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Current Perspective in Quality Control Examining and Extended Researching for Certain Aspects of Active Pharmaceutical Ingredient Using Statistical Process Control

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ABSTRACT

Control charts are an important part of statistical control because they allow the inspection characteristics of manufactured pharmaceutical products to be tracked and controlled. It helps show current processes and status and, if necessary, identifies areas for further development. The investigation and analysis of an initial trend for a few inspection properties of the manufactured chemical 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid is the main focus of the current work. Using the well-known commercial SPC platform for comprehensive SPC analyses. The datasets of the assay and polarization rotation followed the Weibull pattern. While the results of the overall impurities and particle size test data were adopted for Gaussian spreading the Johnson family transformation was implemented for the latter. An exploratory Individual-Moving Range plot is the method used to trend the datasets and capacity analyses were conducted in accordance with that method. Improvements are required to enhance the quality of inspection properties at the preliminary steps since there are signs of a low capability process in the particle size test and the assay to some extent. In addition, the means of the quality tests should be brought to the center since the preliminary data are not in the middle of the specification range. Thus, some inspection characteristics are lower quality than others and need immediate correction and enhancement at the initial stages of the establishment of the manufacturing process and criteria. This perspective highlights the importance of control charts in the examination of the quality of chemically manufactured materials.

INTRODUCTION

In the highly competitive worlds of healthcare and the pharmaceutical industry, many businesses and organizations compete in the drug and medical product market (Eissa, 2016a, 2017, 2021). However, the patient's health should take precedence and not only quality and efficiency (Eissa, 2018a, 2022; Essam, 2019). The active or inactive medicinal substances inspection properties should serve as the foundation for the standard quality before analyzing the inspection properties of the final medication dosage forms.

Using statistical process control (SPC) techniques to reach a high standard of reliable and acceptable quality has become a common and crucial task for all healthcare businesses (Mostafa Eissa, 2018; Essam, 2023; Eissa & Rashed, 2023). The Shewhart trending plot is among the most crucial SPC methodologies (Eissa, 2015). It is extensively utilized to assess and control processes and inspection aspects in both industrial and non-industrial sectors (Eissa et al., 2021a, 2021b, 2023; Eissa, 2019, 2023a). Manufacturers of medicinal-grade raw materials are increasingly growing around the world, which facilitates easy access for brokers and retail markets globally (Eissa, & Mahmoud, 2016). On the other hand, maintaining constant quality assurance levels of the expected physical and chemical properties is essential to guaranteeing the chemical goods' value both ongoing and in the future.

Chemical production facilities are becoming increasingly prevalent, especially in emerging nations. It is doubtful if they follow ethical guidelines in several fields, such as medicine and healthcare (Eissa, & Abid, 2018; Eissa, 2018b). Good Manufacturing practices (GMP) may be used to forecast the quality of the final product (Eissa, 2016). Consequently, an organization with the right quality concept in mind across the board would create products with acceptable, reliable, and predictable features with a low failure rate.

It is important to have strict industrial holistic monitoring and control systems that follow regulatory official agencies to avoid the comptonization risk of their product's safety and quality at the expense of the financial benefits, especially in the developing nations. Owing to the aforementioned challenges, the following detailed perspective explains and assesses the quality and purity of a particular medicinal element that is often used in pharmaceutical preparations by chemical manufacturing companies. Substantial tests, which are officially recognized as a group of the key components of active material assessment, will be the main focus of the present article to show the importance of SPC in the chemical industry.

MATERIAL AND METHODS

The establishment of the milestone for the quality control and monitoring of the inspection characteristics of the synthesized compounds from the chemical manufacturing firms is of paramount importance not only for the manufacturing firm or the final consumers but also for the controlling regulatory official agencies in the countries. The present commentary is a model overview for a series of conducted connected studies performed on medicinal chemical materials that are manufactured in companies from Asian developing nations and received in the Egyptian market.

Case Selection of Calcium Channel Blocker Antihypertensive Molecule

The drug substance that is used in this representative investigation is 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid according to the IUPAC nomenclature. This medicinal chemical compound is a calcium channel blocker drug used to treat variant angina (also known as Prinzmetal angina or coronary artery vasospasm, among other names), excessive blood pressure, and coronary artery disease (CAD) (Amlodipine Monogpraph for Professional, 2016; Goldman & Schafer, 2019). It is ingested orally (by mouth) and shows 64–90% bioavailability with 93% protein binding.

