Use of Product Quality Review to Evaluate Quality and Process Capability: A Case Study of Ibuprofen in a Model Tablet Manufacture

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Product quality review in the pharmaceutical industry is a regulatory requirement comprising periodic evaluation of licensed pharmaceutical products to verify consistency of the manufacturing process and appropriateness of specifications. In this study, product quality and process capability in the manufacture of ibuprofen tablets were evaluated. A quality review of 39 batches produced in the year 2019 was conducted. Components for review included starting materials, critical in-process controls, finished product results, non-conformances, deviations and quality relevant product complaints. Control charts and statistical analysis were used to trend results and compute process capability indices. Starting materials, in-process controls and finished product results complied with quality specifications. Process capability indices for tablet weight, size, dissolution and assay were greater than 1.0. The study showed that the established quality attributes of ibuprofen tablets were consistently produced and it was concluded that the manufacturing process was controlled and sufficient to assure reproducible outcomes.

KEY WORDS: Capability, pharmaceutical, process, product, quality, review.

INTRODUCTION

Product Quality Review (PQR) is a mandatory requirement in Good Manufacturing Practices (GMP) that involves periodic evaluation of all licensed pharmaceutical products by the manufacturer. The aim of this evaluation is to verify consistency of existing processes and the appropriateness of current specifications for both starting materials and finished products in order to highlight any trends and to identify product and process improvements [1-4]. Pharmaceutical GMP guidelines require that all finished products should be reviewed annually for quality standards to determine the need for change in specification or manufacturing process of a drug product [5-7]. The review consists of a comprehensive report that covers all critical elements of the product life cycle. The report includes, but not limited to, list of manufactured batches, starting materials which are used for the product, equipment qualification, critical in-process controls, finished product results, failed batches, deviations, all process and analytical method changes, quality related complaints and recalls [8].

The PQR data is interpreted and evaluated by use of control charts to identify existing trends [9-12]. Statistical analysis is performed to determine process capability indices. The assumption is that the data is normally distributed, where $\bar{x}$, σ, USL and LSL represent mean, standard deviation

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(SD), upper specification limit and lower specification limit, respectively. The mean and SD are used to determine the upper and lower control limits (UCL and LCL) which establish whether a process is out of control. Process capability index, C_p, measures spread of the process data within the specification limits whereas C_{pk} measures centring of data and acceptability of the manufacturing process [13-15]. A process is capable when C_p and C_{pk} values are greater than one (>1.0) and almost all measurements fall within specification limit. A process capability study identifies inappropriate specification limits, highlights variability in process and assists manufacturers to take the required corrective actions to ensure compliance to quality standard.

Periodic quality reviews are usually prepared as a regulatory requirement and for internal consumption by the individual companies. There has not been much independent work in literature on PQR despite it being an important tool for product quality improvement. Furthermore, information on evaluation of PQR reports to identify areas of product and process improvement is limited. Product quality review and process performance evaluation entails application of engineering statistics to manufacturing processes.

In this study, product quality and process capability in the manufacture of ibuprofen 200 mg tablets by Elys Chemical Industries Ltd., Kenya, were evaluated by conducting quality review of the product for the year 2019. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used widely as an analgesic and antipyretic. It has poor aqueous solubility and drug dissolution may be a rate limiting step in oral bioavailability [16-18]. The production process of ibuprofen tablets comprises granulation, blending, compaction, coating of tablet cores and packing of the finished product.

EXPERIMENTAL

Data collection

Product quality review of ibuprofen tablets was conducted for 39 batches which were produced in the year 2019. Ibuprofen tablets contain ibuprofen BP, maize starch, potassium sorbate, polyvinylpyrrolidone, talc, gum acacia, sucrose, calcium carbonate, methyl paraben sodium, propyl paraben sodium, erythrosine pink dye, titanium dioxide and carnauba wax. Data on product quality attributes across the manufacturing process and after sales non-compliances were collected and evaluated. Quality control test results for all batches of active ingredient (drug substance) and excipients were collected and reviewed for compliance with standard quality specifications. Parameters that were evaluated for raw materials included solubility, assay, optical rotation, sulphated ash, loss on drying (LoD), microbial purity and pH. In-process and finished product data on critical quality attributes such as weight of tablet, disintegration time, dissolution and assay were collated for all batches and examined relative to standard specification. In addition, information on significant deviations, non-conformances, change controls, quality related product complaints, stability records, product recalls performed during this period, corrective and preventive actions and qualification status of equipment that were used in the production process were evaluated and documented.

