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Implementation of Modified Q-Control Chart in Monitoring of Inspection Characteristics with Finite Quantification Sensitivity Limits: A Case Study of Bioburden Enumeration in Capsule Shell

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Abstract: Application of statistical process control (SPC) methodologies has become increasingly crucial in various business fields to control, monitor and improve processes, in addition to the support of the management decision-making. However, many inspection characteristics have limited quantification limits beyond which results are reported as either "< lower than" or "> higher than" such as testing of microbiological burden in healthcare products after definite dilution level ex. 1:10, 1:50 or 1:100. The present case study demonstrated the application of combined quality score trending chart concept with Laney-modified attribute process-behavior chart for monitoring the bioburden the quality of successive deliveries of empty hard gelatin capsule. Microbiological database was segmented into intervals based on both the specification limits and the minimum sensitivity limit of the Total Viable Aerobic Count (TVAC) and Total Yeast and Mold Count (TYMC). Each segment was assigned a score starting for low bioburden value to the higher threshold. Preliminary investigation of the dataset pattern showed that the record did not follow any presumed distribution for construction of the ordinary control chart. Data are right (positively) skewed with no apparent tendency to follow Poisson, binomial or normal distribution. Laney-Quality chart demonstrated bioburden contents as CFUs ranks with aberrant results spotted.

Keywords: Quality Score Chart; SPC; Truncated Distribution; TVAC; TYMC

Sonlu Kantitatif Hassasiyet Sınırları ile Muayene Özelliklerinin İzlenmesinde Değiştirilmiş Q-Kontrol Şemasının Uygulanması: Kapsül Kabuğunda Bioburden Numaralandırması Örneği

Öz: Yönetim karar verme desteğine ek olarak, süreçleri kontrol etmek, izlemek ve iyileştirmek için çeşitli iş alanlarında istatistiksel süreç kontrolü (SPC) metodolojilerinin uygulanması giderek daha önemli hale geldi. Bununla birlikte, pek çok inceleme özelliğinin sınırlı nicelik sınırları vardır ve bunun ötesinde sonuçlar, belirli seyreltme seviyesinden sonra sağlık bakım ürünlerindeki mikrobiyolojik yükün test edilmesi gibi "<daha düşük" veya "> daha yüksek" olarak rapor edilir. 1:10, 1:50 veya 1: 100. Bu vaka çalışması, boş sert jelatin kapsülün ardışık teslimatlarının kalitesinin biyolojik yükünün izlenmesi için Laney tarafından değiştirilmiş öznitelik işlem-davranış şeması ile birleştirilmiş kalite skoru eğilim tablosu konseptinin uygulanmasını gösterdi. Mikrobiyolojik veri tabanı, Toplam Canlı Aerobik Sayımın (TVAC) ve Toplam Maya ve Küf Sayımının (TYMC) hem spesifikasyon limitlerine hem de minimum hassasiyet limitine göre aralıklara bölünmüştür. Her segmente düşük biyolojik yük değerinden başlayarak daha yüksek eşiğe kadar bir puan atandı. Veri seti modelinin ön araştırması, kaydın sıradan kontrol grafiğinin oluşturulması için herhangi bir varsayılan dağılımı takip etmediğini gösterdi. Veriler doğru (pozitif olarak) çarpıktır ve Poisson, binom veya normal dağılımı takip etmeye yönelik belirgin bireğilim yoktur. Laney-Kalite çizelgesi, sapkın içeriğini gösterdi.

Anahtar Kelimeler: Kalite Puan Tablosu; SPC; Kesilmiş Dağıtım; TVAC; TYMC sonuçlar tespit edilerek CFU'lar sıralandıkça biyolojik yük

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1. Introduction

Microbiological safety is one of the prime criteria of consumable products, notably healthcare products. Pharmaceutical dosage forms and their constituents are usually consumed by patient category which comprises compromised health people and impaired immunity individuals [1]. Some of those people are critically ill and may suffer from mixed disease conditions [2]. One of the challenges in the healthcare business is the delivery of high-quality safe products to the customers [3]. Every year FDA issues a list of recalled goods for various defects including microbiological causes [4].

The pivotal role of the quality structure entity in any industry is dependent on its directive, control and monitoring of the inspection characteristics of not only the finished goods but also the intermediate and the incoming individual components from the suppliers to the warehouse [5]. However, it has become widely understood that reliance on the view of the analysis of individual batched of materials - and considering merely acceptance or rejection - is not an adequate practice [6]. Control and monitoring of the overall processes and the inspection characteristics stability of the raw and processed items over fairly adequate periods have been adopted in many fields using Statistical Process Control (SPC) methodologies, including control charts which are valuable for judging the overall performance and the compliance with collective good practices (GxP) [7].

One of the obstacles in the application of process-behavior charts is the inspection criteria that have a Limit of Quantification (LOQ) that hinders reporting a definite figure in the final result certificate due to the nature of the test ex. analysis of related compounds or organic impurities in raw organic material. Thus, the result may be reported as "below limit of quantification". The present case study will investigate the implementation of a unique approach of Shewhart charts in the trending and analysis of data that have limited quantification limits beyond which results are reported as either "< lower than" or "> higher than" such as testing of microbiological burden in healthcare products after definite dilution level (for example 1:10, 1:50 or 1:100 dilution levels).