Specifications Criteria of the Raw Material and the Standard Reference Analysis Method

Classical medicinal raw materials usually follow official monographs for their standard analysis and the manufacturers claim their obedience to the specifications mentioned in the respective pharmacopeias. From this standing point, the Specification Limit (SL) could be specified for the range. So, there will be an Upper Specification Limit (USL) and a Lower Specification Limit (LSL) or one of them only based on the test criteria. Apart from the particle size analysis which follows an instrumental method with an upper size threshold of 4,189 μm^3, all other tests follow British Pharmacopeia (2022). These tests include the optical rotation, total impurities and the assay (based on an anhydrous substance).

SPC and the Examination of Selected Inspection Properties of the Manufactured Raw Material

To create a suitable SPC trending profile and check the preliminary test data for distribution fitting, Minitab version 17.1.0 was utilized (Eissa et al., 2015, 2016b; Eissa, 2018c, 2018d). Based on the output findings, the control charts might be applied to ascertain the starting level of control. Shewhart basic structuring and drawing for its basic components have been described in detail before. It has been plotted based on the underlying assumption of the distribution pattern of the datasets. With a Confidence Interval (CI) of 95% and a P-value of 0.05, the statistical process profiling of the capability of the examined inspection properties could be evaluated. If the variation of the process in the chronological order is under control. Then the capability plot could be studied to know whether the investigated characteristic is under control state or needs improvements.

Capability Six-Pack flow could be determined through the following steps. While control charts are used to assess process stability over time, a separate analysis is needed to determine the inherent capability of the process. This capability analysis evaluates whether the process can consistently produce outputs within the specified limits (tolerances). Distribution Analysis: Before constructing control charts, it's crucial to understand the underlying distribution of the data. This can be achieved through techniques like: Exploratory data analysis (EDA): Visualizing the data through histograms or boxplots can reveal potential patterns and departures from normality or other assumed distribution from data spreading fitting study. Formal distribution tests: Statistical tests like the Anderson-Darling (AD) test can help determine if the data follows an assumed distribution, which is a common assumption for control chart calculations. Capability Analysis: Once the data distribution is understood, capability analysis tools like capability plots and indices (Cp, Cpk) can be employed. These tools assess how well the process output falls within the specified limits, considering both process variation and centering.

Confidence Intervals and P-values: Confidence intervals (CIs): These provide a range of values within which the true population parameter (e.g., mean) is likely to lie with a certain level of confidence (e.g., 95%). They don't directly assess capability analysis but can be used to estimate the population mean for further calculations. P-values: These indicate the statistical significance of a hypothesis test in distribution study tests. A low P-value (e.g., 0.05) suggests that the data may not follow hypothesized distribution, potentially impacting control chart calculations. Process Evaluation: By establishing control with control charts and capability with capability analysis, we can gain a more comprehensive understanding of the process performance. Control charts: These help identify process shifts or trends over time, indicating potential issues requiring investigation. Capability plots: These assess whether the process variation is centered within the specified limits and whether improvements are necessary to achieve consistent production within tolerances.

RESULTS AND DISCUSSION

The use of control charts is essential in the inspection of the chemical characteristics of raw compounds in the chemical manufacturing industry. The control chart is a statistical tool that helps in monitoring the quality of a manufacturing process over time. It is used to detect any changes or variations

in the process, which could lead to defects or substandard products. The control chart consists of a central line that represents the process average, and two control limits (upper and lower) that represent the acceptable range of variation in the process. The data points are plotted on the chart, and any points that fall outside the control limits indicate that the process is out of control and needs to be investigated and corrected.

The application of control charts in the chemical manufacturing industry ensures that the raw compounds used in the production process meet the required specifications. This is important because the quality of the raw compounds can affect the quality of the final product. For example, if the concentration of a particular chemical in the raw compound is too high or too low, it could affect the chemical reaction during the manufacturing process and result in a substandard product. Using control charts also helps to identify any trends or patterns in the data, which could indicate a problem in the manufacturing process. For example, if there is a consistent increase or decrease in the chemical concentration of the raw compound over time, it could indicate a problem with the equipment or the manufacturing process itself.

