in tables 1, 2 and figs. 1, 2, 5, 8-9 (R).

Injection Ceftriaxone 500 mg

Individual results of Chemical Analysis of 500 mg revealed that 85.71% (n=24) samples were well within range of pharmacopeial specification that is 90% to 115% while 3.57% (n=1) found out of scale of upper limit that is 133% and like wise 10.71% (n=3) samples could not reach up to lower limits that is 76 to 89%. 25% (n=1) samples from out of specification were very close (89%) to the prescribed limit as shown in table 1, 2 and figs. 1, 3, 6, 8-9.

Injection Ceftriaxone 1000 mg

Individual results of Chemical Analysis of 1000 mg revealed that 79.3% (n=23) samples were well within range of pharmacopeial specification that is 90% to 115% while 11.34% (n=3) found out of scale of upper limit from 119% to 126% and like wise 11.34% (n=3) samples could not reach up to lower limits from 72 to 88%. 50 % (n=3) samples from out of specification were very close (88 to 119%) to the prescribed limit as shown in table 1, 2 and figs. 1, 4, 7-9.

DISCUSSION

Study revolves around fundamental quality (assay/ content of active ingredient in unit dose) of finished drug product (Injection Ceftriaxone Sodium-widely prescribing molecule) available throughout the country right from the

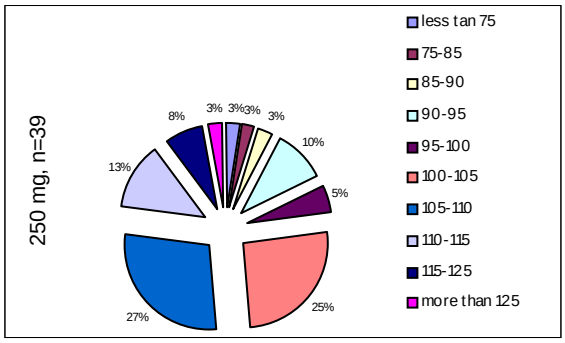

Fig. 5: Percentage distribution profile in different corridors with regard to assay of Injection Ceftriaxone Sodium calculated as Ceftriaxone base 250 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

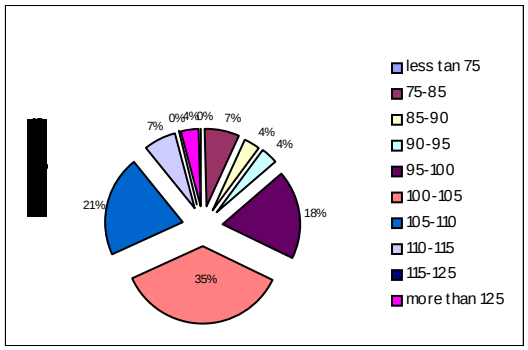

Fig. 6: Percentage distribution profile in different corridors with regard to assay of Injection Ceftriaxone Sodium calculated as Ceftriaxone base 500 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

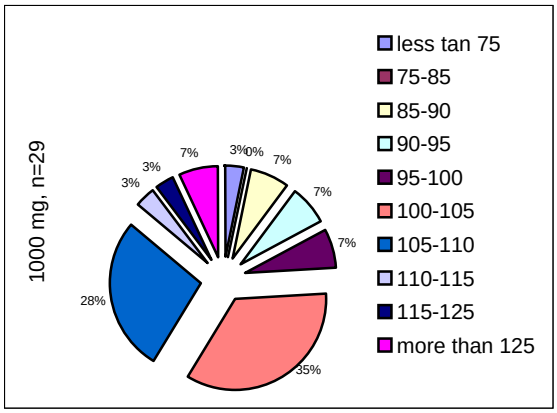

Fig. 7: Percentage distribution profile in different corridors with regard to assay of Injection Ceftriaxone Sodium calculated as Ceftriaxone base 1000 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

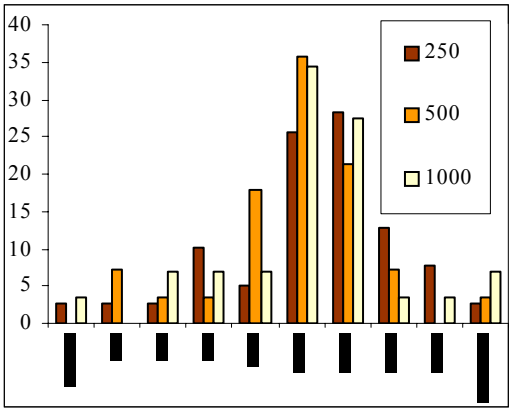

Fig. 8: Elucidates the trend percentage distribution profile in different corridors with regard to assay of Injection Ceftriaxone Sodium calculated as Ceftriaxone base 250, 500 and 1000 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU).

urban areas to rural areas of all four provinces of Pakistan covering all major cities and associated villages. The outcome of this part of the study unfolds the facts about the quality of drug product prevailing around with potential of process capacity of pharmaceutical manufacturing units and imported drug product at large.

