Development of a New Medical Device Production Line Using Systems Engineering

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Abstract *— The design and development of a production line to manufacture a new medical device for clinical trials requires the establishment of a very precise implementation plan. This is especially important since we are dealing with products intended for human use subjected to the rigors of the Food and Drug Administration standards. The Systems Engineering methodology is a framework that can be used to manage complex systems and can be used successfully to bring together all the necessary areas or departments needed to complete a project on time. Following this methodology facilitates the generation of all the required documentation to make sure the production line effectively manufactures the intended product. This project combines the methodology of Systems Engineering with the Food and Drug Administration Quality System Regulations 21CFR Part 820.*

Key Terms *— Clinical Trials, Complex Systems, Production Line, Systems Engineering*

MISSION OBJECTIVES

The objective of the project was the design and manufacture of a new production line capable of producing new components to be submitted for Clinical Trials. The main component which is a rotor and permeable membrane shall be joined together using ultrasonic welding. The purpose of this product is to separate the blood into its components to be used for medical applications.

The different equipment will be validated according to the company established guidelines. Units produced in this line will be tested with life patients and should be performed according to the established standards and FDA regulations 21 CFR Part 820[1].

Complete parts should be able to properly perform a blood donation without leaks, excessive noise, early breakdowns or mixing of blood components.

The production line will be capable of producing 2,000 parts on an eight hour shift. All equipment will be subjected to an Installation Qualification (IQ), Operational Qualification (OQ) and Process Qualification (PQ) to make sure they perform as intended

The different machines will have Programmable Logic Controllers and they will be documented and validated according to the company software validation guidelines in a software qualification.

All equipment parameters for critical processes like ultrasonic, laser welding and Leak Testing [2]-[3]-[4] will be determined using Design of Experiments [5]. For the ultrasonic welding process a Burst Tester [2] will be the method to determine acceptable parts.

There will be several visual inspections for the membrane welding to detect for damages, pin holes, improper welding, lack of seal ring and poor laser welds.

The project management strategy is to use the Systems Engineering Process [6]-[7]-[8]-[9] through all the phases of implementation.

Using this methodology will give a framework and structure to complete all the requirements of the project and achieve our goals.

This Systems Engineering strategy will help in bringing together all the necessary areas to complete the project and will guide the team to complete all necessary aspects and documentation to successfully launch our system.

SYSTEMS ENGINEERING DEFINITION

The following concepts define the systems engineering process and key definitions.

- "The Function of a Systems Engineer is to guide the engineering of Complex Systems" [6]-[7]
- "To guide is to lead, manage or direct". As part of the project different functional areas are involved[6]-[7]
- "System is a set of interrelated components working together toward some common objective."[6]-[7]
- "Integrates all disciplines and specialty groups into a team effort forming a structured development process that proceeds from concept to production to operation"[6]-[7]

There are seven major stages on the System Engineering Methodology [9]:

- **Starting the Problem** – Manufacture the New Product Designed at Research and Development.
- **Investigating Alternatives** – Different Designs, Manual vs. Automatic, Test procedures.
- **Modeling the System** – Interactions between stations, Detail concepts and designs.
- **Integrating** – Putting everything together, equipment validation and testing.
- **Launching the System** – Construction of the equipment based on the detailed designs.
- **Assessing Performance** – Process Qualification and Production.
- **Reevaluating** – Lessons Learn for future projects and Equipment Improvements.

The process can be also divided on different phases with its particular requirements through the project life cycle. The different phases are explained here using the actual project and its components.

- **Pre Phase A** – Defines the Mission [8] – Product Definition, Production Requirements. New Product from Research and Development to be assembled for Clinical Trials.
- **Phase A** – Define Top Level Requirements [8] – Process Flow and Interactions, determination of different production strategies like Ultrasonic Welding, Laser Welding, and Leak Testing.
- **Phase B** – Complete the requirements Preliminary Design [8] – Different Stations Concept. Membrane Bonding Station, Burst Tester, Lubrication Station, Laser Welder, Leak Tester, Spin Tester.
- **Phase C** – Complete the detailed system design. [8] Detailed design of all required stations together with the validation strategies. Complete Design Requirements and Validation Protocols.
- **Phase D** – Build, Integrity, verify, lunch the system and prepare for operations [8] – Building of all the required systems and determination of all required parameters and submission of all necessary documentation. Installation Qualification, Operational Qualification and Software Validations.
- **Phase E/F** – Operate the System and dispose of it properly [8] – From Performance Qualification to Production to process improvement and disposal.