In addition, the use of control charts helps to reduce inspection costs by eliminating the need for 100% inspection of the raw compounds. Instead, a sample of the raw compound is taken and tested, and the results are plotted on the control chart. This reduces the time and cost of inspection while still ensuring that the quality of the raw compound meets the required specifications.

Fast and effective interpretation of the results of the official pharmacopeias tests could be accomplished after identification of the best fitting distribution of the monitored datasets to conduct further analysis as capability plot and histogram associated with the process-behavior chart. The chronological time series diagram that was done batch-wise with the available test material was an Individual-Moving Range (I-MR) chart. Any observable pattern could be detected from the last points of observation. When the test is skipped and not performed in the time series, gaps are indicated in the control charts.

The specific statistical techniques used herein focuses on the implementation of SPC as the following: Individual-Moving Range (I-MR) Charts: This variation is particularly useful for smaller datasets, where subgrouping might not be feasible. I charts monitor individual measurements, while MR charts track the moving range between consecutive measurements. They help identify trends, shifts, and potential outliers. Nuanced Interpretation of Control Chart Signals would be important in this context. While the present analysis mentions out-of-control signals, it's crucial to elaborate on their interpretation, considering some factors. Non-normal data: When data doesn't follow a normal distribution, interpreting control chart signals based on standard statistical assumptions can be misleading. It's essential to acknowledge this limitation and consider alternative approaches, such as control charts for non-normal datasets.

These charts are designed to correct for non-normal data and adjust for control limits of raw values. Cautionary interpretation should be approached when using standard control charts with non-normal data, interpretation out-of-control signals cautiously, considering other process knowledge and potential causes of variation. Causes of variation: Out-of-control signals can arise from various sources, including assignable causes which are specific, identifiable factors causing process variations, such as equipment malfunctions or changes in raw materials. Investigating and addressing these causes are crucial for process improvement. Common causes: These are inherent variations present in any process due to factors like random fluctuations. While not directly controllable, understanding and minimizing their impact is essential for achieving process stability.

Clarifying the Purpose of the AD Test: The AD test, mentioned, refers to the Anderson-Darling (AD) test for normality. This is a statistical test used to assess whether a given sample originates from the assumed distributed population. The AD test is used in the context of control chart construction, where the underlying distribution assumption often underpins

the control chart calculations. By performing the AD test, the study assesses whether the data for each analyzed characteristic (e.g., optical rotation) follows the expected distribution from the screening of the best fitting dispersion of datasets. This information can inform the selection of appropriate control chart types and the interpretation of the resulting control chart signals.

It should be noted that the initial exploratory process-behavior charts were done for preliminary evaluation of small firm of chemical manufacturing company at its infancy to evaluate its starting up synthesis of the medicinal chemical compound. Accordingly, there was evidence of incomplete data collection which could occur due to several obstacles embracing:

Equipment malfunctions: If the instruments used for measurement fail during specific batches, data for those batches would be missing.

Human error: Mistakes during data collection or recording can lead to missing values.

Sample loss or damage: Unforeseen circumstances like sample contamination or loss during processing can result in missing data.

Data exclusion: In rare cases, researchers might intentionally exclude data points deemed outliers or suspected of errors. However, this practice should be clearly justified and documented to avoid transparency concerns.

Optical Rotation Test Analysis

The exploratory preliminary chart showed that the initial batches demonstrated optical rotation data with control limits that are confined within the specification range. The construction of the process-behavior chart was based on the Weibull distribution which was the most fitting type of the dispersion of the dataset. Moreover, the inspection characteristic showed an acceptable capability index, but the process is significantly shifted from the center. Thus, better adjustment is needed to correct the shifting and to guard against any drifts that could lead to excursions in the future. This finding could be deduced visually from Figure 1. The output showed a tendency of oscillation with shifting to the upper side of the centerline.

