Strategy for the Reduction of False Rejects in the Visual Inspection of Injectable Drug Products

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Abstract *— A hundred percent visual inspection is performed as part of the manufacturing process of injectable drug products as a regulatory requirement to detect and remove units with defects to protect the patients. The rejection of acceptable drug products in the visual inspection process increases waste and manufacturing costs. The analysis of historical data identified three vial defect types with a trend of high false reject rates. A second inspection step method with reference standards was designed as a strategy to reduce false rejects in the visual inspection process. The experimental results obtained showed a significant reduction in false rejects during the visual inspection process. The reduction of false rejects translates into fewer financial losses as waste for the organization.*

Key Terms *— False Rejects, Improvement, Pharmaceutical Industry, Visual Inspection*

PROBLEM STATEMENT

As a mandatory regulatory requirement for the manufacturing of injectable products, a visual inspection must be performed on one hundred percent of the products before the final packaging process [1]. As established in chapter 1790 US Pharmacopeia, the intention is to protect the patients against unavoidable defects generated in the manufacturing process such as particulates [1]. However, the visual inspection process increases manufacturing costs and waste such as the rejection of acceptable products as false rejects [2]. In a pharmaceutical company dedicated to the manufacturing of injectable drug products, was observed a sustained increasing trend of non-conformances with reject rate limits during visual inspection [2] [3]. Results of laboratory analyses identified a high number of false rejects as a major contributor to this problem. Visual inspection results that do not meet acceptance criteria have an additional negative impact on manufacturing costs and the supply chain [2] [4]. Therefore, this issue reduces the company's capability to meet the demand for on-time delivery of products at an affordable price to its patients [4] [5] [6]. A strategy that includes specialized staff with appropriate training, tools, and equipment to support inspectors' decision-making with an additional analysis method during visual inspection can be a feasible solution to reduce the rejection of acceptable products.

Research Objectives

This research presents a strategy to provide technical support as a cost-effective solution to reduce false rejects during the visual inspection process. An experimental execution of this method was performed in a simulation environment to determine the effectiveness of implementing this strategy for the following objectives.

- To implement staff with specialized training, technical equipment, and methods into the inspection lines for the immediate assessment of conditions detected on drug product units during the manual visual inspection process.
- To reduce the rejection of acceptable units of injectable drug products by 50% during the manual inspection process by March 2023.

Research Contributions

The implementation of this strategy in the visual inspection process can provide the following contributions:

- Reduce waste of acceptable drug products during the inspection process.
- Reduce rework such as the re-inspection process.

- Overall cost reduction of the manufacturing process.
- Reduce investigations of non-conformances.
- Increase the accuracy of the visual inspection process.
- Reduce risks to the company and its patients.
- Support supply chain on-time delivery of the company's products.

LITERATURE REVIEW

Like many other industries, the pharmaceutical manufacturing industry is consistently investing to improve its processes to deliver high-quality products with agility to satisfy the demand for its products worldwide. The COVID-19 outbreak in addition to the development of more biological treatments for chronic health conditions has increased the demand for the manufacturing of injectable products, such as the delivery of pre-filled syringes for vaccines and other critical treatments [3] [7] [8]. Furthermore, there is a consolidated demand from distributors and healthcare providers to pharmaceutical companies to reduce the costs of injectable drug products [4]. On the other hand, pharmaceutical companies are required to comply with rigorous regulatory and quality standards which increases manufacturing costs and delivery lead time of finished goods [6]. All these factors represent a particular challenge for pharmaceutical companies to deliver a high-quality product on time which can lead to public health threats such as the shortage of treatments for critical health conditions [6] [9].