2. Literature Review

The type of process-behavior chart that will be considered herein is that for a count data which is suited for microbial enumeration. This class of trending graphs is called attribute charts [8]. Attributes charts are control charts that plot nonconformities (defects) or nonconforming units (defectives) [9]. Nonconformity refers to a quality characteristic and nonconforming refers to the overall product. For example, a defect on or in an object is a nonconformity. If several defects or any other abnormalities exist, the entire inspected product may be considered nonconforming [9]. Because a unit may have many quality characteristics, it may have many nonconformities, but the unit itself is either conforming or non-conforming. This is similar in the industry to an example of defects that may include tears, scratches, or punctures [10]. Thus, the count of the number of defects across all items is determined and a rate of occurrence is elicited.

Based on the above description the best type of chart that suits bioburden enumeration in a material is that count the number of defects (as viable microbial particles) in the examined product is C chart [11]. C chart tracks the number of defects and detects the presence of special causes for out-of-control records [12]. There are several programs that construct different types of control charts including C type [13-15]. Each entry in the software matrix column contains the number of defects for one subgroup, assumed to have come from a Poisson distribution with parameter μ. This value is both the mean and the variance. C chart is to be used when the subgroup size is constant. By default, the process average number of defects, μ, is estimated from the data. This value is the

centerline on the C chart [16]. The statistical process program also uses this value to calculate the control limits.

Use C charts to assess whether or not the number of defects in each sample is in control. An in-control process exhibits only random variation in the number of defects per sample. An out-of-control process exhibits unusual variation in the number of defects per sample, which may be due to the presence of special causes [17]. Industrially, a defect is any nonconformity (or flaw) in a product or service that does not render the product or service unusable (or defective). A C chart should not be used when the sample sizes vary because the control limits and the center line change when the sample size changes. This makes the C chart difficult to interpret [18, 19]. U chart implementation will be more helpful when there is variation in the sample size.

3. Material and Methods

The current subject study herein could be classified as pharmaceutical microbiology research from both healthcare and industrial perspective. The present case would cover the assessment of microbial quality inspection of pharmaceutical inventory goods that arrive at a warehouse in a healthcare facility before further processing and manufacturing using a unique investigation approach.

3.1. Material

The subject of the study will be successive deliveries of hard gelatin capsule (HGC) batches that arrived at a warehouse in a healthcare facility to be used in the preparation and filing of healthcare products. The Bioburden content of each lot was analyzed using classical microbiological analysis by applying the standard method according to the United States Pharmacopeia [20]. Capsule shells were dispersed in warm diluent (not more than 45 ºC) at a dilution ratio of 1:10, inoculated in plastic Petri dishes and mixed well with liquified agar media for both Total Viable Aerobic Count (TVAC) and Total Yeast Mold Count (TYMC). After incubation, plates were count for any microbial counts (expressed as Colony Forming Unit (CFU)) [20]. Any count will be averaged and multiplied by the dilution factor. While any clean plates with no observable viable colonies will be reported as “<10 CFU”.

3.2. Methods

Statistical program platform will be used for initial detailed numerical statistical exploration of the pattern of the scored data. This analysis is complemented by histograms and Poisson probability plot drawing for data structure elucidation. Table 1 shows the method of segregation and segmentation of the results at intervals that are dependent on both the specification limits (TVAC Not More Than (NMT) 1000 CFU/g and TYMC NMT 100 CFU/g) and the test sensitivity which is affected by the dilution level (1:10 in the present case). This classification is based on scoring which is a preparatory step for the application of Q-chart (Quality Score Plot) based on the scores given in Table 1. After data transformation into scores, statistical analysis and histogram drawing will be used to examine the dispersion of bioburden count as QTVAC and QTYMC. In addition, descriptive statistical analysis will be conducted on the dataset to visualize its pattern and dispersion [21-23]. On the other hand, Table 2 is a refinement for TVAC intervals to be more sensitive by shortening the periods of CFU ranges ten-time from that of Table. The last table will be used to examine the impact of increasing the score sensitivity in the interpretation of the TVAC.

Primarily, C process-behavior charts will be selected. However, the fitness of data to Poisson distribution will be examined using the diagnostic tool in the statistical program viz. Minitab® v17.1.0 [24]. Each gram of the material being examined can occult one or more viable microbial particles or undesirable characteristics in Statistical Process Control (SPC) term. The mathematical basis for drawing C chart according to Minitab® v17.1.0 is as the following:

Theoretically, k is supposed to be nonoverlapping units that should be sampled and examined and c1, c2 ck are the observed counts. Estimate the process mean count c by equation 1:

$$\bar{c} = \frac{1}{k}(c1 + c2 + + ck) \quad (1)$$

The centerline and control limits for the C chart are shown in equations 2, 3 and 4 as the following [25]:

$$UCL = \bar{c} + 3\sqrt{\bar{c}} \quad (2)$$

$$CL = \bar{c} \quad (3)$$

$$LCL = \bar{c} - 3\sqrt{\bar{c}} \quad (4)$$

If the lower control limit computes to a negative value, then LCL is set to zero because negative counts are not possible. From the previous equations, the upper and the lower limits depend on the number of subgroups and the process mean.