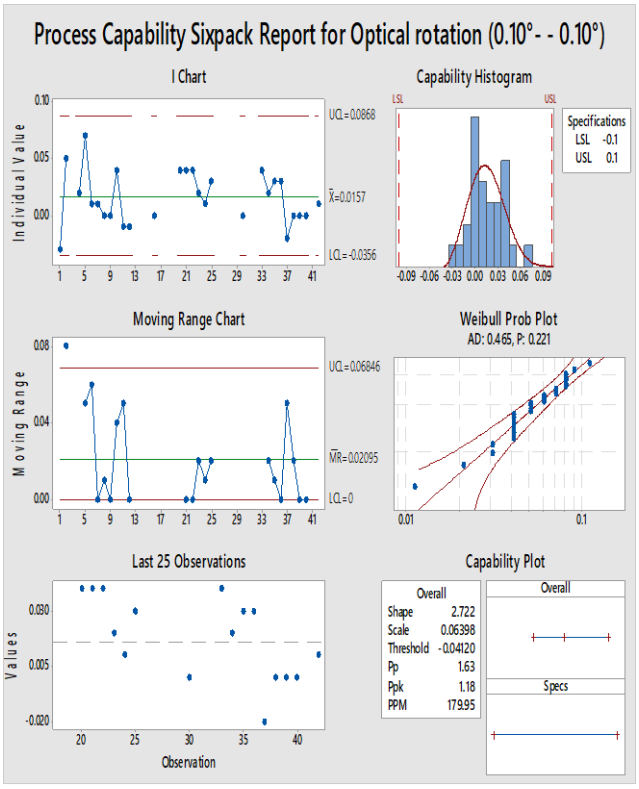

Figure 1. Process capability overview of one of the inspection characteristics of 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid showing exploratory preliminary trending pattern and process behavior of the optical rotation test

Total Impurities Test Analysis

The early batches displayed the total impurities result with control limits that are contained within the specification range, according to the exploratory preliminary chart. Normal distribution, the most appropriate kind of dataset dispersion, served as the foundation for the creation of the trending chart. Additionally, the inspection feature revealed a competence index that is appropriate, but the process is noticeably shifted from the center. However, since the specification of this test is one-sided with an upper limit only and the drift was toward the zero, then no risk could be encountered in this case. Figure 2 might be used to visually infer this conclusion. The general trend line showed descending pattern.

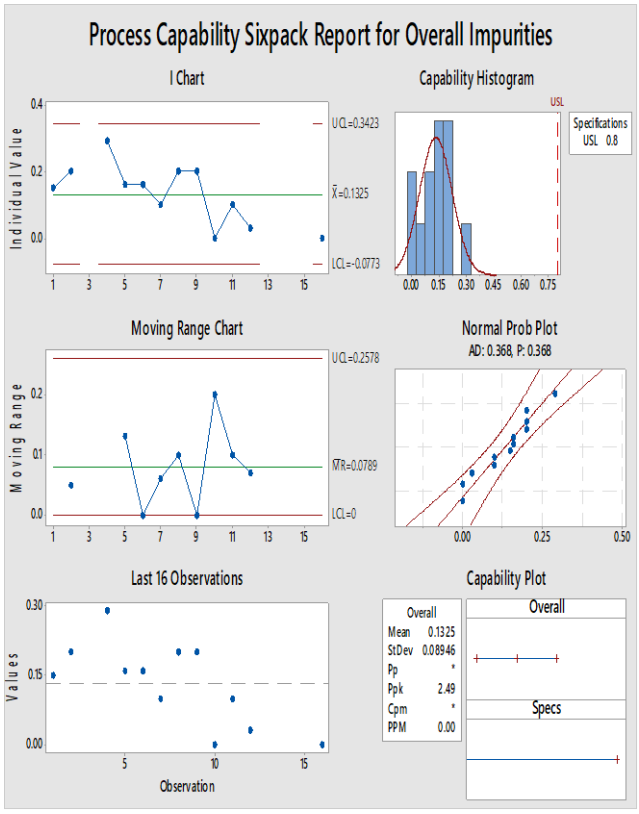

Figure 2. Process capability overview of one of the inspection characteristics of 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid showing exploratory preliminary trending pattern and process behavior of the total impurities test

Assay Determined Based on Anhydrous Substance

The exploratory preliminary chart shows that the assay of the active material - calculated based on the dried substance - for the early batches was within the specification range with control window contained but shifted to the lower border. The trending chart was created using a Weibull distribution, which is the most acceptable type of dataset dispersion. Furthermore, while the procedure is noticeably shifted from the center, the inspection characteristic displayed an adequate capability index. This could be evident from the difference between P_p and P_{pk}. Therefore, more adjustment is required to make up for the shifting and prevent any drifts that can cause excursions down the road. Figure 3 might be used to visually infer this conclusion. When the output shifted to the lower side of the centerline, it displayed an oscillatory propensity.