Data treatment and analysis

The data was subjected to statistical analysis by computation of mean, standard deviation, UCL, LCL and plotting the results. X-bar and histogram charts were used to monitor the process mean and distribution of data. The process capability indices C_p, C_{pku}, C_{pkl} and C_{pk} were computed using a literature protocol [19].

Where:

$$UCL = \bar{x} + 3\sigma; \qquad LCL = \bar{x} - 3\sigma$$

$$C_p = \frac{USL-LSL}{6\sigma}; \qquad C_{pku} = \frac{[USL-\bar{x}]}{3\sigma}$$

$$C_{pkl} = \frac{[\bar{x} - LSL]}{3\sigma}$$

$$C_{pk} = \min\left\{\frac{USL - \bar{x}}{3\sigma}, \frac{\bar{x} - LSL}{3\sigma}\right\}$$

RESULTS

Active pharmaceutical ingredient (Ibuprofen BP) review

Twenty-two batches of ibuprofen drug substance were received in year 2019. The batches complied with standard specification for the parameters that were tested including description of powder, particle size, identification and solubility. A summary of quality control test results for quantifiable specification parameters is shown in Table 1. All the batches complied with the standard specification for ibuprofen. Analysis of assay results using X-bar control chart to monitor variability is shown in Figure 1. All data values were within the specification limits.

Excipients review

All excipients that were used in production of Ibuprofen tablets (Table 2) conformed to the respective preset quality standards. These materials complied with specification for identification, solubility, assay, optical rotation, sulphated ash, LoD, microbial purity and pH, as applicable.

Table 1: Analytical results for ibuprofen raw material and their trending (n = 22)

	Optical rotation (-0.05° to +0.05°)	LoD (<0.5%)	Sulphated ash (<0.1%)	Assay (98.5-101.0%)
Minimum	0.00	0.02	0.02	99.45
Maximum	0.00	0.30	0.09	100.71
Average	0.00	0.07	0.05	100.04

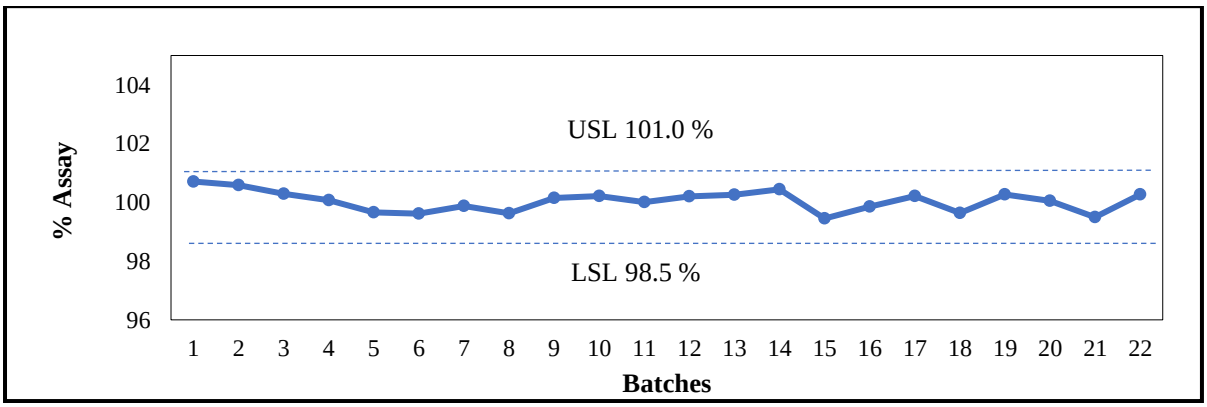

Figure 1: X-Bar chart for assay of ibuprofen active pharmaceutical ingredient (n=22).