U Chart Diagnostic is implemented using statistical software to test for over-dispersion and under-dispersion to avoid false alarms due to skewed control limits. This will help to decide to either execute drawing of the classical type of attribute chart or to make use of Laney-modified trending chart. When the dataset fails to show the appropriate hypothesized distribution shape, Laney's correction of data is applied. Based Minitab® v17.1.0 interpretation method, the calculations for the Laney U' chart include Sigma (σ) Z, which is an adjustment for over-dispersion or under-dispersion. A σ Z value of 1 indicates that no adjustment is necessary and that the Laney U' chart is exactly the same as a traditional U chart [26]. The data will be plotted as the following:

The plotted points and centerlines on a Laney U' chart are the same as those on a traditional U chart. Each data point, u_i, is calculated as in equation 5:

$$u_i = x_i/n_i \quad (5)$$

Center line: The centerline represents the average number of defects per inspection unit, *u* (herein the number of CFU per gram of the appropriately dispersed and homogenized material). Minitab uses Equation 6 to estimate its value:

$$u = Sx_i / Sn_i \quad (6)$$

Control limits: To calculate the control limits, each u_i is converted to a z-score according to Equation 7 as the following:

$$z_i = (u_i - u) / su_i \quad (7)$$

Next, a moving range of length 2 is used to evaluate the variation in the z-scores and calculate σ Z (sz) in Equation 8:

$$sz = MR /1.128 \quad (8)$$

where 1.128 is an unbiasing constant. The standard deviation of each plotted point is calculated as equation 9:

$$sd(u_i) = su_i \, x \, sz \quad (9)$$

Lastly, the adjusted control limits for each subgroup are calculated based on equations 10 and 11:

$$LCL_i = u - K \, x \, sd(u_i); \text{ or LCL = Zero, whichever is greater} \quad (10)$$

$$UCL_i = u + K \, x \, sd(u_i) \quad (11)$$

Where:
x_i = number of defectives in subgroup i
n_i = subgroup size for subgroup i
u_i = proportion defective for subgroup i
su_i = $\sqrt{(u /n_i)}$
z_i = z-score for subgroup i
MR = average moving range of length 2 for the z-scores
K = the parameter that is specified for Test 1 of the tests for special causes, 1 point > K standard deviations from center line.

Table 1. Score rank interval assignment for quantitative microbiological data range covering specification limit (SL) and beyond results as Out-Of-Specification (OOS).

TVAC Score	CFU/Single Score Scale [a]	TYMC Score	CFU/Single Score Scale [a]
0	<=100	0	<=10
1	101-200	1	11-20
2	201-300	2	21-30
3	301-400	3	31-40
4	401-500	4	41-50
5	501-600	5	51-60
6	601-700	6	61-70
7	701-800	7	71-80
8	801-900	8	81-90
9	901-1000	9	91-100
10	1001-1100	10	101-110
11	1101-1200		

[a] CFU = Colony Forming Unit as an expression of the number of the microbial particles per certain weight of the analyzed product.

Detailed conventional statistical analysis will be conducted using GraphPad v6.01 for Windows for descriptive column statistics, including one sample *t*-test that will compare the difference between the actual mean and the theoretical one at not more than (NMT) 100 CFU/g for TVAC and NMT 10 CFU/g for TYMC i.e. score zero and nine, respectively.

Table 2. Improved score rank interval assignment for TVAC quantitative microbiological data range covering specification limit (SL) and beyond results as Out-Of-Specification (OOS) at ten times short periods.

TVAC Score	Lower CFU	Upper CFU	TVAC Score	Lower CFU	Upper CFU	TVAC Score	Lower CFU	Upper CFU
0	0	10	39	391	400			
1	11	20	40	401	410	78	781	790
2	21	30	41	411	420	79	791	800
3	31	40	42	421	430	80	801	810
4	41	50	43	431	440	81	811	820
5	51	60	44	441	450	82	821	830
6	61	70	45	451	460	83	831	840
7	71	80	46	461	470	84	841	850
8	81	90	47	471	480	85	851	860
9	91	100	48	481	490	86	861	870
10	101	110	49	491	500	87	871	880
11	111	120	50	501	510	88	881	890
12	121	130	51	511	520	89	891	900
13	131	140	52	521	530	90	901	910
14	141	150	53	531	540	91	911	920
15	151	160	54	541	550	92	921	930
16	161	170	55	551	560	93	931	940
17	171	180	56	561	570	94	941	950
18	181	190	57	571	580	95	951	960
19	191	200	58	581	590	96	961	970
20	201	210	59	591	600	97	971	980
21	211	220	60	601	610	98	981	990
22	221	230	61	611	620	99	991	1000
23	231	240	62	621	630	100	1001	1010
24	241	250	63	631	640	101	1011	1020
25	251	260	64	641	650	102	1021	1030
26	261	270	65	651	660	103	1031	1040
27	271	280	66	661	670	104	1041	1050
28	281	290	67	671	680	105	1051	1060
29	291	300	68	681	690	106	1061	1070
30	301	310	69	691	700	107	1071	1080
31	311	320	70	701	710	108	1081	1090
32	321	330	71	711	720	109	1091	1100
33	331	340	72	721	730	110	1101	1110
34	341	350	73	731	740	111	1111	1120
35	351	360	74	741	750	112	1121	1130
36	361	370	75	751	760	113	1131	1140
37	371	380	76	761	770	114	1141	1150
38	381	390	77	771	780			

