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EC PHARMACOLOGY AND TOXICOLOGY
Research Article

Role of Statistical Process Control of Pharmaceutical Product to Monitor Consistency of the Manufacturing Operation

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Received: April 19, 2018; **Published:** May 11, 2018

Abstract

Objective: Registered products in the health regulatory agencies should have definite specification acceptance criteria which must be met. However, products that are not manufactured in Good Manufacturing Practice (GMP) environment are not acceptable even if they were complying with the specification limits according to Food and Drug Administration (FDA). Accordingly, an effective monitoring system should be established to detect any deviations in the product manufacturing process before any true excursion would occur.

Methods: The current study aimed to study an oral pharmaceutical product based on gabapentinoid class of active pharmaceutical ingredient (API) by monitoring potency of 96 batches of the product that were manufactured in a new experimental pharmaceutical firm for non-sterile products. The quality unit team collected the assay data from quality control and interpreted it using commercial statistical software programs to interpret descriptive statistics, box plot, variable control chart, normal probability plot, capability plot and histogram.

Results: The assay results of the manufactured product batches showed tendency toward normal distribution with overall shift near the upper specification limit (110%). Thus, the process was not centered. Moreover, intermittent occurrence of out-of-control batches was observed using trending chart for the assay results where variations due to extraneous or process mean shift are expected, although none of the results of the assay was out-of-specification (OOS) limits.

Conclusion: Out-of-control points were detected indicating that further process improvements are required for better control of the product quality. Statistical process control (SPC) tools provide provision of warning for abnormal foreseen events to correct them before any true excursion would be seen in the final medicinal product.

Keywords: *GMP; FDA; Gabapentinoid; Quality Control; Out-of-Control; SPC*

Abbreviations

GMP: Good Manufacturing Practice; FDA: Food and Drug Administration; SPC: Statistical Process Control; SISPQ: Safety, Identity, Strength, Purity and Quality; OOS: Out-of-Control; API: Active Pharmaceutical Ingredient; QC: Quality Control; QA: Quality Assurance; USL: Upper Specification Limit; I-MR: Individual-Moving Range; ROUT: Robust regression and Outlier removal

Introduction

Safety, identity, strength, purity, and quality (SISPQ) are the basic core criteria that any pharmaceutical product should meet [1]. Moreover, any product should be manufactured in good manufacturing practice (GMP) environment, otherwise, it will be considered adulterated even if the medicinal product has met the required specifications and no defect was present as could be demonstrated by Food and Drug Administration [2].

Application and importance of Lean Six Sigma methodologies and quality tools have been addressed before by researchers in the pharmaceutical industry field in various aspects of the quality characteristics monitoring of the medicinal product during manufacturing processes [3].

The basic assumption (theory) that relates SPC with compliance to GMP is based on the following: 1- Product manufactured in GMP environment is crucial by regulatory agencies such as FDA [4]. Otherwise, the medicinal product is considered adulterated. 2- Manufacturing in GMP conditions means that the yielded product characteristics are consistent, reproducible, stable and predictable every time for every manufactured batch (FDA, 2015). 3- These characteristics are attainable when the manufacturing processing steps are done in a state of control each time with the same rules followed exactly as they should be done [5]. 4- When the operation is in control, the Shewhart chart should prove the normal process variability attributed to the common cause variation of the process [6]. Any deviation from the normal process can be detected in the trending chart "red dots" which could stem from special causes assignable to influential factors not related to the ordinary operation [7]. 5- Accordingly, standard operations which are deviated or modified will not be consistent with the other normal operations. This means variation within the process from batch to batch which is violation of GMP concept. 6- Out-of-control points "red dots" may indicate that the operation could lead to unpredictable outcome even if the product has met the specification limits (e.g. assay 90% - 110% for the assay of active pharmaceutical ingredient (API)) [8].

The present study aimed to investigate the product compliance to GMP through statistical process control (SPC) using selected product case based on a non-sterile oral solid product based on gabapentinoid class of API prepared in pharmaceutical form. SPC will show the current state of the process control, consistency, reproducibility, and stability over time.

Materials and Methods

Materials

A newly established pharmaceutical plant for non-sterile manufacturing has produced 96 batches of gabapentinoid class of API in pharmaceutical dosage form over one year from 2016 to 2017 [9].

Methods

The assay of the active pharmaceutical ingredient and results collection were performed by quality control (QC) team of the new experimental firm (BPE facility). Data interpretation and analysis was done by quality assurance (QA) team (BPE facility).

Statistical analysis

Statistical analysis was performed using software programs. GraphPad Prism 6.01 was used for descriptive statistics. Box-and-whisker diagram, individual-moving range (I-MR) control chart, normal probability plot, capability plot and histogram were constructed using Minitab® 17.1.0. The use of these programs has been addressed before [10,11].