In-process controls (core tablets)

Table 3 shows the in-process analysis results (lowest and highest values within a batch) of all batches of ibuprofen tablets that were manufactured during this period. Quality parameters that were tested complied with preset specifications. The weight of the core tablet, friability, and disintegration time ranged from (249–270 mg), (0.03–0.79%) and (17–108 sec), respectively.

Table 2: Analysis results of excipients used in production of ibuprofen tablets

Ingredient	Number of batches	Quality parameters
Maize starch	13	Solubility, identification, pH, LoD, microbial contamination, sulphated ash, oxidizable substances.
Potassium sorbate	1	Solubility, acidity/alkalinity, aldehydes, heavy metals, LoD, assay.
Talc	2	Solubility, identification, acidity/alkalinity, water-soluble substances, loss on ignition, microbial contamination.
Gum acacia	1	Solubility, identification, starch, dextrin and agar, tannins, LoD, microbial contamination.
Sucrose	18	Description, solubility, identification, appearance of solution, conductivity, colour value, specific optical rotation, sulphites, reducing sugars, LoD, microbial contamination.
Calcium carbonate	2	Description, solubility, identification, solubility, chlorides, sulphates, barium, LoD, assay.
Methyl paraben sodium	1	Solubility, identification, appearance of solution, pH, chlorides, sulphates, heavy metals, water, assay.
Propyl paraben sodium	2	Solubility, identification, appearance of solution, pH, chlorides, sulphates, heavy metals, water, assay.
Erythrosine pink	6	Chlorides, sulphates, water insoluble matter, arsenic, lead, mercury.
Titanium dioxide	1	Solubility, identification, appearance of solution, acidity/ alkalinity, water-soluble substances, barium, iron, assay.
Carnauba wax	2	Solubility, identification, appearance of solution, acid value, melting point, saponification value, total ash value.

Table 3: In-process quality data of ibuprofen core tablets

Parameter	Average weight (247.6-273.6 mg)		Friability (<1.0%)		Disintegration time (<15 min)	
	Low (mg)	High (mg)	Low (%)	High (%)	Low (sec)	High (sec)
Minimum	249.00	265.00	0.03	0.13	17	23
Maximum	255.00	270.00	0.18	0.79	58	108
$\bar{x}$	252.51	267.51	0.10	0.28	22	48
σ	1.30	1.24	0.05	0.11	0.08	0.25
UCL	256.41	271.23	0.25	0.60	0.45	1.23
LCL	248.62	263.80	N/A	N/A	N/A	N/A

Key: $\bar{x}$=mean; σ=standard deviation; UCL & LCL=upper & lower control limits; N/A=Not applicable.

Finished pharmaceutical product (ibuprofen coated tablets)

Statistical analysis of ibuprofen coated tablets results for the two-sided specification parameters (assay, weight, length and thickness) using X-bar control charts to monitor process variability is shown in Figure 2. All values for each of these parameters for all batches fell within the control limits. Similarly, results for the other quality attributes (disintegration, friability, moisture content and dissolution) were within specification limits as

presented in Table 4. The mean, standard deviation, upper and lower specification limits, upper and lower control limits are presented. All the data values were within the preset specification limits.

