Cost Improvement Process - LAL Sample Selection Procedure

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Abstract *— The Cost Improvement Process for LAL (Limulous Amoebocyte Lysate) Sample Selection Procedure was identified with the purpose of reduction of cost and increase in revenue. This process was analyzed and overviewed, estimating an annual saving of over $50k. This was all done eliminating the need for use of end-items for testing and using scraped parts instead. DMAIC project methodology was used to attack this project. This methodology was used to develop a new strategy and new process steps to make the use of scraped parts possible. This process underwent changes in various stations, including documentation and layout of the manufacturing process. The steps added to this process attack the LAL sample selection, while introducing new instructions on how to handle material and how to obtain the most out of the lot and out of the line. Implementation of this project is within compliance of the regulation agencies requirements, for the employees engaged with this process and with the technicians performing the LAL testing in the laboratory.*

Key Terms *— DMAIC, End-Item, Limulous Amoebocyte Lysate (LAL), Quality, Regulation Agencies.*

PROBLEM STATEMENT

Research Description

Pyrogen samples should be produced and selected in the finished form, including packaging. Samples utilized for LAL testing may be selected from product that has been rejected for quality issues if the rejected samples are representative of final non-rejected product. Units rejected for contamination cannot be used for LAL testing. The Fixation manufacturing line produces a large amount of scrap in a particular station called the End of Line Tester. An approximate 5 to 20 end items are scraped in this part of the line on every manufactured lot. In this stage of the manufacturing process the product is fully assembled and only missing three more steps of packaging to be completed. These stations include the safety pin installation, (Zero – Load Clip), a packaging installation (Strap to Tray) and sealing (Package Seal). This presents an opportunity to reduce cost and increase revenue in Fixation manufacturing.

Research Objectives

The main objective is to develop a Work Instruction for daily extraction of scraped product that can be used for LAL testing and represent the lot. This includes specified instructions for the operator to follow and successfully complete the sample selection process. Revenue increase will be the focus while maintaining the process between MP lines and in line with the requirements provided by the FDA. A $50K yearly saving is projected and a better handling of the lot.

Research Contributions

The components in this project will be historic data from 12 months, including every lot manufactured for the Fixation devise. This data shows the entire sample selection for a year of manufacturing. With this data, the quantity of manufactured products, cost and savings report will be generated to gain more knowledge of the issue and how the line works. Product control and product handling will also be implemented as well as rearrangement of components in the line and new storage areas for correct and segregated sample handling. Training of personnel will be implemented to assure the process runs smooth and with cero issues. Finally, the process documentation will be reviewed and modified to accommodate all new changes to the BOM and to the manufacturing

process. Therefore introducing a new Work Instruction (WIM) to further explain and standardize the process for future reference.

LITERATURE REVIEW

The topics included in this section were reviewed with the purpose of understanding the testing function, medical devices and classification for manufactured product to ensure a well-designed guide for development.

LAL is a reagent extracted from circulating amebocytes, Limulus Polyphemus of Tachypelus Tridentaus (TAL), that interacts with endotoxin to form a gelatinous clot used to estimate the endotoxin levels. Bacterial Endotoxin Test (BET) is used for measuring active endotoxin by combining a liquid test sample with LAL reagent and measuring the resulting proportional reaction via visual, turbidimetric and chromogenic detection. Bacterial Endotoxin is a high molecular weight complex associated with the cell wall of Gram-negative bacteria that is pyrogenic in humans and specifically interacts with LAL. The Endotoxin Unit (EU) is the standard unit of measure for endotoxin activity [1].

PROCEDURE

LAL testing is performed in duplicate of Endotoxin Standard Dilution Series, this series must be within a one two-fold dilution of the labeled lysate sensitivity. Endotoxin standard dilution series should be prepared according to the manufacturer's instructions. This dilution should be prepared in a depyrogenated test tube, all tubes are gently vortexed to avoid foaming but are thoroughly mixed. All tubes must be incubated at a specific temperature and time. Once the incubation period finishes, each tube is removed. Calculate endotoxin content of test sample extract by multiplying the dilution factor by the labeled lysate sensitivity. The test results are invalid if the control standard dilution series does not confirm the lysate sensitivity, the result of the negative water control are positive indicating contamination in the system, and the UE/Device shown in Table 1 is exceeded. Testing on all products should be under 10 EU/Device to meet regulations. Results indicating an invalid test should result in a re-test. Keep in mind that the endotoxin levels may differ between lots as indicated on the certification received with each lot [1].