4. Results and Discussion

Microbiological quantitative enumeration data are recorded as counts of CFU (observed on or in solid media) per a single unit of the inspected material after taking into consideration the calculation of the dilution factor [27]. Accordingly, the most suitable type of Shewhart charting is the attribute one of C or – more generally - U type. Attributes process-behavior charts show analogous composition to variables trending charts, excluding that they are used to represent enumeration data type rather than a continuous type of data [28]. For example, the microbiological quality of the pharmaceutical dosage forms in aseptic manufacturing may be classified as either sterile (comply) or contaminated (defective). On the other hand, non-sterile medicinal products and raw materials may also be classified by their bioburden count (corresponding to the number of defects in the industry).

Similar to the variables control charts, a process statistic, such as the number of defects, is plotted versus a sample order or time frame. The statistical process program draws a mean line at the average of the statistic being plotted for the time being charted [29]. Moreover, this program also draws two other lines - the upper (UCL) and lower control limits (LCL) at a distance of three standard deviations (s) above and below the centerline, by default.

While the U chart and Laney U' chart divide the number of defects by the subgroup size to calculate the number of defects per subgroup, the C control chart charts the number of defects in each subgroup. Thus, C Chart is used when the subgroup size is constant [30]. For example, if the number of Colony Forming Units (CFU) were counted per one gram of homogenized raw material or final manufactured product, the C chart would plot the actual count of CFUs, while the U plot or Laney U' graph would draw the number of CFUs per specific amount of the material being tested [31]. Thus, the U chart is flexible in the incorporation of variable subgroup sizes rather than the C chart.

The control limits for the U chart and Laney U' chart change depending on the extent of each subgroup. In general, the control limits are positioned away from the centerline for smaller subgroups than they are for larger ones. Nevertheless, the control limits and centerline can be forced to be constant by entering a fixed subgroup size, for example, the average subgroup size. However, when an observation is missing, a gap exists in the chart for that observation [32]. The Laney U' chart is similar to a traditional U chart. Both charts are helpful to monitor the number of defects per unit that are produced by the inspected process [33]. The Laney U' chart can be useful in certain situations of large subgroups and data exhibit over-dispersion or under-dispersion.

Over-dispersion can cause the points on a traditional U chart to appear to be out of control when they are not. For the Laney U' chart, the definition of common cause variation includes not only the within-subgroup variation but also the average variation between consecutive subgroups [34]. If there is over-dispersion, the control limits on a Laney U' chart are wider than those of a traditional U chart. The wider control limits mean that only important deviations in the concerned process are identified as out of control [35]. Under-dispersion, which can occur with subgroups of any size, is often caused by a lack of randomness. Under-dispersion can result in control limits that are too wide for the data [35]. The Laney U' chart corrects for under-dispersion by calculating narrower control limits.

In the real world, many data in nature would be expected to comply with the presumed distribution required for control chart depiction. Despite the fact that the trending charts can still be drawn up, control limits maybe not accurate and false alarming points could be foreseeable [36]. Data transformation might be an exhaustive operation, error-prone and difficult to interpret in the busy

queue of data processing in any organization [37]. This challenge enforced the direction toward a simple and effective way of Laney's correction of Shewhart charting. Another hurdle in the application of the process-behavior chart is the resides in those inspection properties in the quality inspection that possess LOQ boundary which is difficult to interpret in a numerical manner to be translated into the control chart. The solution was established by using a quality score that will divide the database range into ranked intervals that are controlled by the specification limits and the LOQ (herein the dilution factor in the microbial enumeration).

In the case of microbial count data, the lower boundary of the test is always bound by zero value and no negative figure should be expected by the nature of this kind of test [38]. Thus, the distribution of this kind of dataset would be predicted to show an apparent cut-off of the spreading from the left side. Statistically, a truncated dispersion of data may be called conditional distribution that comes about from confining the limit of a few other probabilities' functions. Truncated dispersions emerge in practical situations in cases where the capacity to record, or indeed to know approximately, events is constrained to values that lie over or underneath a given limit or inside an indicated range [39]. The appearance of this kind of distribution could be visualized in Figure 1 for both types of microbial count viz. TVAC and TYMC. This would be anticipated in the failure of the normality test range in Table 1.

The degree of distortion of data spreading and distortion are demonstrated numerically by skewness and kurtosis, in addition to the values corresponding to the percentiles and median intervals [40]. Overall clustering and condensation of dataset occurred toward the lower values (left side of the distribution), indicating considerably fewer values that was higher than 100 and 10 CFU/g for TVAC and TYMC, respectively. Increasing the rank sensitivity apparently lowered the coefficient of variation, skewness and kurtosis values in Table 1. Nevertheless, both extreme-rank interval of TVAC showed significant departure from "NMT 100 CFU/g criterion" by observing one sample *t*-test.