Results and Discussion

Statistical analysis of gathered readings of 96 consecutive batches showed that they passed normality tests with mean; geometric mean and median values are very close accompanied with very low level of skewness [12]. However, the reading range covered 76% of the specification limit, with the greatest value very close to the upper specification limit (USL). These findings were demonstrated in table 1. Accordingly, the spreading of the normally distributed data is relatively high in relation to the specification window.

Column Statistics	Assay of API*
Number of values	96
Minimum	95.20
25% Percentile	100.1
Median	102.2
75% Percentile	104.7
Maximum	109.4
10% Percentile	98.32
90% Percentile	106.5
Mean	102.3
Std. Deviation	3.143
Std. Error of Mean	0.3208
Lower 95% CI of mean	101.7
Upper 95% CI of mean	103.0
Lower 95% CI of median	101.3
Upper 95% CI of median	102.8
D'Agostino & Pearson omnibus normality test	
K2	1.330
P value	0.5142
Passed normality test (alpha = 0.05)?	Yes
P value summary	ns
Shapiro-Wilk normality test	
W	0.9904
P value	0.7252
Passed normality test (alpha = 0.05)?	Yes
P value summary	ns
KS normality test	
KS distance	0.06520
P value	0.2000
Passed normality test (alpha = 0.05)?	Yes
P value summary	ns
Coefficient of variation	3.07%
Geometric mean	102.3
Lower 95% CI of geo. mean	101.6
Upper 95% CI of geo. mean	102.9
Skewness	0.05186
Kurtosis	-0.4857
Sum	9823

Table 1: *Descriptive statistics of readings obtained for the assay of Gabapentinoid class of API in pharmaceutical dosage form from 96 batches (generated using GraphPad Prism 6.01).*

**Active Pharmaceutical Ingredient ns: Not significant; CI: Confidence Interval.*

On the other hand, Box-and-whisker plot, shown in figure 1, showed pattern of data distribution with no outliers could be detected [13]. This finding was confirmed using Robust regression and Outlier removal (ROUT) method at Q = 10.0% by GraphPad Prism 6.01 [14]. Thus the sample is homogenous with no aberrant numbers that cause rejection before conducting further analysis.

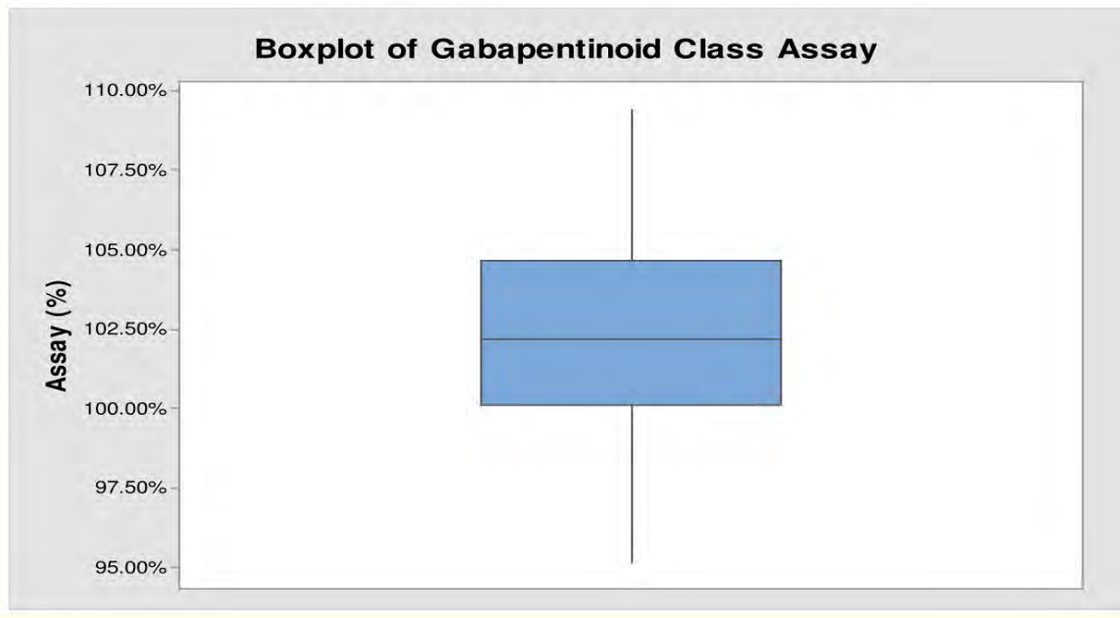

Figure 1: *Box plot diagram showing the pattern of data distribution for the assay of 96 batches of gabapentinoid class of API in pharmaceutical dosage form with no outliers could be detected. (generated using Minitab® 17.1.0).*

Figure 2 illustrated SPC tools performed on raw data. Normality assumption was confirmed by normal probability plot which is prerequisite for trending chart construction. However, capability plot showed that the process is shifted toward the USL. While the short-term process is still within the specification range, over long term it may exceed the USL [15]. Moreover, capability histogram showed in addition to the upper shift, a flattening with plateau appearance indicating possible mix of more than one operation into single process [16].