Table 1
Extraction Procedure for Pyrogen Testing

Extraction Procedure of Pyrogen Testing					
Product	Sample Size	Extraction Process	Specification Limit	Alert Level	Qualified Lysate
Fixation	CDHR Sampling Plan	Extractwith X ml/unit at room temperature for X hour or X temperature for X minutes using periodic agitation	≤ 20 EU / Device	> 10 EU / Device	Associates of Cape Cod

Medical Device

A medical device [2] is any instrument, including instruments that use software and analog equipment that is used to perform diagnostics and/or for therapeutic purposes. These devices are intended to be used for monitoring, treatment, replacement and modification to the human body. There are three types of medical devices:

- **Active Medical Device:** This refers to any medical device that depends on a source of electrical power. These are medical devices intended to transmit energy, substances or other elements between the device and the patient. Medical devices that use software are also Active Medical Devices.
- **Active Implantable Medical Device (AIMD):** Includes any device that is intended to be totally or partially introduced surgically or medically into the human body and which is intended to remain after the procedure.
- **In-Vitro Diagnostic Medical Device Directive (IVDD):** Any medical device which is a reagent, reagent product, calibrator, control material kit, instrument, apparatus, equipment or system, whether used alone or in combination.

Active Implantable Medical Device

These devices are more complex than static medical devices and have more moving parts. These devices function through the application of human movement or by the effect of gravity. In other terms,

active medical devices are those that need some sort of artificial power source, such as a battery, electric power or human movement. These devices are inserted into the body of the patient through a natural orifice or by surgical means and these are intended to remain in the body after the procedure is completed.

Complexity

Due to the internal use of these devices, almost all of them have a highly complex design and use very small parts. Therefore, these devices are some of the most difficult to manufacture. Medical devices that meet patients must meet high standards and those that become part of the body have even higher standards.

Design and Manufacturing

Design and manufacturing of these active implantable medical devices is challenging and requires special considerations beyond those associated with other medical implements. Operating parameters of such devices must be specified to precise tolerances to prevent unintended harm to the patient. One important requirement for such devices is temperature, although these devices may function well on different temperatures, it is required for these devices to operate in no more than 2 ºC above the normal body temperature of 37 ºC. After the design and manufacture process, these products need to be placed in specially designed packages. These implants must be taken care of during their entire transition on their way to the patient. Environmental factors such as temperature, humidity and pressure can cause different effect on the device affecting its performance.

Regulations

The FDA requires active implantable medical devices to demonstrate electromagnetic compatibility. The manufacturer must show how the device interacts when encountered with a magnetic field, radio frequency or other electromagnetic devices. The device must also not significantly interfere with other devices due to its own emissions. Documentation for implantable devices must be controlled and regulated as well. All documentation for devices that will live inside the human body must have their records stored away for life. This data is auditable data that can be verified at any given time.

DMAIC

The DMAIC method is a data driven improvement cycle used for improving, optimizing and stabilizing business processes and designs [3]. The DMAIC improvement cycle is the core toll used to drive Six Sigma projects. A brief description of the process is shown in Figure 1.

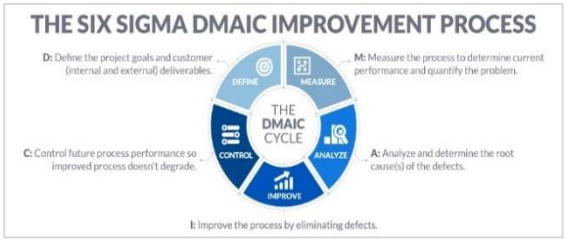


Figure 1
Six Sigma DMAIC Improvement Process [4]

DMAIC process

- **Define** the problem, customer needs and expectations, and if needed, their critical to quality (CTQ).
- **Measure** the performance of the Core Process involved. Develop a data collection plan for the process to determine the types of defects and metrics.
- **Analyze** the data collected and process map to determine root causes of defects and opportunities for improvement; identify gaps between current performance and goal performance.
- **Improve** the target process by designing creative solutions to fix and prevent problems.
- **Control** the improvements to keep the process steady and providing the expected results [3, 4].

