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Impact of Trend Analysis On Quality Of Finished Products In A Pharmaceutical Industry

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Abstract

In this study, trend analyses were carried out on the results obtained for microbiology purity tests and assay of 25 batches of Paracetamol Syrup obtained from a selected Pharmaceutical Industry within Minna Metropolis using the 3-Sigma Method. The results of the trend analyses showed the trend ranges of 60±31; 13.6±31 and 102.31±31 for Total Viable Aerobic Mesophilic Bacteria Plate Count, fungi and the assay respectively. The study showed that the results obtained from the trend analyses carried on all the results obtained for microbiology purity tests and assay of 25 batches of Paracetamol Syrup were within the trend ranges calculated and this suggest that the quality of the 25 batches of Paracetamol Syrup analysed were of good quality microbiologically and chemically.

Keywords: Microbiology Purity Test, Trend Analysis, Paracetamol Syrup, Pharmaceutical Industry

INTRODUCTION

The impact of trend analyses carried out on the results obtained for microbiology purity tests and assay of Paracetamol Syrups cannot be over-emphasised. It is possible to have the microbiology purity tests and assay results within the stated specifications yet the results obtained may be out of trend (OOT) when analysed. Trend analysis is very relevant and has a great impact on annual product review and assist in improving the quality of products in a Pharmaceutical Industry as a result of the corrective and preventive actions (CAPA) taken at the end of the analyses. Basically, pharmaceutical products can be divided into two categories, namely: sterile and non-sterile products. The non-sterile and sterile products must satisfy the appropriate microbiological purity tests and assay specifications that are included in pharmacopoeia monographs to ensure that they are therapeutically effective and safe for the patient/end user. According to McGuire *et al*. (2007), pharmaceutical industry discovers, develops, produces and markets drugs or pharmaceutical drugs for use as medications.

Pharmaceuticals are used in a variety of ways in the prevention, treatment and diagnosis of diseases. In recent years, manufacturers of pharmaceuticals have improved the quality of non-sterile pharmaceuticals such that today such products contain only minimal bioburden (Hugo and Russell, 1998). The occurrence of microbial contamination has been well documented and contaminants range from true pathogens such as *Clostridium tetani* to opportunistic pathogens such as *Pseudomonas aeruginosa* (Aulton, 2002). Several reports have also been published describing clinical hazards that are attributable to microbiologically contaminated pharmaceuticals (Obuekwe *et al.*, 2000; Akarele and Ukoh, 2002; Mwambete *et al.*, 2009). The major health concern is when such microbial contaminants exceed acceptable limits (United States Pharmacopeia (USP), 2003). It must be stressed, however, that the majority of cases of medicine-related infections are probably not recognized or reported as such (Schlegel, 1994).

Paracetamol Syrups are examples of non-sterile products that need to be assessed chemically and microbiologically so as to prevent out of specifications and microbial contamination which can reduce or even eliminate its therapeutic effect or cause drug-induced infections. The presence of microbes in drugs do not only make them hazardous but cause a significant deviation and change in the physical, chemical, contents of active ingredients and organoleptic properties of the drugs (Bhvani Shankar *et al.*, 2016).

In addition, microorganisms in Paracetamol Syrups can also make them toxic. The presence of even a low population of pathogenic microorganisms and opportunistic pathogens at higher levels or bacterial toxic metabolites which persist even after the death of the primary contaminants can make the product less potent and ineffective. Hence, the need to have Paracetamol Syrups that are physically, chemically and microbiologically fit in pharmaceutical industries cannot be over-emphasised.

Paracetamol Syrups are produced in batches and every batch must comply with physico-chemical and microbiological analyses specifications before they can be released for sale by the Quality Control Department. Paracetamol Syrups and other oral liquid preparations must be free of pathogenic bacteria such as: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Shigella dysenteriae* and other Enterobacteriaceae while total viable aerobic mesophilic bacteria plate count and fungi (yeast/mould) count is expected to be within the acceptable limits as stated in British Pharmacopeia (B. P., 2009).

This study focuses on the impact of trend analyses conducted on the results obtained for microbiology purity test and assay of 25 batches of Paracetamol Syrups from a selected Pharmaceutical Industry within Minna Metropolis. This becomes necessary so as to validate the production process and improve the quality of finished products (Paracetamol Syrups) physically, chemically and microbiologically.

MATERIALS AND METHODS

Study Area

The study area covered a selected Pharmaceutical Industry within Minna Metropolis.