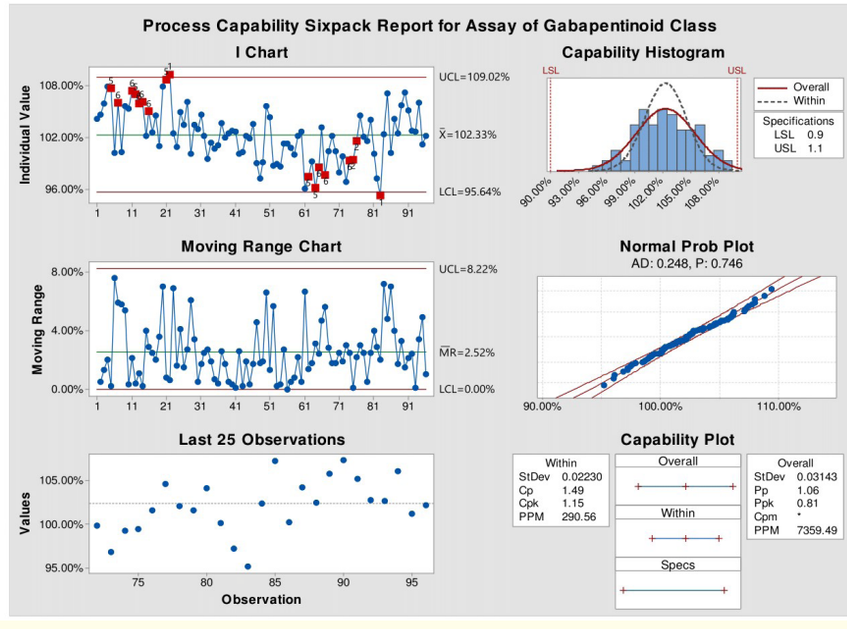

Figure 2: *Capability Sixpack quality tools for normally distributed assay results of 96 batches of gabapentinoid class of API in pharmaceutical formula (generated using Minitab® 17.1.0)*

I-MR chart is composed of two charts: MR which provides measure for process variation and should be investigated first before I chart to exclude that variation in the mean of I chart is not attributed to the process variability. MR chart showed normal variability pattern with no out-of-control points [Interpret the key results for I-MR Chart - Minitab Express. Support.minitab.com, http://support.minitab.com/en-us/minitab-express/1/help-and-how-to/control-charts/how-to/individuals-data/i-mr-chart/interpret-the-results/key-results/, last accessed on 12/09/2017]. However, I chart showed clusters of special-cause variation points "red-dotted batches". The last 25 readings did not show any kind of specific or recurring pattern that influence the process. Interestingly, the assay mean that was shifted toward upper limit initially, was drawn in the lower limit side direction. The general trend is decreasing with time then rising again at the end, indicating a fluctuation in the apparently oscillating process. Further investigation is required to determine the root cause of such behavior during manufacturing process, especially capsule filling operation. It should be noted that all results of the assay were within the acceptance criterion. Extraneous factors associated with process shift of the assay results should be investigated. For example, one of the assignable causes was found during investigation (at least partially) could be attributed to the machine wearing, where scheduled maintenance interval time should be shortened and/or partial or total replacement should be conducted. Moreover, the manufacturing machine operation should be conducted with the same processing parameters in each shift without deviation throughout the whole operation period of the manufactured product.

The current process needs improvement and not centered with the risk of drifting toward the USL. Thus, the capability values provided under the capability plot in figure 2 cannot provide true measure for the process efficiency because it was unstable and hence unpredictable. Out-of-control batches should be investigated and the causative factors should be corrected before reestablishing new process monitoring parameters. SPC detected spots that should be investigated to achieve better GMP control in the process which is considered by the definition provided by FDA crucial for the release of pharmaceutical products.

Conclusion

SPC could detect out-of-control batches for single monitored process. By spotting these aberrant points, non-compliance to GMP should be elucidated even though these batches had met the specification limit and the factors these deviation should be investigated to prevent their reoccurrence. Yet, they provided early warning for the possible excursions that could emerge if these deviations were not properly corrected before any true out-of-specification results would occur.

Acknowledgements

None.

Conflict of Interest

Author has declared that no competing interests exist.

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Volume 6 Issue 6 June 2018