As a key element of quality management, the Quality by Design (QbD) concept was introduced to consistently deliver a high-quality product thru a robust product and process design [10]. Later, regulatory agencies such as the International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) and Food and Drug Administration (FDA) identified the important contributions of the QbD concept to the quality assurance and quality control of the manufacturing of pharmaceutical products and include it as part of the pharmaceutical manufacturing guidelines [10]. Furthermore, the adoption of QbD by the pharmaceutical industry has proven to be an effective approach to preventing manufacturing problems with possible harmful adverse effects on the health of patients and improving business efficiency [6] [10]. However, there are several unavoidable factors in the manufacturing process of injectable products that can contribute to contamination and primary container functional defects [2] [3] [11]. Based on the latter and the lack of quantifiable data on the possible adverse effects on the patient's health, United States Pharmacopeia (USP) in alignment with European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) requires a hundred percent visual inspection to detect and remove any product with defects [1] [5] [11]. These defects can vary from primary container defects to foreign particle contamination, where the presence of particles is considered critical [5] [11]. The two principal methods for visual inspection are manual inspection, which is performed by highly trained persons, and automated inspection which involves the use of machinery [5] [12]. Still, factors such as maintenance, mechanical problems, and ejected units from the automated process demand human intervention for manual visual inspection [2] [3]. Thus, manual visual inspection has a fundamental role in the manufacturing of injectable drug products which in fact, is the reference standard method for visual inspection by pharmacopeias [1] [3] [5]. As part of the acceptance criteria for visual inspection, each batch must comply with established statistically acceptable quality limits (AQLs) such as a statistical acceptance sampling plan (ASP) and reject rate limits [9] [13]. Regulatory standards require a thorough investigation and Corrective Actions and Preventive Actions (CAPA) on any batch that fails to meet one or more of the established AQLs during visual inspection to be authorized for further processing [1] [14].

The increase in complaints and product recalls due to product defects has triggered companies in the industry and regulatory agencies to adopt a conservative approach at the time to accept or reject [5] [13] [15]. Moreover, in 2018 Hallie Forcinio

highlights the following, "In addition, there continues to be a shift toward lower acceptable quality limit (AQL) values for acceptance sampling after 100% inspection" [13]. Consequently, there has been an increasing trend of batches that fails to meet acceptable quality limits as has been the case in a pharmaceutical company with established manufacturing operations in the southeast of Puerto Rico. The company dedicated to the manufacturing of biological injectable products identified that one of the major offenders was the non-conformance due to high reject rates during the visual inspection. Further analysis results determined that the condition detected was not considered a defect based on the current SOPs for defect classification.

As described by Lynn D. Torbeck, "Despite all these reviews, 100% visual inspection by even well-trained and experienced production inspectors is only about 80-85% effective. Is not humanly possible to visually inspect and remove 100% of occurring defects even in the best conditions" [16]. As human beings, physiological and behavioral factors can affect decision-making, creating a chain reaction to become hypersensitive and reject acceptable product units [16]. A high level of false rejects contributes to higher manufacturing costs and environmental impact [2] [3] [8]. Besides, accepting defective products increases the risks of complaints and adverse effects on patient's health.

Therefore, pharmaceutical companies are consistently investing in research for the development of new strategies or applications of methodologies such as lean manufacturing and six sigma for the continuous improvement of their processes. From a pure lean manufacturing perspective, visual inspection is a non-value-added step of the manufacturing process considered waste because customers should not have to pay a higher price due to deficiencies in the manufacturing process [17]. On the other hand, a visual inspection can be considered a six sigma method to control the output variability of the final products, assuring the delivery of a high-quality product [17]. The application of both methodologies in addition to risk management to reduce waste and improve quality compliance can be an effective approach to improving the visual inspection process [2] [17].