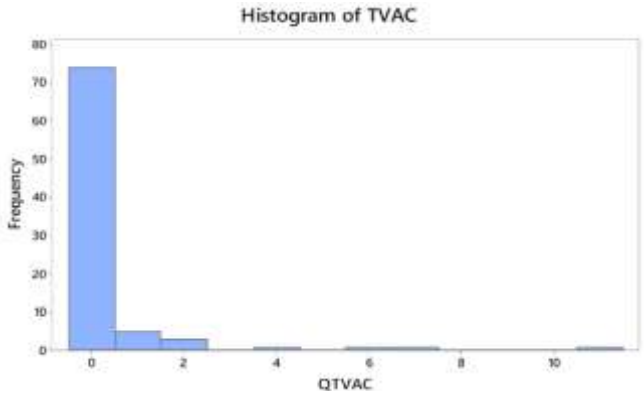
While TYMC scores were governed by the narrow specification range, TVAC ranking was customized into two extreme intervals ten CFU and 100 CFU per rank. The two approaches were analyzed simultaneously to elucidate the contrast, benefits and drawbacks. Concerning outlier's detection using Robust regression and Outlier removal (ROUT) method (at Q = 0.1-10.0 %) [41]. While TYMC score showed aberrant values at a percentage of 2.3%, TVAC and the improved or refined TVAC ranks showed rates of 0.14 and 0.12 to 0.27. In layman's terms, this means that the segregation improved the detection of the unusual count numbers by 1.5 to 1.9 times. However, if there is an inspection result record that has been registered as ≤100 CFU/g rather than ≤10 CFU/g, it would not be translated into the improved score of Table 2 and a gap would exist. Thus, refined TVAC was less than the normal-rank TVAC by one result. i.e. 85 instead of 86. Henceforth, the analysis of quality scored dataset for TVAC, TYMC and sensitized TVAC would be referred to as QTVAC, QTYMC and improved (refined) QTVAC.

Since the histogram showed a simple binary pattern of QTYMC spreading, there were not enough unique values in the data column to interpret the Poisson probability pattern in the diagnostic tool. The case is somewhat variable for QTVAC based on the sensitivity. For the lowest QTVAC sensitiveness the exact Poisson probability plot statistic cannot be calculated due to the fact that variation in the middle half of the dataset is zero [4, 42-43]. On the other side, the diagnostic analysis tool worked for the highest sensitive ranking QTVAC and the stated result by the software was "Ratio of observed variation to expected variation = 201.1%. 95% Upper Limit for ratio if the process mean is constant = 132.5%, Using a U chart may result in an elevated false alarm rate. Consider using a Laney U′ chart instead." In all cases, both types of charts were applied in parallel

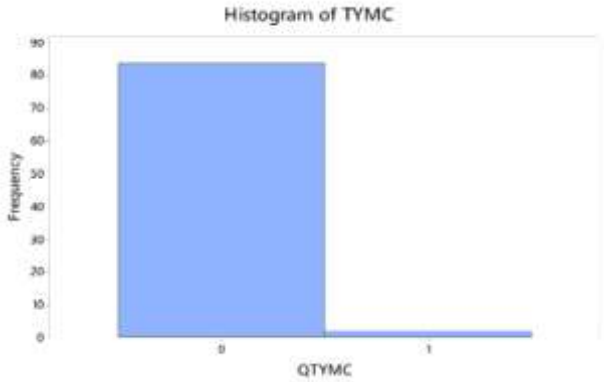
for comparison with preference already selected for the Laney attribute plot. Diagnostic tool results for the examination of applicability of conventional attribute C chart are shown in Figure 2.

Chronological control charts are shown in Figures 3, 4 and 5 for QTVAC (for both low and high sensitivity) and TVAC. While C and Laney charts showed the same LCL and process mean, the UCL
varies greatly for both TVAC and TYMC due to the correction for the dispersion by a factor of 0.82 and 0.17, respectively. Thus, the modification yielded more tight threshold windows. However, the alarm rates in both types of graphs are the same in the same locations. The detailed test "1" alarm – indicated by red dots in figures 3 and 4 for QTVAC and QTYMC showed defects in batches 10, 11, 12 and 49 for the first and 16 and 17 for the second chronologically, respectively. Excursion number "1" means that a single point is more than three standard deviations from the centerline. Another type of alarm viz. "2" – not demonstrated in the graph – is indicative of the shift of the process mean and is located the green line of the average rank score value [44-46]. This warning drift signal occurs when several (e.g. nine) consecutive tests occur in a row and in one side of the mean line. By contrast, these alarms are indicative of the areas of improvement that should be approached and are desirable. They were reported in all charts. In these circumstances, the conditions that favored low bioburden levels in the manufacturing of products should be revealed, enhanced and boosted.