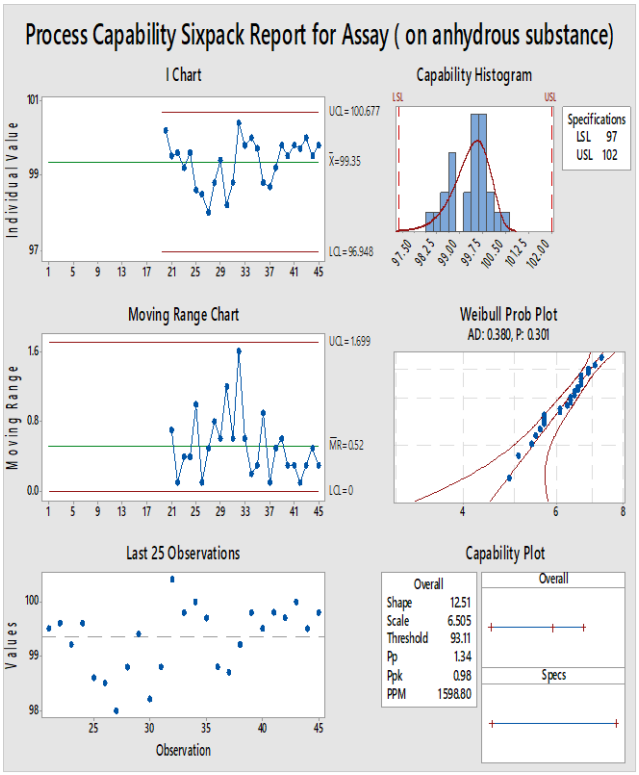

Figure 3. Process capability overview of one of the inspection characteristics of 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid showing exploratory preliminary trending pattern and process behavior of the assay test (based on anhydrous material)

Particle Size Determination

In contrast to the other previous tests, the examination of this instrumental test showed provisionally a control limit exceeding the specification threshold state that need immediate action to control the particle size distribution. Accordingly, the overall capability plot and histogram showed a control window that exceeded the specification range. The prevalence of the alternating pattern can be seen visually in Figure 4. The best fitting distribution was the Gaussian one but after using the SU distribution type of the Johnson family type of distribution. Minitab's Johnson transformation is a statistical technique used to transform non-normal data into a normal distribution. This transformation allows for the application of control charts and other statistical methods that typically assume normality.

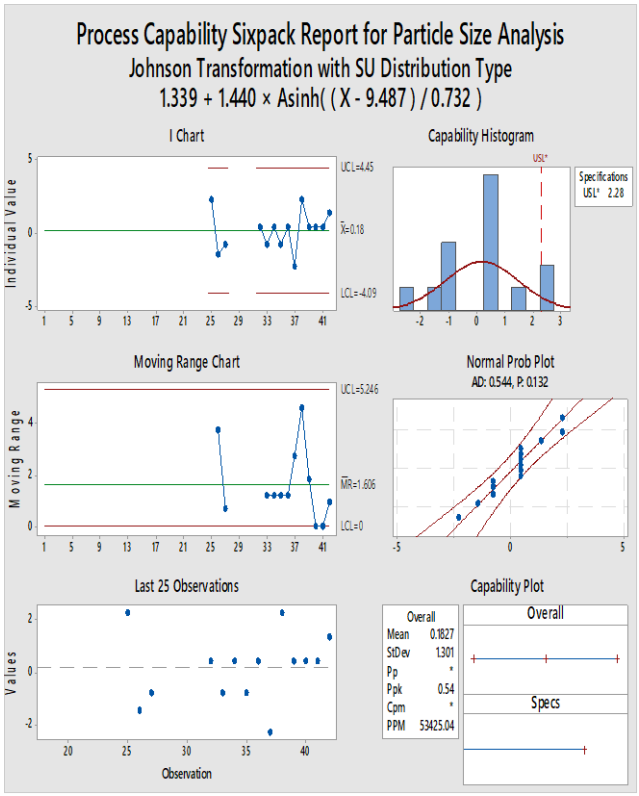

Figure 4. Process capability overview of one of the inspection characteristics of 3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonic acid showing exploratory preliminary trending pattern and process behavior of the particle size analysis test