For instance, the adoption of a Dirt Estimation Chart from the Technical Association of the Pulp and Paper Industry (TAPPT) has proven to be an effective method to control the variability output of the manual visual inspection process [16]. The implementation of this tool as a reference standard was an effective application of lean and six-sigma methodologies to reduce waste and variability. Results demonstrated a reject rate reduction from twenty percent to a range between two and five percent [16]. Another interesting initiative to improve visual inspection is the proposal to include artificial intelligence in machines for automated inspection processes [11]. This method can introduce the advantage of continuous improvement for the detection and classification of defects, reducing false rejects [11]. However, the lack of machine capacity to detect primary container defects and high implementation and maintenance costs are limiting factors when considering this method [11]. Focused on the severe losses of acceptable products generated by false rejects, Dr. Martin Becker presented a methodology for the re-inspection of defect fractions with acceptance criteria based on a statistical risk analysis. [2]. The risk analysis establishes a statistical rationale for the re-inspection of the rejected fraction of a batch during the first visual inspection. If re-inspection results meet the acceptance criteria, the accepted units of the rejected fraction can be returned to the original batch without affecting the product quality [2]. A similar method has been successfully adopted for the handling of ejects of the automated visual inspection process, and it has the advantage of being introduced to manual visual inspection also [2]. Still, the cost of a manual visual re-inspection must be considered to determine the feasibility of this method as a cost-effective solution to recover false rejects of acceptable units.

The purpose of this research is to establish a strategy to reduce false rejects during visual inspection. The introduction of a method of analysis with appropriate tools into the manual visual

inspection lines can provide a fast response to support decision-making for inspectors during the process [16].

METHODOLOGY

As established by regulation, laboratory analyses of samples of the rejected portions show a high number of false rejects, which increases operational costs [2]. This research project aims to implement a strategy to reduce false rejects during visual inspection. A step-by-step methodology of four phases, planning and design, execution, analysis, and submission of the project results was used in this project. The collected quantitative data was analyzed to determine the feasibility of the proposed strategy.

The planning and design phase was completed in three steps. The first step was to identify the organization's functional areas required to execute the project to which the proposal was presented. After the approval of the research project, a search in the Trackwise quality system focused on deviations generated due to non-conformance with the reject rate limits during the previous one-year period. During the second step, the data collected was distributed and organized in the table presented in Figure 1 using Excel to establish the project scope and baseline for comparative analysis with the execution results. In the project team meeting the historical data collected was analyzed. A total of 53 deviations were related to 10 defect types for non-conformance with reject rate limits. The vial defect types of loose crimp, flip-off, and surface abrasion were identified as the major offenders with a higher false reject rate.

In the next project team meeting an assessment was performed to design a feasible method of evaluation for the loose crimp, flip-off, and surface abrasion defect types. The use of standards of vial units was determined to be the best option as a reference tool for the qualitative evaluation of units detected with these defects in a second visual inspection step. This method complies with standards established in the general chapter 1790 of the USP compendial reference method for visual inspection in addition to avoiding the risk of an additional impact to the vial or the solution inside with other methods that require the use of tactical tools [1]. In addition to a relatively low implementation cost, other benefits of this method are that does not require the use of magnification tools, or a workstation, which is not recommended by the USP compendial method for visual inspection [1].

During the third step of the planning and design phase, the experimental execution strategy was designed as follows. Three repetitions of manual visual inspection for experimental batches with equal specifications were determined as the execution strategy to validate this method. A request was submitted to the Process Development laboratory management to create three experimental batches of 1,000 units each and reference standards that include vials with a variation of these defects and acceptable conditions. The making of an experimental execution protocol with specific requirements and instructions as the procedure to perform three consecutive simulations of manual visual inspection of the experimental batches completed the first phase.

With the experimental batches and reference standards created by the Process Development Laboratory, the execution phase started with the training of the inspection method described in the execution protocol to the manufacturing staff. The execution phase was performed with the same validated instruments and conditions for the manual visual inspection of commercial drug products. The manual visual inspection of the experimental batches was performed by certified inspectors with the validated inspection technique for vials following the applicable SOPs. After the experimental simulations, the accepted and rejected units were delivered to Process Development Laboratory for further evaluation. The second phase was completed with the processing of data collected from the execution of simulations and laboratory analysis for analysis as presented in Figure 2.