The major goal of Systems Engineering is coordinating the engineering, design, and development of an Architecture and Design that meets the Requirements, is consistent with the Operations Concept, operates in the mission environment, and can be developed on schedule and within cost [8].

To understand how useful the systems engineering methodology is in bringing together the necessary groups and tools the following definition of the FDA 21 CFR Part 820 on design controls and development is offered.

"Design and development planning. Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or

activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and approved as design and development evolves."[1]

SYSTEMS ENGINEERING AND PROJECT REPORTS

The required reports and phases of the systems engineering methodology and a comparison of the requirements based on the 820 CFR part 21 are given on Table 1.

Table 1
Required Reports

Phase	Systems Engineering Reports [8]	Project Reports Based on 820 CFR 21
Pre Phase A	Mission Concept Review (MCR)	Design Specifications and Requirements
Phase A	Mission Design Review (MDR)	Validation Specifications and Requirements
Phase B	Systems Requirement Review (SRR), System Concept Review (SCR), Preliminary Design Review (PDR)	Failure Mode Efficiency Analysis, Validation Plan, Installation Requirements, Safety Assessments.
Phase C	Critical Design Review (CDR)	Complete FMEA, Design Plans, Validation Plan.
Phase D	Mission Operations Review (MOR), Pre Environmental Review (PER), Operations Readiness Review (ORR)	Installation Qualification, Operational Qualification, Gage R&R's, Process Qualifications, Standard Operational Procedures, Preventative Maintenance Procedures, Spare Parts
Phase E/F	Disposal Review (DR)	Production Data, Overall Equipment Efficiency, Equipment Removal, Lessons Learned

ADVANTAGES OF SYSTEMS ENGINEERING

The Systems engineering is a structured Methodology to manage complex systems which is compatible with FDA regulations 21 CFR Part 820 in terms of documentation data collection and Management.

The methodology establishes with specific details the steps to complete the project and the required reports creating a baseline to manage all the aspects of the project. This baseline will be a history of lessons learned for future projects.

As a management tool, the systems engineering strategy brings together all the necessary groups and functions to complete the project across the product life cycle.

PROJECT REQUIREMENTS VERIFICATION

Table 2 shows the requirement goals for the project and the proposed strategy to comply with them and launch the production line.

Table 2
Goals and Verification

Requirement or Goal	Proposal or Solution
Manufacture 2,000 parts per shift	• Membrane Bonding Equipment with automatic transportation • Laser Welding equipment
Membrane should be ultrasonically welded	• Membrane Bonding Equipment
Plastic Components should be Laser Welded	• Laser Welding Equipment
Membrane should resist a minimum of 5 psig	• Burst Tester Equipment
Parts should be leak free	• Leak Tester Equipment
Complete assemblies should rotate freely	• Spin Tester Equipment
Case Bottom and Lower Caps should be lubricated to avoid excess friction	• Lubrication Station

Table 3 shows the validation strategy for the proposed manufacturing equipment.

Table 3
Validation Strategy

Equipment	Parameters	Strategy	Outputs
Membrane Bonding	• Energy • Time • Pressure	Design of Experiment	• Visual Inspection • Burst Test Results

				• Weld Height
Leak Tester	• Fill Time • Stabilize Time • Test Time • Leak Rate		Design of Experiment	• Equipment should be able to discriminate between good and bad parts.
Lubrication	• Position • Velocity		Design of Experiment	• Weight of Applied silicone
Burst Tester	• Air Pressure		• Equipment Calibration • Gauge R&R	• Validated together with Membrane Station
Laser Welding	• Power • Time		Design of Experiment	• Seal Strength • Visual Inspection
Spin Tester	• Rotational Spin		Gauge R&R	• Validated together with Laser Welder

EQUIPMENT DESIGN REVIEW

Based on the requirements established at the mission objectives several equipment designs were proposed. This equipment will manufacture the required product using different technologies.

Tables 4, 5,6,7,8 and 9 show the basic design specifications for the different equipment as specified on table 2 Goal and Verification following the Systems Engineering key functions Figure 1[8].

Figures 2, 3,4,5,6 and 7 show the required equipment design concepts.