Quality of injection Ceftriaxone sodium

96 representative samples randomly collected based on availability and consumption from different pharmacies and medical stores, hospitals of the entire region of the country to get access to verify the label claim of Ceftriaxone in Injection Ceftriaxone Sodium (tables 3 and 4) and (figs. 1-9). The evaluation of demographic information of all 96 samples revealed that the samples varied with regard to their manufacturing plant and batch numbers. These samples including reference samples of innovator and were aseptically filled by various 33 pharmaceutical manufacturing units of Pakistan and other exporting country like Switzerland, Korea etc. Total sample size consisted 40.62% of 250 mg, 29.16% of 500 mg and 30% of 1000 mg samples of Ceftriaxone injection.

15.62% (15) samples were found out of specification range i.e. 90-115% (USP 29) in which 46.6% (7) samples was found above the specified limit whereas, 53.3% (8) were found below the specified limit. The out of specification was observed higher up to 26.6% in injection 1000 mg, while 14.3% in 500 mg and 12.8% in 250mg. this shows a clear linear relation to each other and the value of R^2 = 0.88. Likewise, compliance to specifications was also found to behave in a similar manner as 79.3% in injection 1000 mg, while 85.7% in 500 mg and 87.1% in 250mg (tables 1 and 2).

The out of specification samples were equally distributed in both ends of the specification corridor in injection 1000 mg, while percentage of below standard samples was

higher than the samples crossed above permissible limit in 500 mg and found vise versa in 250 mg (tables 1 and 2).

All 15 OOS samples belong to 11 different Pharmaceutical manufacturing units and explore the non-conformance to quality and cGMP at large as weight of material in vials was also observed low in each case (tables 1 and 2).

100% (4) Samples of T33 manufactured in same Manufacturing unit exhibited out of specification results in which 75% of it were below standard (table 3, 4 and figs. 1-9).

Figs. 8-9 elucidate quality of the product Injection Ceftriaxone and risk areas possess potential to produce harm with high severity and degree of uncertainty around the product. Taylor RB, *et al* 2001 like various studies of the developing world reported in his study conducted in Nigeria that 48% samples does not comply with set pharmacopoeial limits, and this proportion was uniform for the various types of drugs tested. Although some preparations contained no active ingredient, most had amounts just outside the pharmacopoeial limits. study identified samples with both too much and too little active drug content but the situation is observed different in Pakistan as result of our study indicates that no sample was found without drug therefore may be called as fake drug in common terminology and spurious drug in legal terminology of the country, therefore, need of spot testing might not be useful like other comparable developing countries on one hand and result of study demands serious regulatory action and political willingness to combat the situation in order to protect the consumer life. All deviations seem to be process error. Hence, process controls and qualification of manufacturing instrument and process validation with appropriate quality management system adhered with cGMP needs to be ensured. However report Lambert *et al.* (2003) about quality of generic Ceftriaxone in UK could not verify.

Powders for injection constitute an important category of dosage forms for active molecules and relatively simple formulations with regard to the number of excipients and the manufacturing process. Ceftriaxone because of its instability in the aqueous environment cannot be marketed as ready-to-use injectable (Boylan and Fites, 1979). Complexities resulting from the presence of an excipients (e.g., interactions with the active molecule and product performance) are absent in powders for injection containing only the active drug. Formulations containing a drug and excipients also are relatively simple in terms of number and variety of excipients. For this reason, formulation development scientists tend to underestimate the development process of powder for injections (Bansal, 2002). Substandard drugs are contributing to global microbial resistance and therapeutic failure of infectious diseases as also reported by Taylor *et al*. (2001). The process capacity and performance capability in line with contemporary science based tools may reduce the scale of issues.

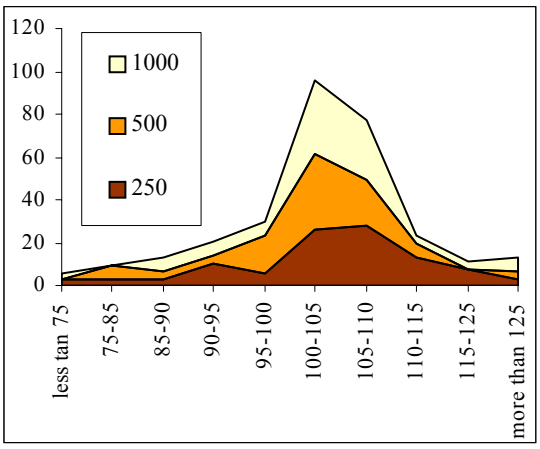

Fig. 9: Reviews the trend percentage distribution profile in different corridors with regard to assay of Injection Ceftriaxone Sodium calculated as Ceftriaxone base 250, 500 and 1000 mg, aseptically filled in various Pharmaceutical Manufacturing Units (PMU) and telltales about total capability index.

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