METHODOLOGY (CURRENT METHODOLOGY FOR LAL SAMPLE SELECTION)

Current Manufacturing Process

The Fixation manufacturing line is composed of approximately 10 different stations. The main focus on this analysis impacts 4 stations of the process. These go hand to hand with each other in order to finish the assembly of this Fixation device and bring it to packaging, inspection and all the way to the LAL sampling and laboratory. Those 4 sections are:

- **End of Line Tester**
  Once the product is fully assembled it comes to this station where it undergoes testing. This testing is specifically for performance, functionality and quality purposes. It goes through a set of tests that verify that each component is working properly, and that the product is in the condition required for use of the customer and patient. For the start of this testing a line clearance must be performed, to verify that there is no material from previous lots and there is no particles or debris in the station that could compromise the product its testing and the LAL testing performed after quality. After the line clearance is performed the operator places the product in the end of line tester and commences the test. It is an automated process, and the ELT provides the operator with a Pass of Fail sign to notify the status of the test. If the test fails, the part is scraped. Everything that goes through this step and all others is documented in the LHR Traveler (Lot History Record), which carries all the information of the lot being manufactured and it keeps the good parts from the scraped parts segregated and accounted for.
- **Zero Load Clip Installation**
  A line clearance is to be done in order to start the assembly process on this station. After the parts are received, they get a zero load clip (safety clip) installed. This clip prevents any damage from occurring during transport and ensures that the product will arrive in operating conditions to the patient. After the zero load clip is installed, the next step is to place it in its tray. This tray is specially designed to accommodate the Fixation device and protect it from transportation.
- **Strap to tray installation**
  Following the previous step, line clearance must be performed in order to continue manufacturing on the strap to tray step. In this step the operator uses a rivet to attach the zero load clip on to the tray. This rivet is placed at X psi, in order to have a secure fit while also having a loose fit, so the Fixation device can come out easily and without any chance of damaging it.
- **Package Seal**
  After performing line clearance and making sure all other material is stowed away the operator performs an inspection on the sealer. This inspection measures that the machine is within the determined parameters of pressure, temperature and time to ensure a good seal is delivered. After this process, all of the parts that come from the previous line are then inspected to make sure they have all the necessary parts and hardware as specified in the Bill of Materials (BOM). Finally, after completion of the sealer verification and the product inspection the operator starts the sealing process. This process is done taking into consideration the quality of the seal, the size of the seal, and verifying for any bubbles or any defects. After the Fixation device is sealed, it is labeled and taken to a rack for further inspection and LAL sample selection.

Quality inspection

After the entire manufacturing process is complete, all of the manufactured products undergo a thorough inspection. Here the quality specialist selects a specific percentage of pieces from the lot to verify. Seal strength is verified along with all the documentation and review of used materials. The presence of vacuum is verified, loose components

inside the device, label integrity, and that there are no holes in the bag that could compromise the product.

LAL Sample Selection

Once the quality inspection is complete, the quality specialist selects ten random pieces of the lot following a Standard Operating Procedure (SOP) which defines the specific quantity for LAL testing. Refer to Table 2 and Table 3 for a clear explanation of the sample selection process. This process can be done at any point of the lot, this being the start of the lot, halfway through manufacturing or at the end. These ten samples are taken away from good, manufactured product that is ready for shipping and ready to sell. The product used for this test must represent the entire manufacturing process in order for it to be done correctly.

Table 2
Quantity of Test Samples per Lot

Prodcut	LAL / Pyrogen	BI	Sterilization Method
Fixation	CDHR / per Manufacturing Lot	See Table 3	Gamma

Table 3
CDHR Sampling Chart

Lot Size	Sample Quantity
0 - 99	3
100 +	3% of Lot Size up to Maximum of 10

METHODOLOGY (PROPOSED LAL SAMPLING METHODOLOGY)

Proposed Manufacturing Process

This method will be included as a new step in the manufacturing process traveler. This new step goes hand to hand with the new Work Instruction which will guide the operator to the selection, completion, inspection and segregation of all scraped product that will be selected for the use of LAL samples. The operation will remain the same for all manufactured products. The manufacturing process changes include the selection of the samples, manufacturing throughout the remainder of the line and quality inspection.