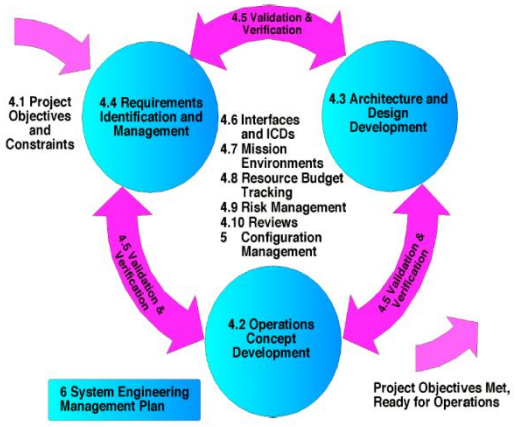

Figure 1

Systems Engineering Key Functions

Table 4
Membrane Bonding Design Review

Section	System Engineering Key Function [8]	Design or Specifications
4.1	Understanding Objectives	Membrane should be ultrasonically welded to the rotor.
4.2	Operations Concept Review	A transport system will move the parts from station to station to be ultrasonically welded
4.3	Archuitecture and Design Development	Equipment uses three stations of ultrasonic welding to seal the membrane to the parts. Branson Ultrasonic 2000. All functions are PLC controlled. A/B Micrologix 1200. A Control Panel will activate all stations and monitor them.
4.4	Requirement Analysis, Identification and Management	Equipment Inputs: Rotor, Membrane.
4.5	Validation and Verification	The ultrasonic parameters like, energy, weld time and pressure will be determined using a Design of Experiments.
4.6	Interfaces And ICDS's	This equipment will complete the main rotor parts to be moved to the next stations like the laser welder. The produced parts will be sampled at the Burst Tester.
4.7	Mission Environments	Power : 120V, 20 A Clean and Dry Air : 80-100 psig Vacuum : 6-10 SCFM
4.8	Technical Resource Budget Tracking	Ultrasonic Equipment : 2 PLC : 1 Controller : 1 Transport Track : 1
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

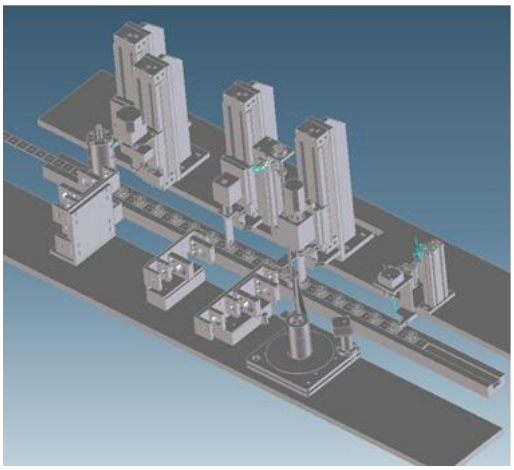

Figure 2
Membrane Bonding Design Concept

Table 5
Burst Tester Design Review

Section	System Engineering Key Function[8]	Design or Specifications
4.1	Understanding Objectives	A sample of the membrane welded parts should be burst tested.
4.2	Operations Concept Review	A regulator will increase the pressure to the failure point to test the weld strength.
4.3	Architecture and Design Development	Equipment uses a proportional valve controlled by an analog PLC Analog Micrologix 1200. A regulator will display the failure point.
4.4	Requirement Analysis, Identification and Management	Equipment Inputs: Welded Membrane Rotors.
4.5	Validation and Verification	A gage R&R will be performed to determine the accuracy and repeatability of the test equipment.
4.6	Interfaces And ICDS's	This equipment will only test sample parts of the components out of the membrane bonding station.
4.7	Mission Environments	Power : 120V, 20 A Clean and Dry Air : 80-100 psig
4.8	Technical Resource Budget Tracking	Proportional Valve: 1 Analog PLC : 1 Pressure Display : 1
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