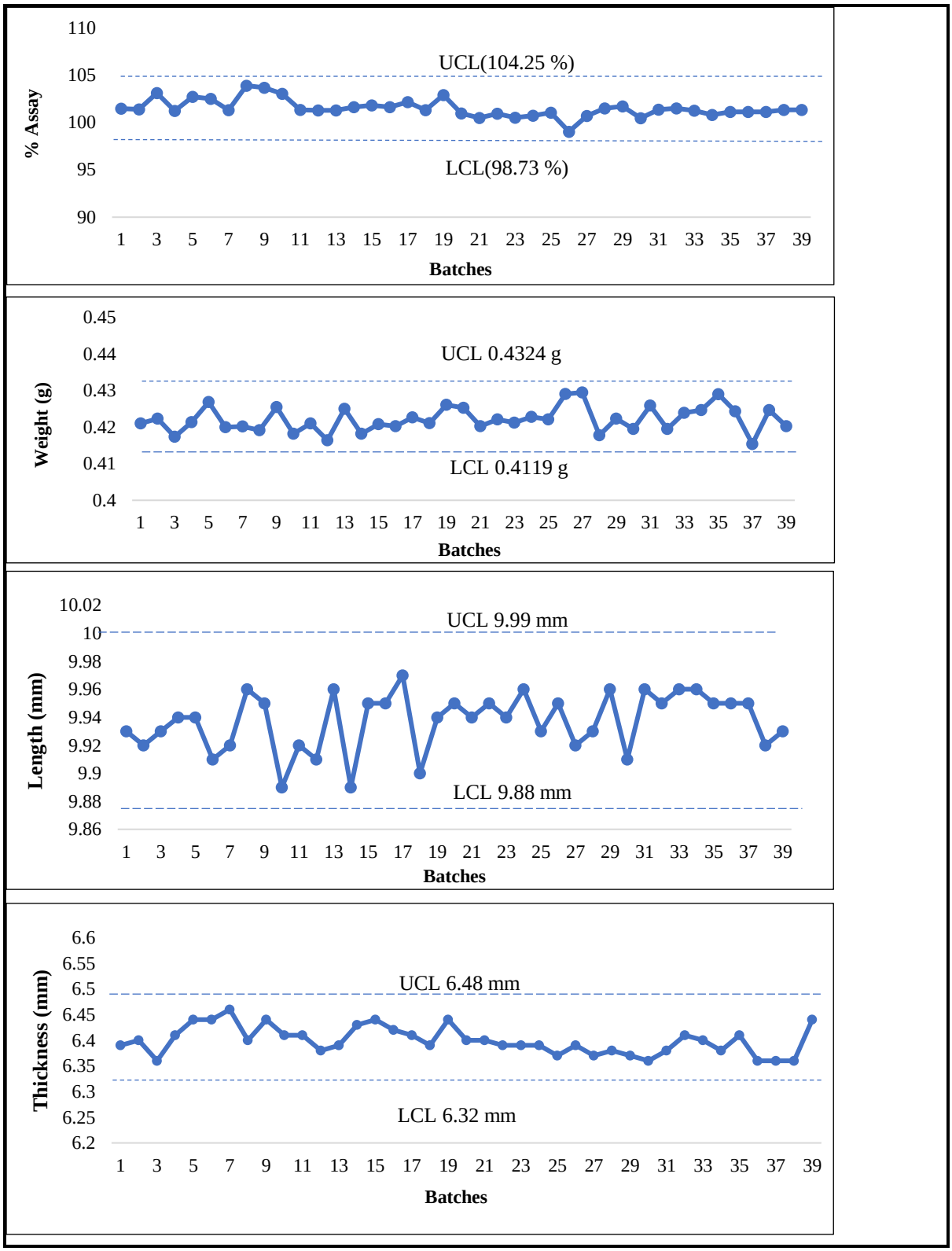

Figure 2: X-bar charts for the assay, weight, length and thickness of ibuprofen coated tablets (n=39). UCL and LCL = upper control limit and lower control limit.

Table 4: Quality data for the finished ibuprofen coated tablets

Parameter	Weight (0.444 g±10%)	DT (<60 min)	Friability (<1.0%)	Length (10.0±0.2 mm)	Thickness (6.3±0.2 mm)	Moisture (1-5%)	Dissolution (> 85%)	Assay (95-105 %)
Minimum	0.4154	10.1	0.08	9.89	6.36	1.36	95.30	99.02
Maximum	0.4295	27.87	0.31	9.97	6.46	2.39	104.42	103.8
$\bar{x}$	0.4221	15.08	0.20	9.94	6.40	1.89	100.52	101.4
σ	0.0034	3.81	0.052	0.020	0.03	0.28	2.15	0.92
UCL	0.4324	26.07	0.35	9.99	6.48	2.73	NA	104.2
LCL	0.4119	NA	NA	9.88	6.32	1.05	94.08	98.73
USL	0.4884	60.0	1.0	10.2	6.5	5.0	NA	105
LSL	0.3996	NA	NA	9.8	6.1	1.0	85.0	95.0
C_{pku}	6.49	3.97	5.16	4.30	1.25	3.71	NA	1.27
C_{pkl}	2.21	NA	NA	2.24	3.72	1.06	2.41	2.35
C_p	4.35	NA	NA	3.27	2.48	2.39	NA	1.81
C_{pk}	2.21	N/A	N/A	2.24	1.25	1.06	N/A	1.27

Key: DT=Disintegration Test; NA=Not applicable; $\bar{x}$ = mean; σ = standard deviation; UCL and LCL = upper control limit and lower control limit; USL and LSL = upper specification limit and lower specification limit; C_p, C_{pku}, C_{pkl} and C_{pk} = process capability indices.