Sample Selection

Scraped product will be placed in enclosed bins, prepared for LAL sampling to ensure no debris or any particles meet the scraped product. After the shift has ended and all documentation is finished on good product, the operator will continue to follow to step 15 on the LHR Traveler and start with the LAL Sample Selection procedure. The operator will then select samples to be used for LAL testing following the WIM0307 (Work Instruction).

Manufacturing Procedure

The scraped product selected for LAL testing will undergo Zero Load Clip Installation, Strap to Tray Installation and Package seal. This process will be under the same instructions and same parameters as the good, manufactured product. The operator at package seal must inspect every sample to ensure all manufacturing processes have been correctly performed and that the sample is qualified for LAL testing following the SOPQ0065 and WIM0307.

Inspection Procedure

Inspection procedure will consist of the same parameters. A new table will be added in the LHR Traveler for the purpose of selection and inventory. This table will include quantity of samples for LAL selected from scarped parts as well as quantity of samples selected from the lot if the scraped parts do not meet the amount of ten minimum samples needed for LAL testing.

RESULTS AND DISCUSSION

Define Phase

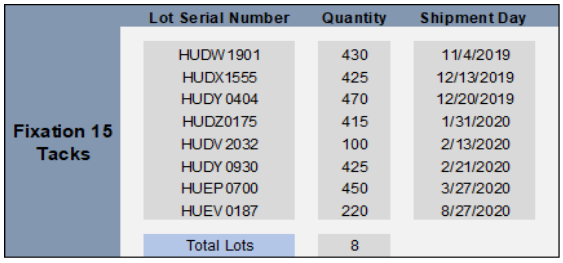
Final Selection for LAL Samples is done in the inspection process. In every lot the inspection specialist withdraws 10 pieces from the lot to take them to the laboratory for LAL testing. This method of selection takes End-Items that could be sold to the customer.

Measure Phase

As part of this phase, measurements from data recorded over a year was observed. It was found that

during the past year 30 lots where manufactured in which 10 End-Items form the manufacturing line were taken for LAL testing. The Cost per part was obtained and a Cost Analysis was generated to have a projected cost/savings report. This analysis is shown in Figures 2, 3 & 4.

This data analysis was taken to know the actual status of the process. The current cost for sampling is an average of 100k yearly. This shows that there is enough data and enough value to implement a new Sample Selection process to reduce those costs and improve efficiency. The analysis also shows the projected savings for this current year. This project is being implemented in February 2021 and BD currently closes the year in October. So there are 8 months left in this year to obtain the projected savings of 50k. Shown in Figure 4 is the projection for this year coming up to 60k.



	Lot Serial Number	Quantity	Shipment Day
Fixation 15 Tacks	HUDW1901	430	11/4/2019
	HUDX1555	425	12/13/2019
	HUDY 0404	470	12/20/2019
	HUDZ0175	415	1/31/2020
	HUDV 2032	100	2/13/2020
	HUDY 0930	425	2/21/2020
	HUEP 0700	450	3/27/2020
	HUEV 0187	220	8/27/2020
	Total Lots	8	