Historical Data Collected from the Research of Deviations for Exceeded Reject Rate Limits During Visual Inspection	
Number of deviations found for exceeded reject rate limits	53
Number of deviations found for exceeded reject rate during visual inspection of vials	32
Number of deviations found for exceeded reject rate limits during the visual inspection of pre-filled syringes	21
Number of vial defect types reported to exceed reject rate limits	5
Number of syringe defect types reported to exceed reject rate limits	5
Number of vial defect types with recurrence trend	3
Number of syringe defect types with recurrence trend	2
Number of deviations that required for re-inspection of batch	42

Vial defect types	Number of events	Units evaluated by PD lab	Units confirmed for defect	Units not confirmed for defect	Number of re-inspections after events	False reject ratio	Occurrence ratio for vial events	Occurrence ratio for total events	Classification of defect type
Particulate in solution	2	118	115	3	2	2.54%	6.25%	3.77%	Critical
Residue on external surface	4	236	209	27	3	11.44%	12.50%	7.55%	Minor
Loose crimp	8	472	331	141	8	29.87%	25.00%	15.09%	Critical
Flip-off	11	649	343	306	6	47.15%	34.38%	20.75%	Major A
Surface abrasions	7	413	260	153	5	37.05%	21.88%	13.21%	Major A
Totals	32	1888	1258	630	24	33.37%			
The ratio of the total number of deviations for exceeded reject rate limits generated during visual inspection of vials									60.38%

Syringe Defect Types	Number of events	Units evaluated by PD lab	Units confirmed for defect	Units not confirmed for defect	Number of re-inspections after events	False reject ratio	Occurrence ratio for syringe events	Occurrence ratio for total events	Classification of defect type
Incomplete coating of plunger	2	118	99	19	2	16.10%	9.52%	3.77%	Major A
Bent needles	3	177	140	37	0	20.90%	14.29%	5.66%	Minor
Malformation of plunger	7	413	398	15	7	3.63%	33.33%	13.21%	Critical
Displacement of needle guard	4	236	179	33	2	13.98%	19.05%	7.55%	Major A
Incomplete needle guard	5	295	274	21	5	7.12%	23.81%	9.43%	Major A
Totals	21	1239	1090	125	16	10.09%			
The ratio of the total number of deviations for exceeded reject rate limits generated during visual inspection of syringes									39.62%

Figure 1
Historical Data Table

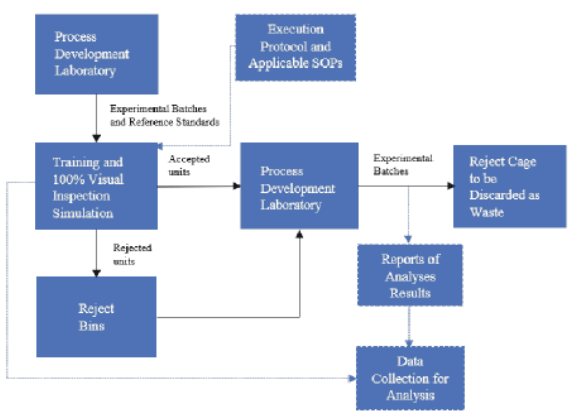

Figure 2
Experimental Execution Process Map

The data of experimental results confirmed by the Process Development Laboratory was distributed in tables at the beginning of the analysis phase. The false reject rate was established as the key indicator for the analysis of the data. The false reject rate of each defect type was calculated for each experimental batch independently. Also, a false reject rate including all defect types was calculated for each batch. Next, a total false reject rate for each defect type was calculated with the sum of the three batches. Once more, the data of experimental results was distributed as a total including all defect types in the study to calculate a total false reject rate. The same analysis process was performed with the historical data of the same defect types of loose crimp, flip-off, and surface abrasion to calculate the false reject rates. A comparative analysis between the historical data and experimental results was performed.

Next, a statistical analysis of these results was performed to determine if there was a significant difference. In the next analysis, the calculated proportion of changes between the baseline and experimental false reject rates of each defect type was applied to the baseline data to observe the possible effect and perform a cost analysis. The analysis phase was completed with a calculation of the average costs of a vial unit applied to the baseline data and improved baseline to obtain an approximate amount of cost reduction. Some limiting factors of this project were the costs of required instruments and equipment, the availability of staff for training and execution, regulatory limitation of the visual inspection method, and the small number of experimental samples for the data analysis.