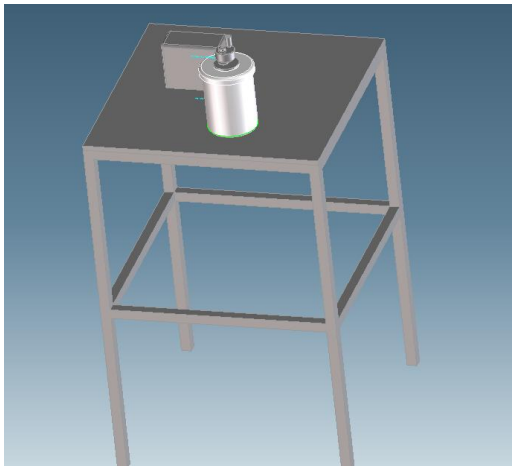

Figure 3
Burst Tester Design Concept

Table 6
Leak Testing Design Review

Section	System Engineering Key Function[8]	Design or Specifications
4.1	Understanding Objectives	All parts should be leak tested.
4.2	Operations Concept Review	A pressure decay system capable of fixture the parts and pressurize them to test them and detect a minimum leak rate of 1.5 cc/min
4.3	Architecture and Design Development	Equipment uses a pressure decay custom leak tester. Uson Qualiteck. All functions are PLC controlled. Micrologix 1200 PLC.
4.4	Requirement Analysis, Identification and Management	Equipment Inputs are completed parts after the Laser welding process
4.5	Validation and Verification	The minimum leak rate will be challenged. The system parameters like, test pressure, test time, decay time and stabilization will be determined using a Design of Experiment.
4.6	Interfaces And ICDS's	This equipment will determine if the complete assemblies are acceptable and free of leaks.
4.7	Mission Environments	Voltage = 120 V, Current = 20A, Clean And Dry Air = 120 psig.
4.8	Technical Resource	Pressure Decay Leak Tester = 1 PLC Controller = 1

	Budget Tracking	Pneumatic Actuators and Valves = 4
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

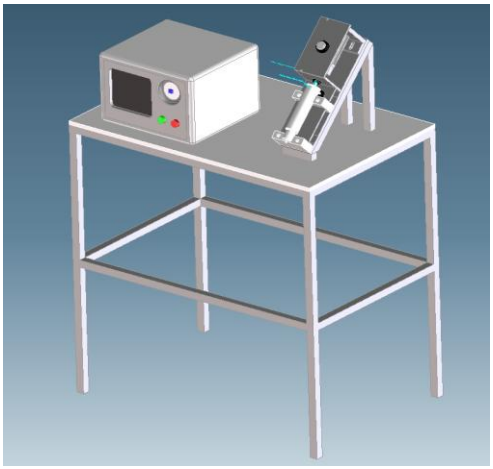

Figure 4
Burst Tester Design Concept

Table 7
Lubrication Station Design Review

Section	System Engineering Key Function[8]	Design or Specifications
4.1	Understanding Objectives	Parts should be lubricated using 350centistokes medical grade
4.2	Operations Concept Review	A servo driven rod will deliver the silicone precisely to the parts
4.3	Architecture and Design Development	Equipment uses a servo controlled motor Emerson Control Techniques Model NTE-207 and a precision ball screw THK to move the silicone from a reservoir to the parts.
4.4	Requirement Analysis, Identification and Management	Equipment Inputs : Case Bodies, Case Caps and Case Bottoms
4.5	Validation and Verification	The operational parameters like velocity and position will be determined using a Design of Experiments.
4.6	Interfaces And ICDS's	The equipment will lubricate the rotor caps and bottom. These parts will be used at the laser welding bottom. These parts will be used at the laser welding station to complete the components.
4.7	Mission Environments	Power : 208 V 3p, 30A,L1,L2,L3,N,G Presure : 70 -90 psig
4.8	Technical Resource Budget Tracking	Servo Motor : 1 Controller: 1 Precision Ball Screw Actuator: 1
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

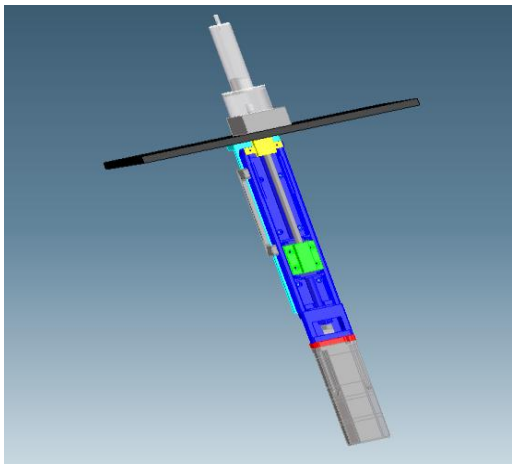

Figure 5
Burst Tester Design Concept

Table 8
Laser Welding Design Review

Section	System Engineering Key Function[8]	Design or Specifications
4.1	Understanding Objectives	All plastic parts should be ultrasonically welded.
4.2	Operations Concept Review	A standalone equipment that will fix the parts to performed laser welding to join all plastic components
4.3	Architecture and Design Development	The Laser Welding equipment will be an off the shelf Leister Novalas WS-AT This laser system is a 50 Watts Diodes Laser. The Laser is applied to the parts through a system of Fiber optics. The Laser Head is moved to position using a Servo Cartesian System programed with CNC Codes.