On the other hand, improved-sensitivity quality score charts in Figure 5 showed a higher alarm level by one (25) in the Laney chart and six (25, 34, 35, 36, 48 and 50) in the conventional C chart. The mean and UCL have changed normally due to a ten-times increase in the scoring level. The alarming sensitivity increased slightly in Laney's chart. However, cutting the UCL of C chart by almost half of that of Laney doubled the alarms which are expected to be false. However, it should be noted that Laney attribute charts should be used practically in the current case rather than the C control chart to avoid false warning signals due to the non-complying dispersion of data that impacted UCL of the dedicated trending chart. Thus, this challenge might blur an effective and efficient investigation and control of the characteristic or process being monitored in the world seeking the finest quality in the competitive industry. The present study showed a satisfactory combination of both the quality score chart and the Laney modification approach for the correction of the non-conforming dispersion for the intended type of the process-behavior chart. The future prospects of this analysis will be projected to the other types of quality inspection tests such as limits of impurities in the manufactured chemical compounds which also have LOQ.



(a)



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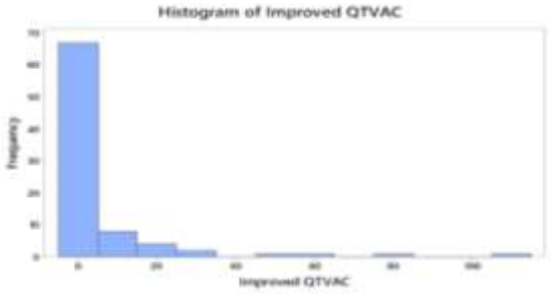


(c)

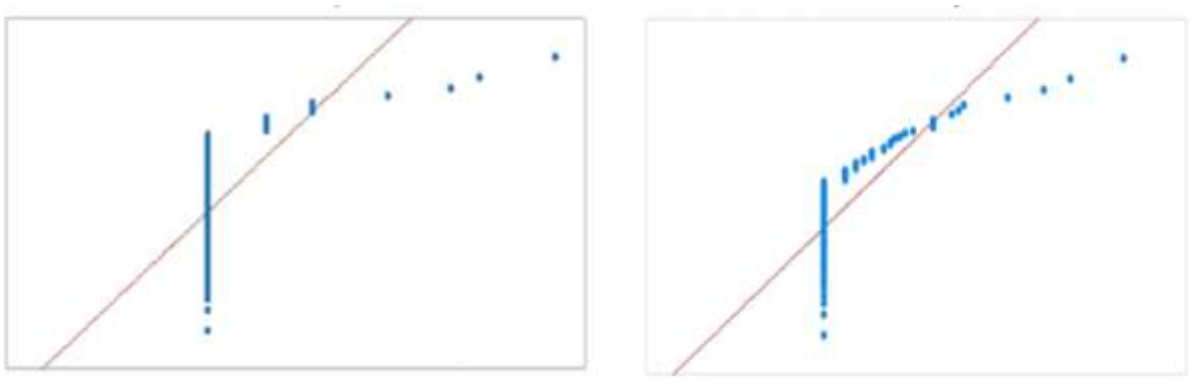
Figure 1. Histograms showing ranked microbial bioburden count as Total Viable Aerobic Count (TVAC), Total Yeast and Mold Count (TYMC) and refined ranking of TVAC scores.

Table 3. Descriptive statistical analysis of Q-score Total Viable Aerobic Count (QTVAC) and Total Yeast, Mold Count (QTYMC) and tuned QTVAC.

Number of values for column statistics = 86[1,2] 85[3]	**QTVAC[1]**	**QTYMC[2]**	**Improved QTVAC[3]**
Minimum	0.0	0.0	0.0
25% Percentile [g]	0.0	0.0	0.0
Median	0.0	0.0	0.0
75% Percentile [g]	0.0	0.0	3.500
Maximum	11.00	1.000	114.0
10% Percentile [g]	0.0	0.0	0.0
90% Percentile [g]	1.000	0.0	17.00
Mean	0.4535	0.02326	6.153
Std. Deviation	1.614	0.1516	17.34
Std. Error of Mean	0.1740	0.01635	1.881
Lower 95% CI of mean [a]	0.1075	-0.009247 [b]	2.413
Upper 95% CI of mean [a]	0.7994	0.05576	9.893
Lower 95% CI of median [a]	0.0	0.0	0.0
Upper 95% CI of median [a]	0.0	0.0	1.000
D'Agostino & Pearson omnibus normality test			
K2	118.5	146.2	109.4
P value	< 0.0001	< 0.0001	< 0.0001
Passed normality test (alpha=0.05)?	No	No	No
P value summary [c]	****	****	****
Shapiro-Wilk normality test			
W	0.3172	0.1365	0.4021
P value	< 0.0001	< 0.0001	< 0.0001
Passed normality test (alpha (α) =0.05)? No		No	No
P value summary [c]	****	****	****
KS normality test			
KS distance [d]	0.4711	0.5377	0.3614
P value	< 0.0001	< 0.0001	< 0.0001
Passed normality test (α = 0.05)?	No	No	No
P value summary [c]	****	****	****
One sample t test			
Theoretical mean	0.0	0.0	9.000
Actual mean	0.4535	0.02326	6.153
Discrepancy [e]	-0.4535	-0.02326	2.847
95% CI of discrepancy [a]	0.1069 to 0.8000	-0.009303 to 0.05581	-6.593 to 0.8992
t, degree of freedom (df)	t=2.606 df=85	t=1.423 df=85	t=1.514 df=84
P value (two tailed)	0.0108	0.1585	0.1338
Significant (α = 0.05)?	Yes	No	No