Results and Discussion

This company site is dedicated to the manufacturing of a wide diversity of injectable drug products for the treatment of critical health conditions which delivers a high volume of units as vials or pre-filled syringes. To identify defect types reported as the root cause of investigations of exceeded reject rate limits, research of historical data for deviations was performed. As presented in Figure 3, a total of 53 deviations related to exceeded reject rates were found, where 32 were generated during the visual inspection of vials and 21 during the visual inspection of pre-filled syringes. During the data collection, a total of 10 defect types were identified, where 5 are vial defects and 5 are defects found in pre-filled syringes.

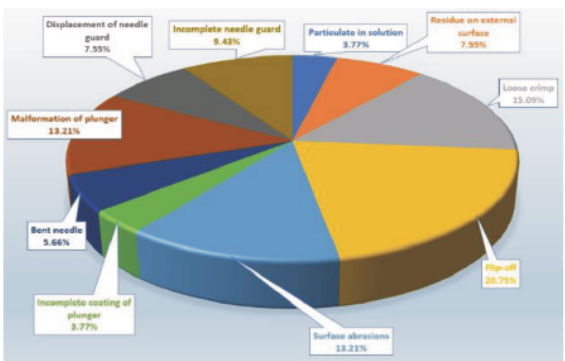

Figure 3
Defect Type Distribution Pie Chart

The false reject rates of each defect type were calculated by dividing the number of false rejects by the number of rejects evaluated by the Process Development Laboratory. The defect types of loose crimp, flip-off, and surface abrasion were identified as major offenders with a higher false reject rate value after the analysis. As shown in Figure 4, the false reject rates obtained were 29.87% for loose crimp, 47.15% for flip-off, and 37.05% for surface abrasion defects. The total of false rejects of these three defect types represented 19.19% of 1534 rejected units evaluated, and 77.02% of the 779 false rejects of all defect types analyzed, as shown in Figure 4.

The total false reject rate of each defect type of loose crimp, flip-off, and surface abrasion was reorganized as a single total value to calculate for analysis. A result of a 39.11% false reject rate shown in Figure 5 was obtained where it can be observed the ratio between false rejects and rejects. The results of this analysis were used to design a method focused on the evaluation of the loose crimp, flip-off, and surface abrasion defect types as a strategy to reduce false rejects during the visual inspection process.