Collection of Results

The results of microbiology purity tests and assay of 25 batches of Paracetamol Syrup were obtained from a selected Pharmaceutical Industry and subjected to trend analyses.

Computation and Trend Analyses using 3-Sigma Method

The results of microbiology purity tests and assay obtained for 25 batches of Paracetamol (P) Syrup coded P1-P25 were computed using 3-Sigma Method as outlined by Pradeep (2015) and *www.pharmaguideline.com*. A spread sheet was used to compute the average and standard deviation of the data. The range for the trend was computed by adding 31 to the average value (Upper Limit) and deducting 31 from the average value (Lower Limit) of the 25 batches. The alert limit was obtained by multiplying the standard deviation with 2 plus the average value while the action limit was obtained by multiplying the standard deviation with 3 plus the addition of the average value of the 25 batches.

RESULTS

Microbiology Purity Tests

The results of the microbiology purity tests are presented in Table 1. The 25 batches of the Paracetamol (P) Syrups did not contain any pathogenic bacteria such as of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus and Salmonella typhimurium* but contain Total Viable Aerobic Mesophilic Bacteria Count and Fungi (Yeast/Mould) counts that were within the specifications stated in B. P. (2009).

Table 1: Results of Microbiology Purity Tests of Twenty five (25) Batches of Paracetamol Syrup Subjected to Trend Analysis

Batches	Microbiology Purity Test Parameters					
	E. coli (cfu/ml)	*P. aeruginosa* (cfu/ml)	*S. typhimurium* (cfu/ml)	*S. aureus* (cfu/ml)	TVAMBPC (cfu/ml)	Fungi (cfu/ml)
P1	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P2	NIL	NIL	NIL	NIL	4×10^1	1×10^1
P3	NIL	NIL	NIL	NIL	5×10^1	2×10^1
P4	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P5	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P6	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P7	NIL	NIL	NIL	NIL	1.2×10^2	3×10^1
P8	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P9	NIL	NIL	NIL	NIL	3×10^1	1×10^1
P10	NIL	NIL	NIL	NIL	1×10^1	3×10^1
P11	NIL	NIL	NIL	NIL	2.2×10^2	2×10^1
P12	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P13	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P14	NIL	NIL	NIL	NIL	9×10^1	1×10^1
P15	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P16	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P17	NIL	NIL	NIL	NIL	1×10^1	3×10^1
P18	NIL	NIL	NIL	NIL	1.7×10^2	1×10^1
P19	NIL	NIL	NIL	NIL	8×10^1	1×10^1
P20	NIL	NIL	NIL	NIL	3.1×10^2	1×10^1
P21	NIL	NIL	NIL	NIL	1×10^1	2×10^1
P22	NIL	NIL	NIL	NIL	2.4×10^2	1×10^1
P23	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P24	NIL	NIL	NIL	NIL	1×10^1	1×10^1
P25	NIL	NIL	NIL	NIL	1×10^1	1×10^1

KEY: TVAMBPC- Total Viable Aerobic Mesophilic Bacteria Plate Count with B. P. specification of $\leq 1 \times 10^3$ cfu/ml; cfu/ml- Colony Forming Unit per millilitre; B. P. specification for Fungi (Yeast/Mould Count) is $\leq 1 \times 10^2$ cfu/ml; B. P specification for *E. coli*, *P. aeruginosa*, *S. aureus and S. typhimurium* is 0 cfu/ml

Trend Analysis of TVAMBPC

Average Value of TVAMBPC = 60 cfu/ml; Standard Deviation of TVAMBPC = 85.73 cfu/ml
Range for TVAMBPC = 29 – 91 cfu/ml (60±31 cfu/ml)
Alert Limit = Average Value of TVAMBPC + (2 x Standard Deviation)
= 60 + 171.46 = 231.46 cfu/ml
Action Limit = Average Value TVAMBPC + (3 x Standard Deviation)
= 60 + 257.19 = 317.19 cfu/ml

Trend Analysis of Fungi (Total Yeast and Mould Counts)

Range for Fungi = -17.4 – 44.6 cfu/ml (13.6±31 cfu/ml)
Alert Limit = Average Value + (2 x Standard Deviation)
= 13.6 + 14 = 27.6 cfu/ml
Action Limit = Average Value + (3 x Standard Deviation)
= 13.6 + 21 = 34.6 cfu/ml

Assay of Twenty five Batches of Paracetamol Syrup

The results of the assay of 25 batches of Paracetamol Syrup are presented in Table 2. The results of the 25 batches of the Paracetamol Syrups were within the specifications stated in B. P. (2009) (that is 95.0-105.0%).