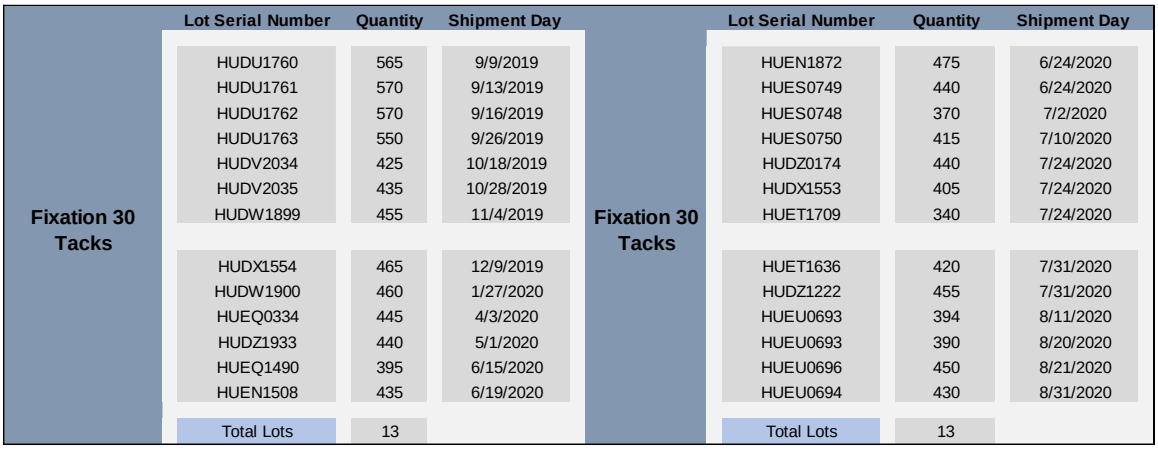
Figure 2
Fixation 15 Count Lot Review

Analyze Phase

During this phase, the root cause of this process will be addressed using a fishbone diagram (Figure 5) to show the differences and the cause-and-effect analysis. Potential causes identified in the fishbone diagram will be prioritized on their critical level. Critical level legend is shown on Table 4.

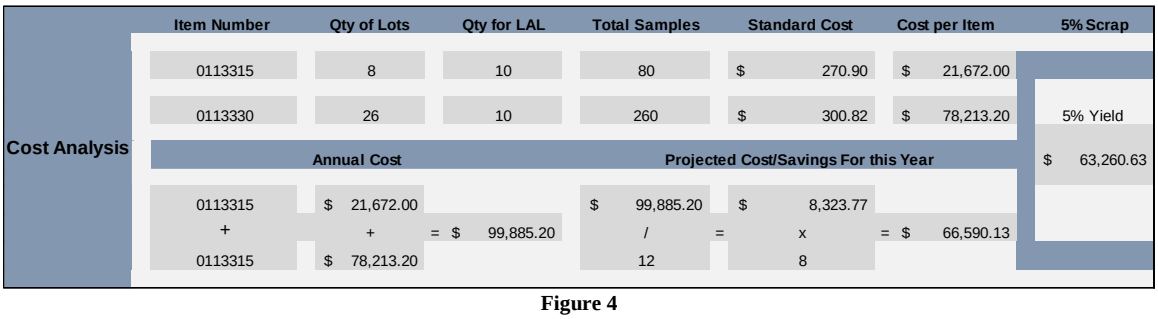
Table 4
Critical Level Legend

Critical Level	Scale
(1)	Low
(3)	Medium
(5)	High



	Lot Serial Number	Quantity	Shipment Day		Lot Serial Number	Quantity	Shipment Day
Fixation 30 Tacks	HUDU1760	565	9/9/2019	Fixation 30 Tacks	HUEN1872	475	6/24/2020
	HUDU1761	570	9/13/2019		HUES0749	440	6/24/2020
	HUDU1762	570	9/16/2019		HUES0748	370	7/2/2020
	HUDU1763	550	9/26/2019		HUES0750	415	7/10/2020
	HUDV2034	425	10/18/2019		HUDZ0174	440	7/24/2020
	HUDV2035	435	10/28/2019		HUDX1553	405	7/24/2020
	HUDW1899	455	11/4/2019		HUET1709	340	7/24/2020
	HUDX1554	465	12/9/2019		HUET1636	420	7/31/2020
	HUDW1900	460	1/27/2020		HUDZ1222	455	7/31/2020
	HUEQ0334	445	4/3/2020		HUEU0693	394	8/11/2020
	HUDZ1933	440	5/1/2020		HUEU0693	390	8/20/2020
	HUEQ1490	395	6/15/2020		HUEU0696	450	8/21/2020
	HUEN1508	435	6/19/2020		HUEU0694	430	8/31/2020
	Total Lots	13			Total Lots	13	

Figure 3
Fixation 30 Count Lot Review



	Item Number	Qty of Lots	Qty for LAL	Total Samples	Standard Cost	Cost per Item	5% Scrap
Cost Analysis	0113315	8	10	80	$ 270.90	$ 21,672.00	
	0113330	26	10	260	$ 300.82	$ 78,213.20	5% Yield
	Annual Cost			Projected Cost/Savings For this Year			$ 63,260.63
	0113315	$ 21,672.00		$ 99,885.20	$ 8,323.77		
	+	+	= $ 99,885.20	/	= x	= $ 66,590.13	
	0113315	$ 78,213.20		12	8		