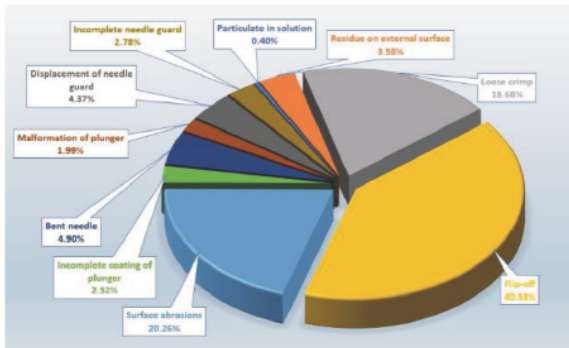

Figure 4
False Reject Rate Pie Chart

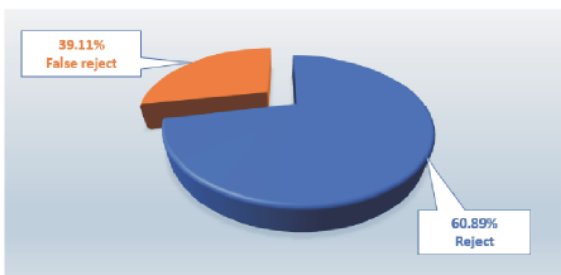

Figure 5
Historical Data Total False Reject Ratio Pie Chart

Experimental Execution Results of the Visual Inspection Simulation of Vials

	Units Inspected	Accepted units	Rejected units	Rejected units by defect type	Reported defect type	Defect type classification	Reject rate	False reject rate by defect type	Total false reject ratio of batch	Process performance yield
Batch 1A	1000	976	24	5	Loose crimp	Critical	0.50%	20%	8.33%	97.60%
				9	Flip-off	Major A	0.90%	0%		
				10	Surface abrasion	Major A	1.00%	10%		
Batch 2B	1000	978	22	4	Loose crimp	Critical	0.40%	0%	0%	97.80%
				9	Flip-off	Major A	0.90%	0%		
				9	Surface abrasion	Major A	0.90%	0%		
Batch 3C	1000	977	23	5	Loose crimp	Critical	0.50%	20%	4.35%	97.70%
				9	Flip-off	Major A	0.90%	0%		
				9	Surface abrasion	Major A	0.90%	0%		

Figure 6
Experimental Execution Results Table

The execution results obtained from the experimental simulations shown in Figure 6 above, were 2 false defects of 24 rejected units for batch 1A, no false rejects of 22 units rejected for batch 2B, and 1 false reject of 23 rejected units for batch 3C. The

false reject rate result for batch 1A was 8.33%. No false rejects were reported for batch 2B for a 0% of false reject rate, and a 4.35% false reject rate for batch 3C as presented in Figure 4. The data of experimental results for each defect type of the total number obtained from the execution of simulations was redistributed for analysis. The false reject results in Figure 7 were 14.29% for loose crimp, 0% for flip-off, and 3.57% for surface abrasion defect. In addition, the data was redistributed and analyzed once again with a result of a 4.35% of false reject rate from the accumulated values of defects and false rejects presented in Figure 8.

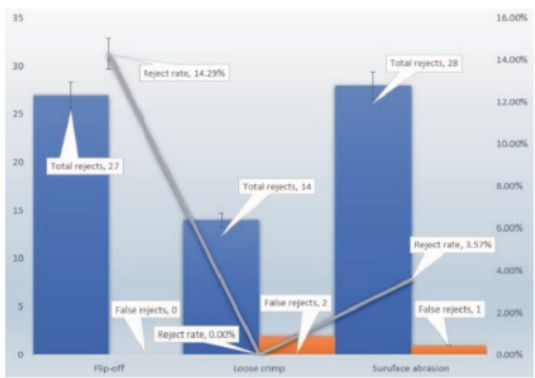

Figure 7
Experimental Results Bar Chart

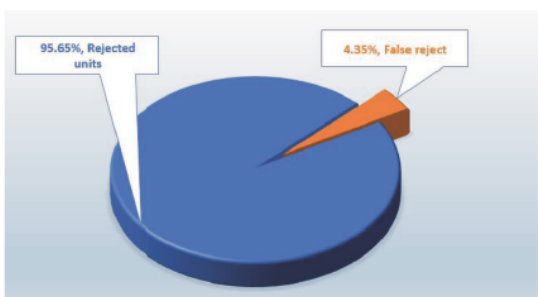

Figure 8
Experimental False Reject Ratio Pie Chart

A comparative analysis of the false reject rates of historical data and experimental results was performed to evaluate the method tested as an additional visual inspection step for these defects. The proportion of the difference in false reject rates of the historical data when compared to the experimental results was calculated. As illustrated in Figure 9, the analysis result for the loose crimp defect type was a reduction of 45.46% of the false reject ratio. The flip-off defect type showed a decrease of 100% in false reject rate, and a 90.36% of reduction for the surface abrasion defect type. Then, the calculated 0.3911 false reject rates of the historical data and 0.0434 of experimental data were analyzed to calculate the difference. The result of the analysis for the total false reject rates of the historical data and experimental results was an 88.88% in reduction.