4.4	Requirement Analysis, Identification and Management	Equipment Inputs : Complete Rotor, Rotor Caps, Rotor Bottom, Case , Case Caps and Case Bottoms
4.5	Validation and Verification	The ultrasonic parameters like, energy, weld time and pressure will be determined using a Design of Experiments.
4.6	Interfaces And ICDS's	This equipment will receive parts from the Membrane Welder and from the Lubrication Station. The completed parts will be sent to the spin and leak tester.
4.7	Mission Environments	Power : 230V, 20 A Clean and Dry Air : 90-100 psig
4.8	Technical Resource Budget Tracking	Laser Welder : 1
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

Figure 6
Laser Welder Design Concept

Table 9
Spin Tester Design Review

Section	System Engineering Key Function[8]	Design or Specifications
4.1	Understanding Objectives	Completed parts should rotate freely after laser welding.
4.2	Operations Concept Review	This will be a standalone station containing a servo motor, a fixture to turn the whole assembly and an inductive sensor to detect if the part is rotating at a certain rate
4.3	Architecture and Design Development	Equipment uses a servo motor Emerson Control Techniques Model NTE-207 controlled by a PLC Micrologix 1200 to rotate the parts. As the parts rotate an inductive sensor will detect the stainless steel rotor of the rotor cap and determine the rotational rate of the part.
4.4	Requirement Analysis, Identification and Management	Equipment Inputs : Completed parts
4.5	Validation and Verification	This equipment will be challenged with a gage R&R and with known good and bad parts. The equipment will be used to validate the Laser Welding station
4.6	Interfaces And ICDS's	This equipment will determine if the completed components were welded properly and with all the required components.
4.7	Mission Environments	Power : 120V, 20 A Clean and Dry Air : 80-100 psig
4.8	Technical Resource Budget Tracking	Servo Motor : 1 PLC : 1 Controller : 1 Inductive Sensor : 1 Pneumatic Actuator : 1
4.9	Risk Analysis, Reduction and Management	Equipment and Process Fault Tree and Failure Mode and Effects Analysis

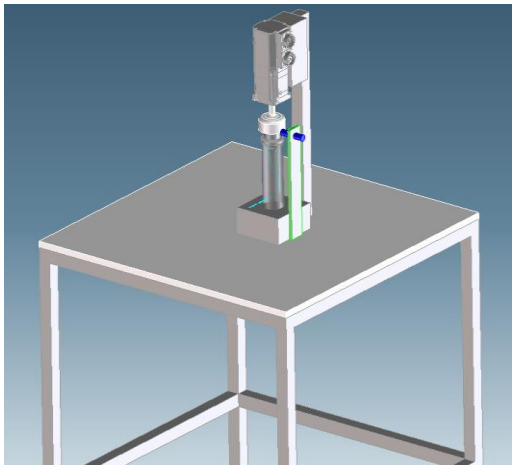

Figure 7
Spin Tester Design Concept

PROJECT IMPLEMENTATION

The next phase on the Systems Engineering Life Cycle is Phase D. Figure 8 [8] shows graphically the process from Fabrication to implementation.

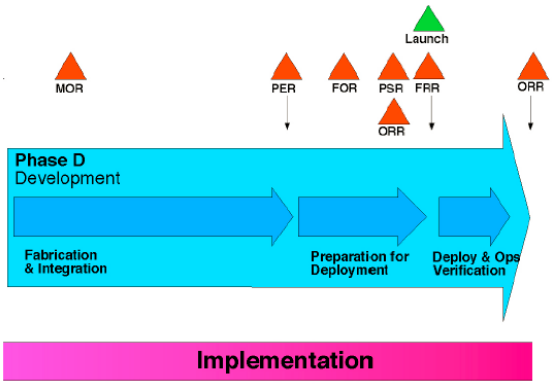

Figure 8
Phase D Phase Implementation Diagram

This phase specifies the requirements to build and implement the required system. Based on the design details established on previous phase C. The continuation of this phase is the preparation for launch and implementation of the proposed solutions.

In order to complete a qualification several documents are required. These requirements as specified by the Food and Drug Administration are to make sure that the production line is capable of safely making the product.

"Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented". [1]

"Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled". [1]

"Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications". [1]

This verification takes the form of an Installation Qualification to test that the equipment was installed according to the specified environments. The systems engineering process on section 4.7 requires that the Mission Environments for every station or equipment be specified. The other part of the validation process is the Operational Qualification where the required operational parameters are verified and the Process Qualification were the equipment or processes are tested on the manufacturing environment. Section 4.5 Verification and Validation specifies the validation requirements to make sure that the objectives section 4.1 and the operations concept section 4.2 are met.