Process capability indices review (coated tablet)

The capability indices (C_p and C_{pk}) obtained for the evaluated parameters were greater than 1. The lowest value of C_p and C_{pk} was 1.81 (assay) and 1.06 (moisture content), respectively. Figure 3 presents histogram chart with normal distribution overlay of assay results showing low spread and centering of values within specification limits; with $\bar{x}$ (101.49%), σ (0.92), C_p (1.87) and C_{pk} (1.27).

Equipment qualification, batch failures, deviations, investigations, change controls, stability and product complaints review

Critical equipment that were used in production of ibuprofen tablets were reviewed and found to be in qualified state. There was no out of specification result on starting materials, in-process controls and the finished product. One deviation related to equipment failure was observed during this period. This incident was investigated following the standard procedure in place for handling deviations. Subsequent corrective and preventive actions were implemented. No changes were made to the manufacturing process, product formulation or analysis procedures. Stability studies for the finished product were carried out as per the existing stability monitoring program. There were no product recalls or quality related complaints reported on ibuprofen tablets over the PQR duration.

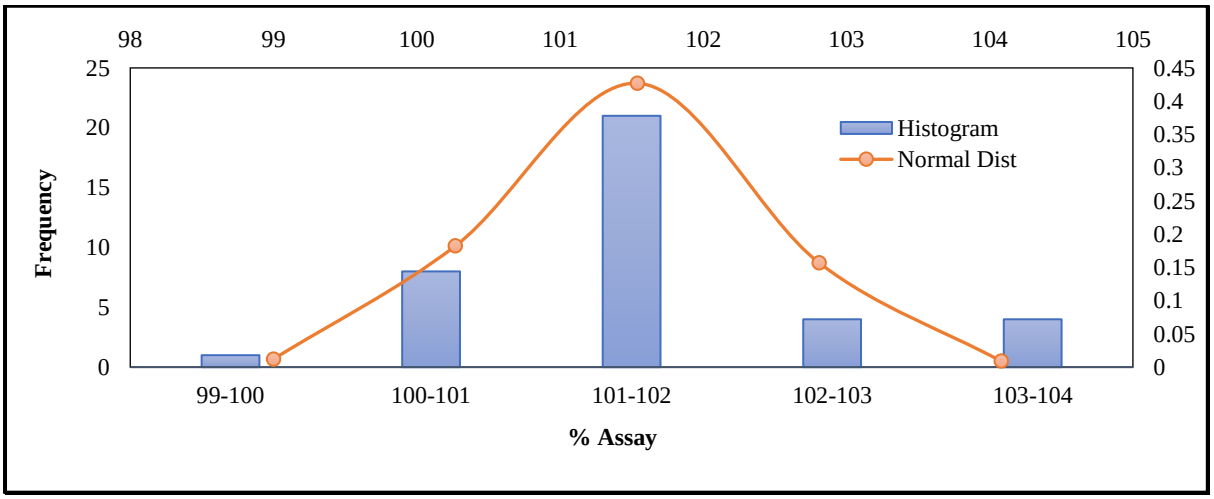

Figure 3: Assay results for ibuprofen coated tablets represented with a histogram and normal distribution overlay.

DISCUSSION

Poor quality drugs may result in serious health implications, including treatment failure [20-22]. Consequently, the pharmaceutical manufacturing industry is stringently regulated to ensure consistent production of quality products. Periodic PQR is a regulatory requirement that provides sufficient evidence of GMP compliance in the pharmaceutical industry. The findings of this annual product quality review evaluation suggest that the manufacturing process of ibuprofen tablets is capable of consistently producing tablets that are within the established specifications. The X-bar control charts demonstrated that product variability is under control. The process capability indices verify consistency of the process and appropriateness of specifications for both starting materials and finished products.