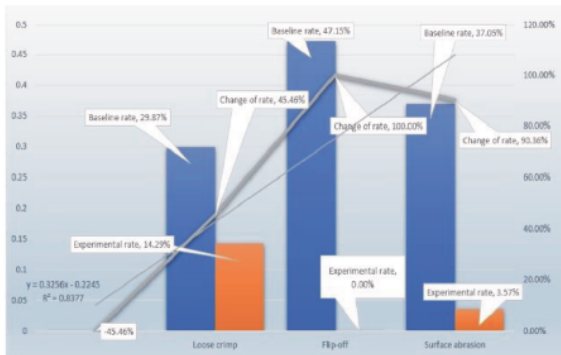

Figure 9
False Reject Rate Analysis Bar Chart

Statistical analysis of the false reject rates of defect types of historical data and experimental results data was performed. The analysis of a t-Test performed in Minitab with a 95.0% of confidence level resulted in a P value of 0.017 as illustrated in Figure 10. The P value obtained indicates that there was a significant difference in the false reject rate. This difference can be observed in Figure 11 where is no overlapping of values under a normal distribution. This result validates the effectiveness of this method for the evaluation of loose crimp, flip-off, and surface abrasion defect types during the visual inspection process of vials.

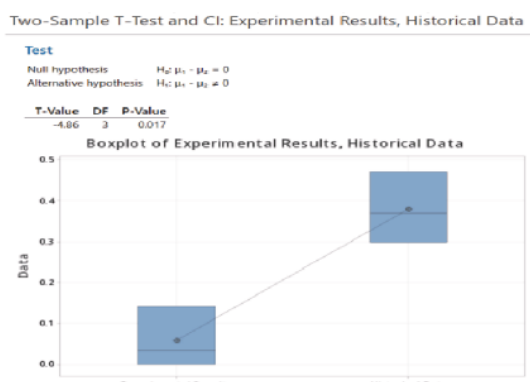

Figure 10
T-Test Statistical Results Table

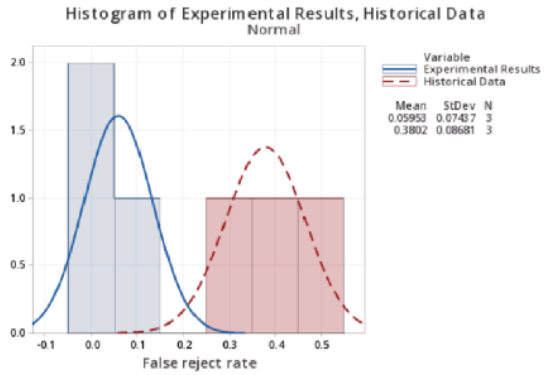

Figure 11
Histogram of Distribution

The reduction rates calculated for each defect type were applied to the historical data values for analysis. The experimental analysis results were a 16.29% false reject rate for loose crimp, 0% for flip-off, and 3.57% for surface abrasion defect type. In addition, the false reject rate calculated considering all the defect types combined was 6.00% for a reduction of 77.22% from the 39.11% total false reject rate of the historical data presented in Figure 12. Therefore, there is a high probability to meet reject rate acceptance criteria during the improved visual inspection of vials.

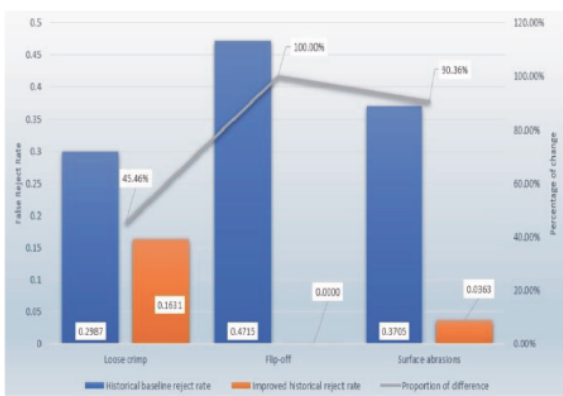

Figure 12
Bar Chart of Improved False Reject Rate

The cost per unit of seven products produced in vials on this site provided by management was calculated as an average cost of $689.00 per unit. This cost per unit was applied to the number of 600 false rejects retrieved from the historical data resulting in $413,400.00. On the other hand, the average cost per unit applied to the experimental result of 92 false rejects for the same population of data is $63,388 for this scenario. This translates into a reduction of $350,012.00 for the same number of rejects reported as loose crimp, flip-off, and surface abrasion during the visual inspection process shown in Figure 13.