VALIDATION AND VERIFICATION RESULTS

The validation process produces several data and results. The following information will show the different data and results obtained on the different equipment in order to make sure that the equipment will perform as intended.

As stated on Table 3 the validation strategy for the membrane bonding station was a Design of Experiments to determine the ultrasonic welding parameters.

The design is a fractional factorial with 6 Factors, Resolution VI, 1 center point, 1 replicate producing 33 runs.

Figure 9 shows the critical parameters obtained from the design of experiments.

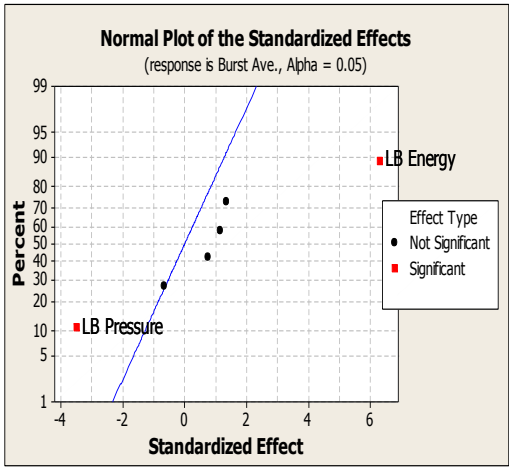

Figure 9

Ultrasonic Welding Process Effects Plot

The critical parameters were tested with an additional surface central composite design of experiments with 2 factors, 1 replicate for a total of 14 runs.

Figure 10 shows the results of this further testing on the ultrasonic welding parameters for the membrane bonding station. These parameters will be the ones used for the Process Qualification to be challenged and also for the production phase.

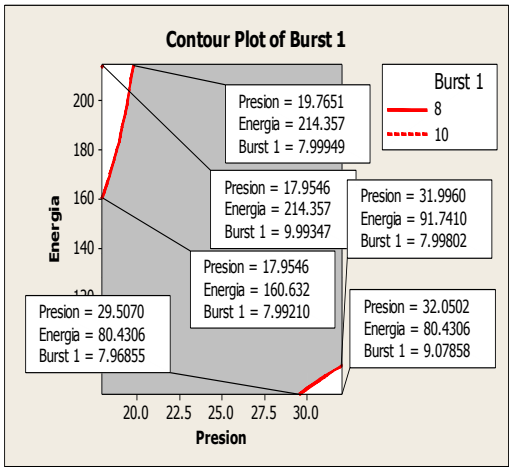

Figure 10
Ultrasonic Welding Process Effects Plot

The produced parts should be 100% leak tested. To determine the operations parameters of this equipment a Design of Experiments was performed.

Figure 11 shows the effects and Figure 12 shows the results of this experiment. The design was a full factorial with 4 factors, 2 replicates and 1 center point.

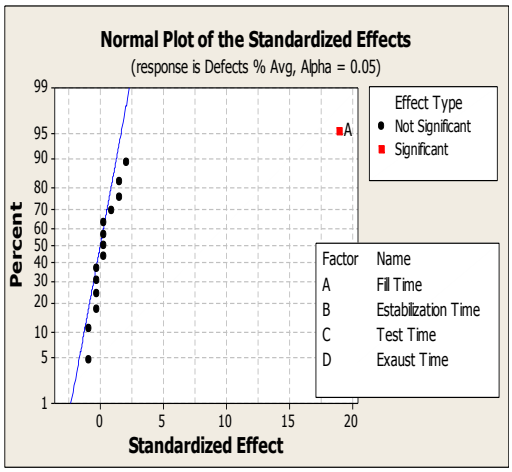

Figure 11
Leak Tester Effects Plot

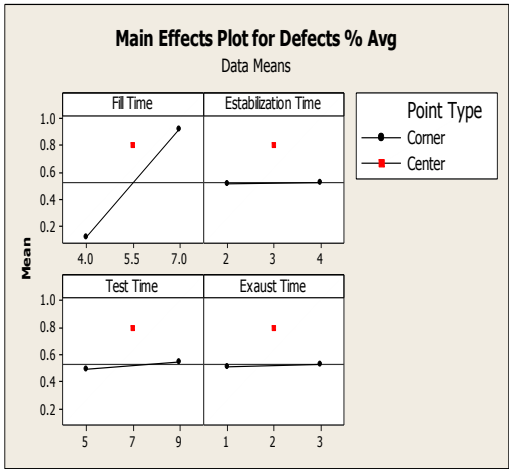

Figure 12
Leak Tester Design of Experiments Results

To test the results of the experiments the leak rates were analyzed to make sure that the obtained parameters are effective. These results are contained on Figure 13