Table 2: Assay Values of Twenty five Batches of Paracetamol Syrup Subjected to Trend Analysis

Batches	Assay Values (%)
P1	101.85
P2	101.85
P3	101.85
P4	100.05
P5	100.98
P6	100.35
P7	101.68
P8	100.70
P9	102.53
P10	101.06
P11	103.71
P12	100.11
P13	102.93
P14	101.42
P15	101.43
P16	104.56
P17	103.56
P18	103.47
P19	103.80
P20	104.35
P21	102.66
P22	103.51
P23	102.11
P24	103.71
P25	103.58

Trend Analysis of Assay Results

Average Value of Assay = 102.31%; Standard Deviation of Assay = 1.36%

Range for the Trend Analysis of Paracetamol Syrup = 71.31 – 133.31% (102.31±31%)

Alert Limit = Average Value + (2 x Standard Deviation)

= 102.31 + (2 x 1.36) % = 105.03%

Action Limit = Average Value + (3 x Standard Deviation)

= 102.31 + (3 x 1.36) % = 106.10%

DISCUSSION

The results of microbiology purity tests in Table 1 were in agreement with the ranges set for bacteria (60±31 cfu/ml) and fungi (13.6±31 cfu/ml). However, the values of 310 cfu/ml and 240 cfu/ml TVAMBPC obtained for batches P20 and P22 respectively were higher than the alert limit of 231.46 cfu/ml even though the values obtained were within B. P. specifications of ≤ 10^3 cfu/ml as stated in B. P. (2009). These results obtained for P20 and P22 and which were above the alert limit suggest that the Quality Control Manager needs to draw the attention of the Production Manager to the need to improve in the sanitation and hygiene of the production personnel especially those that are involved in the compounding of the Paracetamol Syrup. The results also suggest that there is a need to sanitize the production utensils. Production utensils if not proper sanitize have the potential to contaminate Paracetamol and other pharmaceuticals as opined in the work of Mugoyela and Mwabete (2010). Mugoyela and Mwabete (2010) also reported that medicines can be microbiologically contaminated as a result of improper handling and poor hygienic procedures. The results in Table 1 also showed that the values obtained for TVAMBPC for batches P1-P25 were below the value obtained for action limit for TVAMBPC. This suggest that taking a major action to overhaul or change formulation procedure may not be immediate but it is necessary to draw the attention of the Production Manager to the batches concerned to avoid any repetition of such results when subjected to trend analysis in the future. In addition, the results of fungi obtained for batches P7 (30 cfu/ml), P10 (30 cfu/ml) and P17 (30 cfu/ml) in Table 1 were above the value obtained for alert limit (27.6 cfu/ml) although the results were in agreement with the specifications stated in B. P. (2009) for fungi for non-sterile products like Paracetamol Syrups.

The results possibly suggest that there is a need to draw attention to proper aeration of the production room to prevent the escalation of fungi growth. However, the value obtained for all the batches were below the value obtained for the action limit. Hence, this suggests that taking major action may not be necessary now.
Furthermore, the values obtained for the assay of 25 batches of Paracetamol Syrup in Table 2 were within the range set for the trend analysis (102.31±31%). In the same vein, all the values obtained for P1-P25 were below both the alert and action limits (Table 2). These results suggest that the strict observance of GMP should be sustained in the manufacturing procedure of Paracetamol Syrup. As reported in the work of De La Rosa *et al*. (1995), the failure of strict observation of good manufacturing practice at any stage of production may greatly affect the microbiological and chemical quality of the end products.

CONCLUSION

The study showed that all the results obtained for the 25 batches of Paracetamol Syrup were not out of trend (OOT) and they were within the calculated ranges for the trend analyses.

RECOMMENDATIONS

From the results obtained in the trend analyses performed on the results of the 25 batches of Paracetamol Syrup, the following possible recommendations are necessary:
(i) It is possible to have results that are within the B. P. specifications but when subjected to trend analyses may become OOT hence it is recommended for every Pharmaceutical Industry to subject their results to trend analyses in order to improve the quality of their products.
(ii) Trend analyses are useful and have great impact in annual product quality review, thus, it is highly recommended.

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