Figure 4
Cost Analysis for Fixation 30 Count & Fixation 15 Count

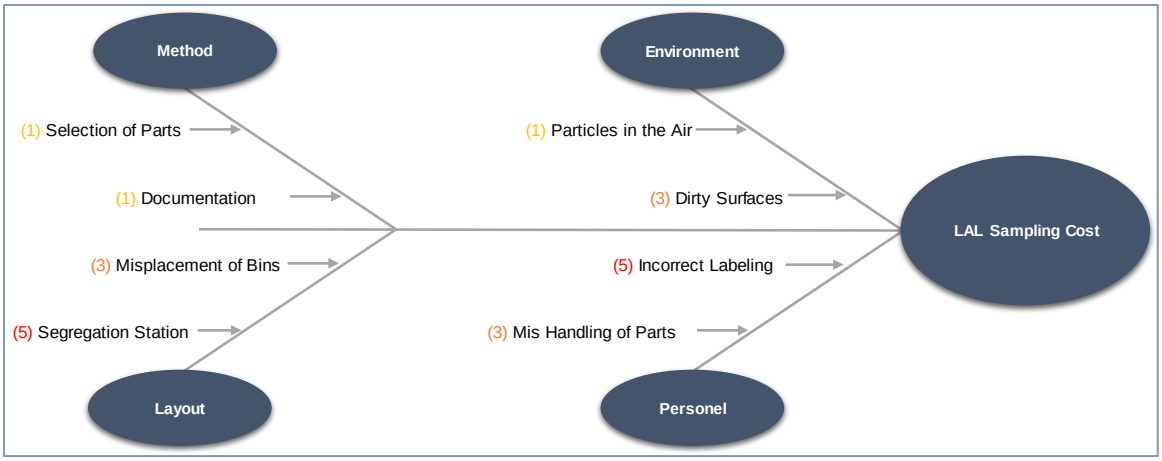


Figure 5

Value Stream Map for the Operations Contained in the Scope of This Project

As part of the Analyze Phase, each assessment will be evaluated individually and verified to select which continue to the next phase. This step ensures that these causes will be accessed, and they will not affect the finished method. All 8 will undergo verification to reduce the probability of issues due to effects causes in the manufacturing process. Refer to Table 5 for details on the critical component analysis (Cause-and-Effect Analysis).

Table 5

Cause and Effect Analysis for Critical Components

Cause	Effect	Effect on Project?
- Selection of Parts - Documentation	Error in Documentation	NO NO
- Segregation Station - Misplacement of Bins	Manufacturing Mix-up	YES YES
- Particles in the Air - Dirty Surfaces	Contamination on Product	NO YES
- Incorrect Labeling - Mis Handling of Parts	Product Mix	YES YES

Improve Phase

Each critical and high alert element was analyzed and evaluated in to understand each one and find the best way to tackle it. This is another critical component of this assessment and must be verified carefully. Within this analysis various components were taken into consideration. These include organization, labeling, segregation, cleanliness and mis-handle of product. All variables for each component were analyzed and only the critical components were included in this assessment. Table 6 shows each critical component of the new method being implemented along with a brief description and its proposed improvements.

Control Phase

After applying the improvement plan, the final process for the Sample selection of LAL Test Samples reduces the quantity manufactured products to be used. The operation adds a new step to the entire process. This step helps the operator identify scraped product that can be used for testing and it also shows how to select it, segregate it and finish it. As part of this control phase, the Log History Record Travelers (LHR traveler) were updated to include information regarding this new step and the new method selection. Detailed tables have been added with specific information and instructions regarding the sample selection process per Work Instruction (WIMXXXX). This Work Instruction has also been created to provide more detailed information of the process and assure it is accomplished according to the instructions. In this work instruction, important information like specific values and timing is determined in order to maintain control of the entire process and assure the documentation practices are done correctly. Non-conformances are not acceptable and attach a bad review to the product. FDA regulations require testing for this product, part of this control phase is to ensure that all regulations are met, and the product delivered to the customer is within spec and up to BD standards.