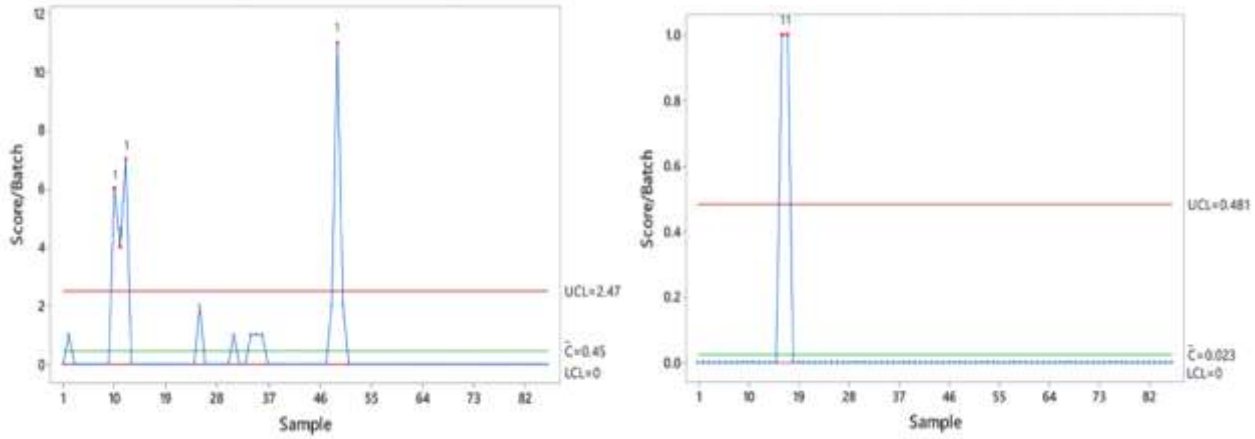
Wilcoxon Signed Rank Test			
Theoretical median	0.0	0.0	9.000
Actual median	0.0	0.0	0.0
Discrepancy	0.0	0.0	9.000
Sum of signed ranks (W)	78.00	3.000	-2295
Sum of positive ranks	78.00	3.000	637.5
Sum of negative ranks	0.0	0.0	-2933
P value (two tailed)	0.0005	0.5000	"< 0.0001"
Exact or estimate?	Exact	Exact	Exact
Significant ($\alpha = 0.05$)?	Yes	No	Yes
CV [f]	355.82%	651.88%	281.80%
Skewness [g]	4.799	6.439	4.395
Kurtosis [h]	25.45	40.40	21.67
Sum of scores	39	2	523

[a]Confidence Interval that include range of values that cover the true target value (mean, median or discrepancy) with 95% certainty.
[b]Explicated to zero since there is no negative value in microbiological results and its corresponding scores.
[c]Four asterisks with tiny P values (****) i.e. $P \leq 0.0001$.
[d]Kolmogorov-Smirnov D: Determine the distance between two cumulative relative frequency distributions at the farthest point.
[e]If the mean is less than 0.05 (small P-value), then the difference between the mean of the sample and the hypothetical mean is unlikely to be due to a coincidence resulting from random sampling. The discrepancy is not a coincidence, and the mean value of the population is different from the hypothetical value chosen. The disparity is important statistically.
[f] Coefficient of Variation (relative variability) = Std. Deviation/Mean.
[g]A perfect Gaussian distribution is zero, skewness value increase positively with right tailing and vice versa.
[h]Measure data density in the tails, if more than normal distribution (reference zero) then it will be (+) and vice versa.
[g]Centile rank = (desired centile e.g. 10, 25, 75 and 90%) x (Number of values in the descriptive statistics + 1)/100



(a) (b)

Figure 2. Diagnostic analysis for fitness of data to Poisson distribution for 100 CFU interval QTVAC (upper graph) and 10 CFU interval QTVAC (lower graph).



(a) (b)

Figure 3. Data trending using C chart showing Total Viable Aerobic Count (TVAC) and Total Yeast and Mold Count (TYMC) showing Upper Control Limit (UCL), Lower Control Limit (LCL) and mean (C bar).