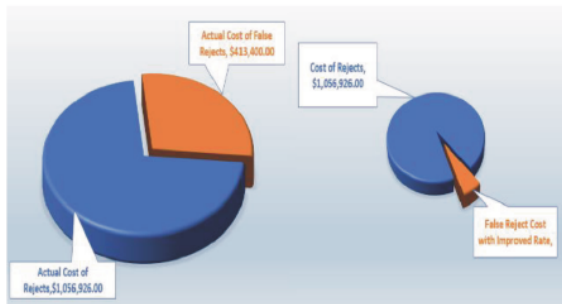

Figure 13
Pie Chart of Experimental Cost Analysis Results

False rejects are a significant contributor to the investigations of exceeded reject rate limits of the visual inspection process. The reduction of false rejects contributes to the reduction of many additional processes shown in orange in Figure 14 triggered by exceeded reject rates during the visual inspection process. As observed in Figure 14, some of these events include the creation of a deviation, the evaluation of a sample of the rejected units by the Process Development Laboratory, and a 100% re-inspection of the batch which elevates the benefits of a reduction of false rejects in the visual inspection.

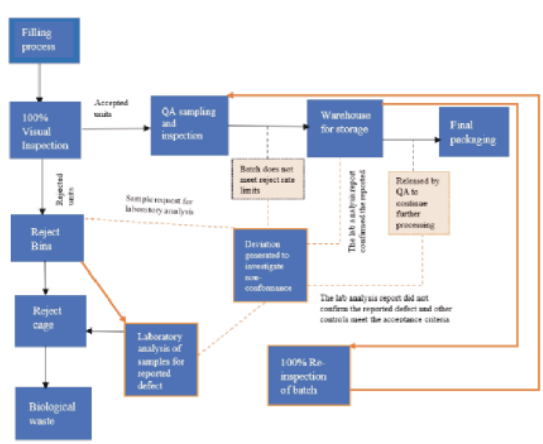

Figure 14
Visual Inspection Process Map with Exceeded Reject Rate

The objective of a 50% reduction in the rejection of acceptable drug products was achieved with false reject rates of 100.00% for flip-off,

90.36% for surface abrasion, not far from the objective, 45.46% for loose crimp, and 88.88% for the combined total of all defects. The result of this research was submitted to management with an action plan for the implementation and a suggested follow-up effectiveness check.

CONCLUSION

A hundred percent visual inspection is a non-value process with a high cost performed as a mandatory requirement for the manufacturing of injectable drug products [1] [5] [6] [11]. A high number of false rejects was observed in the evaluation of defects for the investigation of non-conformances with reject rate limits of the visual inspection [9] [13] [14]. Therefore, false rejects are a significant contributor to non-conformance deviations that generates additional waste increasing the manufacturing costs of these products [2]. Even in automated inspections, manual inspection is required of the ejected units by the inspection equipment [2] [3]. As presented by Lynn D. Torbeck, the implementation of an additional step using reference standards to confirm specific conditions improves the visual inspection process output [16].

The experimental results showed to meet and exceed the expected result of reducing more than 50% of false rejects during the visual inspection with a dramatic cost reduction of acceptable units discarded as waste [2]. The improvement of the false reject rates reduces the frequency of non-conformance with the reject rate limits which prevents other activities such as investigations and re-inspections trigger as consequence [9] [13]. Therefore, the preventive approach of this method is the greatest advantage over the CAPAs actions deployed as a reactive approach to non-conformances with reject rate limits [14].

Is recommended to increase the frequency of the evaluation of the visual inspection process output to identify defect types with a trend of high reject rate even with results inside the accepted limit [10]. Continuous improvement such as the application of Lean Manufacturing methodology is recommended as a preventive approach to reduce the opportunity for non-conformances and eliminate waste [10] [17]. To conclude, the results of this project contribute to the company's objective of cost reduction improvement for the next year, in addition to enhancing the company's competitiveness and marketplace.

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