Table 6
Critical Elements Assessments

Cause	Description	Proposed Improvement
Misplacement of Bins	Bins are paced under the tables without any coverage. Scraped parts often receive debris and other particles which are not tolerated by the laboratory for LAL testing.	Bins shall remain in their designated location and shall be labeled. Selected bins for scraped samples must have a lid and a bag. This will ensure protection of the samples from any debris or anything that could compromise the part and the testing.
Incorrect Labeling	Incorrect label placement can result in a major issue. Regulated industries like BD cannot afford to have any product go out of the facility and ship if it is not meant to be for human use. This will cause a major recall and several regulation actions including the possibility of shut down. These mishaps could cause a regulatory event with the FDA or other agencies. Which could lead to a serious investigation and even shutting down the facility.	This is a very delicate part of the entire process and it is one that should be verified with much care. Labels will be placed on each sample, inside and outside to make sure there are no issues. The process will also select these samples at the end of the shift or at the end of the lot. This way the supervisor can make reconciliate and know how much manufactured product there is and verify that quantity to the one at the end of the lot with all of the scraped parts accounted for. This way there is very little room for any mishaps.
Segregation Station	Currently all of the samples used for LAL testing are selected at the end of the Shift/Lot in the inspection section of the manufacturing process. Given the fact that these are good products, no labeling needs to be used until this point. For the proposed method, the selection will be in the same station but, the product will already be scraped before it arrives to the inspection section.	Segregating the parts is a must. For this reason, once the parts are scraped the first thing that the operator will do is place a red label of Manufacturing Stop and a label of LAL sample to the part. This label will go directly on the handle, where it is most visible to ensure that no mix-up happens during the manufacturing process and no part scraped leaves the manufacturing line with the lot. After the samples are sealed another label will be placed on the outside of the pouch containing the lot number information, the reason of scrap and specifically identifying the part for LAL testing with a yellow label. Station for these samples shall be marked as LAL Samples and shall not be together with the lot.
Dirty Surfaces	Surfaces must remain clean; contamination of product is not acceptable. This will cause loss of product and increase in work.	Operators will perform line clearance before each sampling selection to undergo final stations. Every table and tool must be cleaned following the respective SOP, and this will include cleaning and maintaining the bins in optimum conditions.
Mis-handling of Parts	Adding scraped parts to the manufacturing line while it is running is not allowed. This could cause a major mix-up with the lot and samples could be added to the final lot by mistake.	Process documentation will specifically state that the sample manufacturing process will be performed at the end of the shift or at the end of the lot. Once the supervisor has reconciliated all manufactured product and the only remaining product is the scrap to be used for LAL testing.

CONCLUSION

After the successful implementation of the LAL Sample Selection Procedure, the manufacturing line is running smoothly and effectively. Following this implementation plan, the cost was updated to the exact cost of production until the extraction point from the line. The projection of cost reduction/saving for the remainder of the year 2021 is of approximately $60,000. Refer to Figure 6 and Figure 7 for the projection data and savings analysis.

By eliminating the need of selection of samples from end-items per applicable SOP, a savings projection of approximately 60K is acquired. This projection places the Company above the established goal of 50K for the year. All ten (10) samples passed the testing performed by the lab technicians. Currently the new method has been used in the last lot manufactured in February and the 4 lots manufactured on March and a current 100% of the samples selected for LAL testing have been selected from the scrap of the manufacturing line. A total of 50 samples have been used from the scrap of the line. This provides a savings of $10,925.70 for the first two months of production with the new method. No quality events have been generated nor any MRR's, method is working accordingly, and all staff is executing the tasks in order as per WIMXXXX.

Lots to be Manufactured per Month								
Month	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
Fixation Device 15	0	1	1	1	1	1	1	1
Fixation Device 30	1	3	3	3	3	3	3	2

Figure 6
Projection of Lots to be Manufactured

	Item Number	Qty of Lots	Qty for LAL	Total Samples	Standard Cost	Cost per Item		Projected Saving (2021)
Cost Analysis	0113315	7	10	70	$ 200.81	$14,056.70		
						+	=	$ 60,874.10
	0113330	21	10	210	$ 222.94	$46,817.40		

Figure 7
LAL Related Savings Projection 2021

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