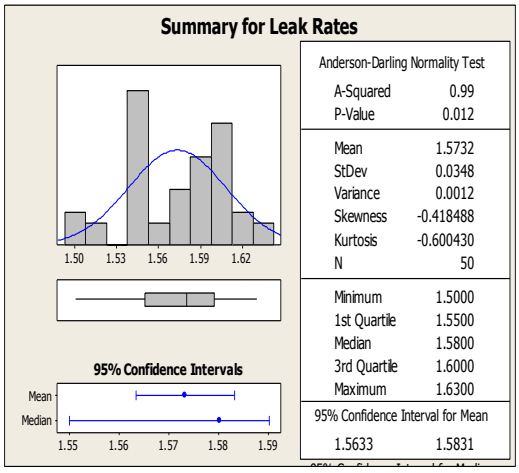

Figure 13
Leak Rates Statistics

All products should be lubricated in order to function properly. A Design of Experiments will be performed to determine the critical operational parameters. The results of this experiment are shown on Figures 14 and 15.

The design is a full factorial with 2 factors, 1 replicate and 1 center point.

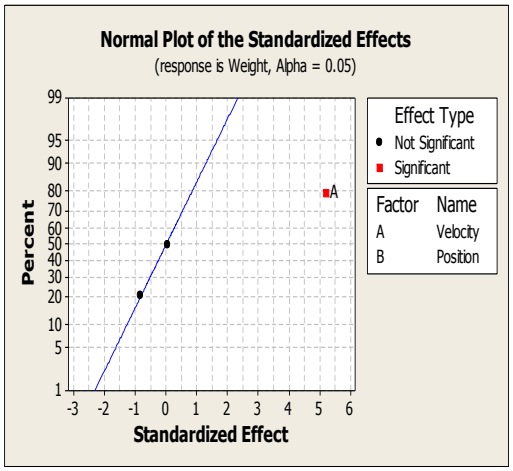

Figure 14
Lubrication Station Effects Plot

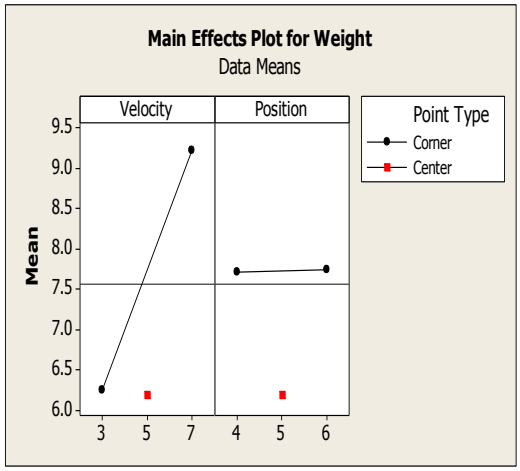

Figure 15
Lubrication Station Experiments Results

To test the results of the experiments the lubrication weight was analyzed to make sure that the obtained parameters are effective. These results are contained on Figure 16.

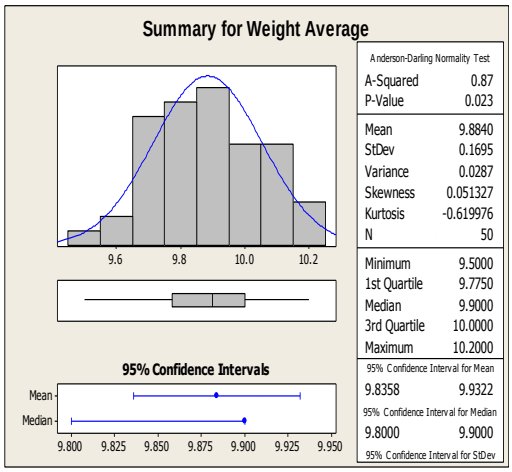

Figure 16
Lubrication Station Weight Statistics

The validation strategy for the laser welder is a Design of Experiments to determine operational parameters. The results of the Design of Experiments for the Laser welder are shown on Figure 17.