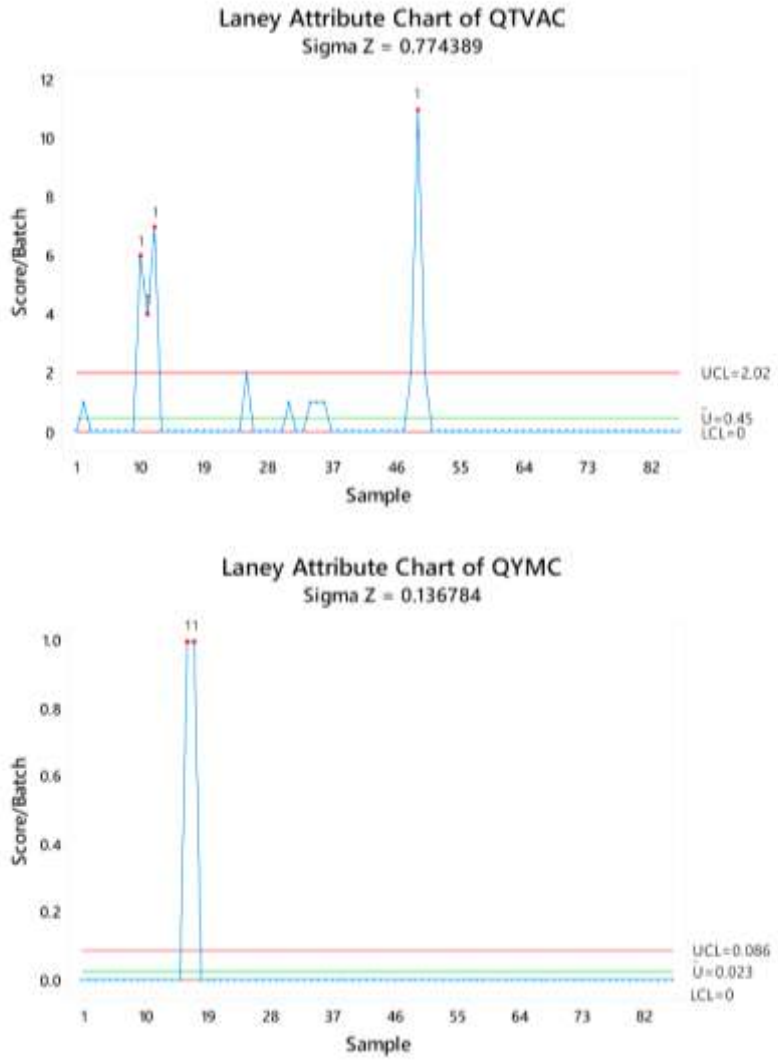


Figure 4. Quality score chart of Total Viable Aerobic Count (TVAC) and Total Yeast and Mold Count (TYMC) showing Upper Control Limit (UCL), Lower Control Limit (LCL), mean (U bar) and dispersion factor (σZ).

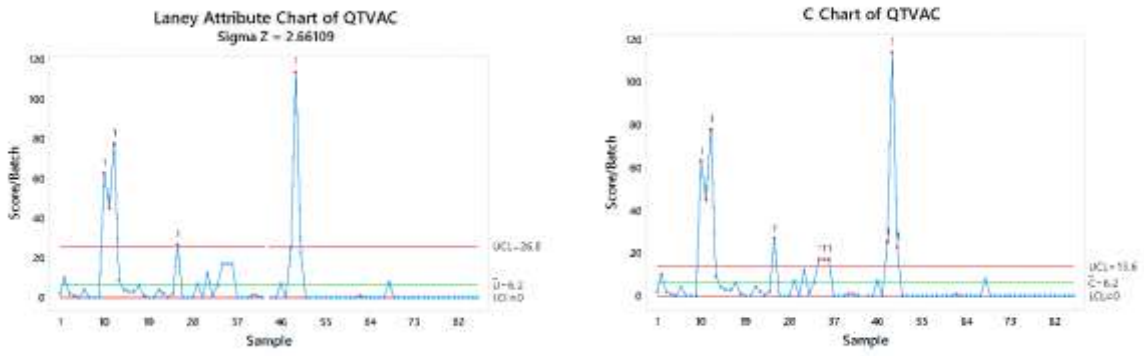


Figure 5. Modified quality score chart of Total Viable Aerobic Count (TVAC) with improved sensitivity scale of ten CFU/ml interval rather than 100 CFU/ml shown as both conventional and Laney attribute control chart.

5. Conclusion and Recommendations

Control charts are useful tools to monitor and investigate the inspection property and process quality and stability before any true excursion would happen. Quality score charts are useful for controlling and trending characteristics with LOQ cut-off values that curb reporting of true figure value essential to generate the process-behavior charts. Ranking intervals affect the sensitivity of the Shewhart charts for low-level noise data that appear in chronological order and modify the control limits values. Accordingly, the alarming points number might change. The extent to which the sensitivity could be changed is dependent on the LOQ threshold and the specification and measurement ranges. Otherwise, it is up to the organization or plant to customize the sensitivity required based on true business convenience. The unique application of this type of control chart in microbiological trend analysis would help to overcome the sensitivity limit affected by conditions of experiment design such as dilution level or factor. This kind of analysis would be useful in other quality control tests for inspection of other properties such as impurities in chemical compounds. Trend monitoring using process behavior charts is crucial to control and ensure the stability of the quality criteria before any true excursions might occur that would lead to undesirable consequences.

Authors' Contributions

Conceptualization, DE and ER.; methodology, ME; software, ME; validation, ER, DE and ME; formal analysis, ME; investigation, ER; resources, DE; data curation, ME; writing—original draft preparation, ME; writing—review and editing, ER; visualization, ER; supervision, ER; project administration, DE; funding acquisition, DE. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors declare that they have no competing interests.

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