All the batches of ibuprofen tablets that were manufactured by Elys Chemical industries Ltd., Kenya, in the year 2019 complied with the standard quality specification. The results were within the upper and lower control limits indicating that the process of manufacture is in control. This may be attributed to adherence to GMP requirements by the manufacturer. Pharmaceutical ingredients are adequately controlled through a standard procedure for qualification of vendors to minimize the risk of non-compliance. In addition, consistent manufacture of pharmaceutical products can result from the engagement of personnel that are qualified and appropriately trained to perform the production activities. Furthermore, capability of processes could be credited to validated equipment, manufacturing process and method of analysis. This ensures process consistency and quality control results that are accurate and reproducible.

Capability process indices, C_p and C_{pk} for two-sided specification parameters that were tested (tablet weight, tablet size, water content and assay) were greater than 1.0 indicating that the manufacturing process is capable of producing tablets that are within the specified limits and is operating close to the process mean. However, a C_{pk} value of > 1.33 is desirable as this gives sigma level of 4 and provides better centering of the process and unlikely that any item will be outside the specification limits [13]. The C_{pk} value for moisture content for the finished product in this review was 1.06 (mean value 1.78%, LSL 1%, USL 5%, C_p 2.39). The test values exhibited low dispersion but it may be appropriate to consider revision of the current specification limit to 0.5 – 4 % in order to enhance the C_{pk} value. This proposal will translate the C_p and C_{pk} values to 2.09 and 1.66, respectively. The review will improve the centering of values relative to the specification limit and avoid the risk of obtaining non-compliant result. The proposed change should be evaluated for any product quality related risks and executed following a standard change control procedure. It is noteworthy to highlight the observation that was made on assay results for the finished product, where the values of C_p and C_{pk} were 1.87 and 1.27, respectively.

Despite all values being within the specification limits, the mean (101.49%) was close to UCL (105%) indicating that the values were not sufficiently centered. It was also noted that the assay values for all batches ranged between 99.02% and 103.88%, with UCL of 104.25%. As such, there is a possibility that a data value could fall out of the USL, and hence, a potential risk of batch failure. This observation was investigated expansively and the cause of the drift identified as a titration error arising from difficulty in identification of the endpoint during quality control testing of the product. Consequently, a more accurate and pharmacopoeial method (high-performance liquid chromatography) has now been adopted for analysis of this product.

This study demonstrates the necessity of PQR evaluation and statistical computation of capability indices for critical process parameters and quality attributes of a pharmaceutical product. The evaluation is vital in identifying the level of process performance, potential quality risks and also detects trends which can be investigated and corrected to minimize failure thus improving quality and the robustness of the manufacturing process. Product quality review is powerful tool for detecting out-of-control variables, appropriateness of specifications and capability of the manufacturing process as has been shown in previous PQR studies [14, 15]. The capability indices are useful for improvement of both process and laboratory analytical performance.

It is therefore important for all pharmaceutical manufacturers to perform regular PQRs as required by GMP regulation and embrace statistical data evaluation techniques and process control in order to minimize or eliminate instances of nonconformity to quality standards. Further, the national DRAs are required to ensure that regulatory obligations are being met through regular and stringent inspections of manufacturing sites. The inspectors should ensure that PQR is performed in a timely manner, the report is accurate, comprehensively evaluated and recommendations are implemented promptly. A well conducted PQR provides essential quality data across the whole product life cycle and could be adopted by government policy makers and nongovernmental organisations as a tool for performing risk-based desk assessments for prequalification of pharmaceutical manufacturing sites for emergency procurement of pharmaceutical products.

CONCLUSION

In this study, annual PQR of ibuprofen tablets manufactured by Elys Chemical Industries Ltd. in the year 2019 was conducted. Analysis of data captured by the pharmaceutical quality system at the manufacturing site verified the suitability of existing specifications for both pharmaceutical ingredients and finished product and repeatability of the current manufacturing process. Evaluation of critical product quality parameters and process capability indices showed that the established quality attributes of ibuprofen tablets were consistently produced. It was concluded that the manufacturing process was controlled and capable of producing tablets that are within the established specification limits.

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