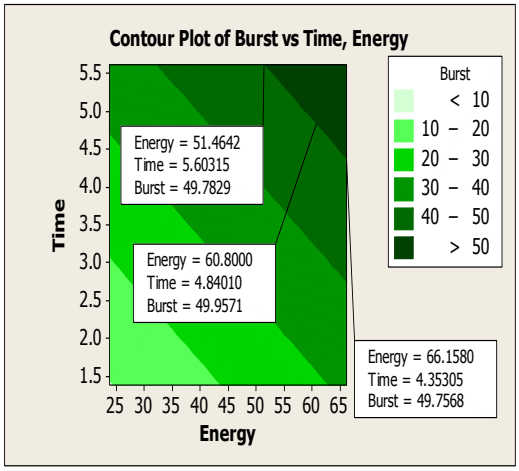

Figure 17
Laser Welder Design of Experiments Results

The Burst Tester and the Spin Tester are equipment intended to test other production equipment. The Burst Tester will be used to test the strength of the ultrasonic bond of the membrane performed at the membrane bonder and the spin tester will test that the parts function properly by checking that they rotate freely as intended. This equipment will be tested and validated with a Gauge Reproducibility and Repeatability Test. Table 10 shows the result of the burst tester gauge

test and Table 11 shows the results for the spin tester.

Table 10
Burst Tester Reproducibility and Repeatability Test Results

Source	Variability	% Contribution
Total Gage R&R	0.035	10.35
Repeatability	0.035	10.35
Reproducibility	0	0
Part-To-Part Variability	0.29	89.65
Total Gage Variation	0.32	100
Number of Distinct Categories	4	

Table 11
Spin Tester Reproducibility and Repeatability Test Results

Source	Variability	% Contribution
Total Gage R&R	1.7337	3.94
Repeatability	1.1317	2.57
Reproducibility	0.602	1.37
Part-To-Part	42.2364	96.06
Total Variation	43.9701	100
Number of Distinct Categories	6	

CONCLUSIONS

The original purpose of this project was to design and create a production line for a new medical device. The fact that the product is a medical device intended for human use creates the need to comply with the FDA Regulations as stated on the Quality System Regulation 21 CFR 820.

The intent of the project was to use the Systems Engineering Methodology and all its phases to comply the required objectives by building the necessary equipment to produce the product and meet the quality criteria.

Through the project life cycle the design requirements and concepts were reviewed and implemented to complete the different important aspects of the product through the production line including the testing equipment to ensure the quality of the produced parts following the Systems Engineering Key functions.

The different reports specified on all phases from pre phase A to phase F gives a complete set of documentation from design to production data to equipment disposal. This methodology as defined complies with the requirement stated by the Food and Drug Administration that the plans for a project or new process shall be reviewed, updated, and approved as design and development evolves.

Every equipment concept was subjected to all Systems Engineering functions during the different project phases. The application of these phases and functions subjected the designs to the verification and approval of all departments. The proposed concepts were modeled and verified to comply with the required objectives and the necessary regulations.

The validation process was followed as stated on the Food and Drug Administration Regulation 21 CFR 820 and as stated on the System Engineering Methodology Validation and Verification key function through its different tests and experiments to determine the proper operational parameters necessary to produce the required parts. The obtained operational parameters ensure that the parts produce are capable of efficiently perform the required blood donation during the clinical trials. The validation process also ensures that the processes are consistent and that each component produced is consistent and complies with the required quality.

The main reason to use the methodology is to manage a complex system. In this case the complexity was derived from the variety of equipment necessary to manufacture the product. Also the complexity of managing the different

departments and the documentation required. The complete set of documentation included on all the phases like the design requirements, installation qualification, operational qualification, process qualification and software qualifications were completed at the end of the system engineering phases.

The methodology framework gives a standard process to complete the projects and to establish a common language across functions. These different functions play an important role to complete the project through all phases successfully. The different departments for these functions on the project were Design Engineering, Technical Services Engineering, Quality Engineering, Maintenance, Planning and Manufacturing. The Systems engineering process brings all these departments together and leads them through its key function to complete the project objectives. The important lesson obtained from the application of the methodology to a regulated industry like a medical devices manufacturer is that the rigid regulations imposed are fulfilled through the project life cycle and through the systems engineering key functions.

Throughout the development of this project a new technology like laser welding was introduced and fully characterized to manufacture this product.

The next step for this project is the creation of automated equipment for commercial mass production. The lesson obtained during all the studies and process development throughout the Systems Engineering functions will be the base to design this equipment.

All the documentation will be the guide to design and develop this new line towards the successful launch of the product to the market in time and with the required quality.

This process could be easily applied to a new company or business looking to start up an operation with a proven and successful methodology.

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