The Johnson transformation system actually consists of three families of distributions: S_B (bounded), S_L (lognormal), and S_U (unbounded). SU Distribution Type: "SU" in the text refers to the unbounded family of distributions within the Johnson transformation system. Unbounded distributions are suitable for data that can theoretically range from negative infinity to positive infinity, but in practice, may have a lower bound of zero. For example, particle size measurements typically don't have negative values, but they can range from zero upwards. Minitab and SU Distribution: Minitab automatically selects the most appropriate Johnson transformation family (S_B, S_L, or S_U) based on the characteristics of dataset. If the "SU distribution type" is mentioned, it indicates that Minitab identified the unbounded (SU) family as the best fit for the specific dataset being analyzed. This implies the data likely has a lower bound of zero but can theoretically extend infinitely upwards.

Process Versus Customer and Total Quality Management

The Voice of Process (VoP), or the width of the inspection characteristic variation, should be less than the Voice of Customer (VoC) in the capability analysis. The indicator for performance centering is P_{pk} (Advantive, 2023). It measures the extent to which the data is centered within the given parameters. P_p, on the other hand, is the performance indicator (Eissa, 2023b). It calculates the extent to which the data might fall inside the given parameters (USL, LSL) (Eissa, 2023b). However, it makes no difference if it is positioned in the middle of the borders window. The following guidelines would be used to calculate the average and the control window.

Normally, the center line (CL) of an individual (I) chart: Mean of the individual data points. For the I chart, the upper control limit (UCL) is CL + 2.66 x Avg Moving Range (MR). The Lower Control Limit (LCL) for the I chart is equal to CL - 2.66 x Average MR or zero in the event that the MR is negative. The center line (CL) of the MR chart represents the mean of MR [27, 28]. The UCL for the MR chart is 3.27 times the Average Moving Range. LCL for MR charts is zero. The strength of the evidence opposing the null hypothesis is evaluated using a probability known as the p-value (Eissa, 2023b). In an AD test, the predicted distribution of the data is the null hypothesis (Eissa, 2023b). Thus, lower p-values provide greater evidence that the data deviate from the distribution.

Establishing comprehensive SPC methodology implementation is crucial for chemical manufacturing organizations, as it forms an essential component of Total Quality Management (TQM) across the whole enterprise. To enforce safety and quality ideals, however, regulatory monitoring and surveillance in the industrial sector are essential. Until the SPC procedures are properly integrated into the foundations of the legislation governing the chemical sector, the receiver customer should monitor the given lots using appropriate statistical tools to keep a watch

on the goods they get. This is particularly crucial for emerging and economically distressed countries.

CONCLUSION

The current study identifies a significant and distinctive viewpoint in the physical and chemical criterion-based API trending and monitoring. The highly competitive world of pharmaceutical and medical products demands acceptable monitoring and control of the production field's quality. The fundamental components of this concept are the raw ingredients. An important task that, by tracking the trend of the properties of the chemical entities under examination, provides insight into how the inspection characteristics behave with the manufactured batches that are marketed and represents the quality of the final customer's organizations' deliveries. Control charts are essential for time-sequence or serial process monitoring. In order to detect changes in the qualities under examination and ascertain whether these changes are most likely the consequence of common or particular sources of variations, they display the mean and establish limiting thresholds. For the parties concerned and the governing governmental official agencies in the industrial sphere, SPC studies would be beneficial in understanding the trending pattern and the properties (chemical and physical) of the chemical substance that is given as a raw material. Ensuring the production of medical supplies that meet consistent, dependable, and satisfactory quality standards is an essential industrial duty. In conclusion, the application of control charts in the inspection of the chemical characteristics of raw compounds in the chemical manufacturing industry is important for ensuring the quality of the final product, identifying process problems, and reducing inspection costs. It is a valuable tool for ensuring that the manufacturing process is under control and producing high-quality products.

Recommendations

It is recommended that strict governmental rules should be established to monitor and control the indigenously and exported chemical goods by the official agencies. Meanwhile, the final customer firms and companies must keep statistical quality control on the received manufactured chemical to preserve the quality of their final products. Nevertheless, the original manufacturing firms should provide evidence for their SPC implementation on their final manufactured chemical compounds, especially those used in the medicinal, healthcare and pharmaceutical sectors for the sake of human safety and health protection.

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Compliance with Ethical Standards

Conflict of Interest

The author declares that there is no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

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Data Availability

The author confirms that the data supporting the findings of this study are available within the article.

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