Process Analysis of Breakage and Cracks in Pharmaceutical Vials Using DMAIC Problem Solving Methodology.

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THESIS
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LIST OF ABBREVIATIONS

VHP Vaporized Hydrogen Peroxide

DMAIC Define Measure Analyze Improve Control

RABS Restricted Access Barrier System

ASQ American Society for Quality

ANSI American National Standards Institute

PDS Pre-Delivery Samples

AQL Accepted Quality Level

USP United States Pharmacopoeia

WFI Water for Injection

HEPA High Efficiency Particulate Air

MPPS Most Penetrating Particle Size

MSA Measurement System Analysis

ANOVA Analysis of Variance

API Active Pharmaceutical Ingredient

VIM Visual Inspection Machine

PPV Positive Predictive Value

NPV Negative Predictive Value

FDR False Discovery Rates

FOR False Omission Rate

CAD Computer Aided Design

Summary

A process analysis of the vial breakage and cracks in a pharmaceutical company has been conducted. Current method of incoming inspection procedure has been carefully studied. Then the Visual Inspection Machine working has been studied and the rejection rates has been analyzed using various statistical analysis tools like Hypothesis testing, ANOVA testing, Box Plots and Sensitivity vs. Specificity. The statistical analysis showed that the 33% of vials accepted vial are bad vials.

Then stress analyses were conducted for the vials which get collide with each other at two locations in the process. The stress analysis showed that the stress developed in first location was not enough to cause the crack, but the stress developed in second location was enough to cause the crack. Cost Analysis has been performed to identify the cost associated with the vial breaking phenomenon for one shift which is equal to $16,000. Finally, this thesis provides a step-by-step project plan to eliminate the vial cracking phenomenon.

1 INTRODUCTION

As the humankind is evolving towards modernization and industrialization, new types of disease and viruses are born. The scientific evolution of humans has led to discovery of lot of vaccines, drugs, and medicines to all the diseases. Every year billions of life-saving drugs and medicines are delivered around the world successfully. It is of extremely high importance for manufacturing this life-saving medicine effectively and efficiently. This year (2020) has been a year that required a vaccine for the novel coronavirus that caused the disease COVID-19. This virus has claimed thousands of lives across the globe. Since the vaccines for COVID-19 have been discovered, it is an absolute necessity to manufacture vaccines at high production rates and without any foreign contamination or the vaccine will be scraped during the production process due to quality non-conformance. Just like COVID-19, there are many other rare diseases which requires vaccines and drugs continuously.

1.1 Motivation

Through emphasizing the importance of vaccines, drugs and medicines, its important to determine which factors led to the subject matter of this masters thesis project. These vaccines are filled in glass vials and rubber stopper are used to seal the vials. There has been a lot of recall of vaccines due to presence of crack in the vials (Sterility risk associated) (Schaut et al., 2017) [1].The number of cases associated with vial recalls have been shown in Table I. Injectable vaccines require protection from microbial contamination. These cracks can lead to contamination of vaccines. When a contaminated vaccine is administered (administered through blood) fungus or bacteria enters the blood stream which might then reach the heart or brain leading to coma or even death of people. These cracking of vials can be also called as non-catastrophic breakages. Non-Catastrophic breakages eventually develop into catastrophic breakages. These breakages occur most during the fill/finish process in a pharmaceutical company. When filling those vials suddenly, if the vial breaks, the entire batch will be scraped due to the possibility of microbial contamination.

TABLE I: VIAL RECALL HISTORY

TABLE I
Eleven Recalls Issued for Injectable Pharmaceuticals within the Last 5 Years due to a Lack of Sterility Associated with Cracked Glass Containers

Drug	Date	Company	Country	Source	Recall Number
Yervoy	10/18/2014	Bristol-Myers Squibb	Canada	http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/41861a-eng.php	*
Amoxil	10/15/2014	GSK	UK	https://www.gov.uk/drug-device-alerts/drug-alert-amoxil-vials-for-injection-500mg-and-1g-augmentin-intravenous-600mg-and-1-2g-cracks-in-vials-used-for-packaging	*
Methotrexate Sodium	12/18/2013	Teva	Canada	http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/37319a-eng.php	*
Oncaspar	11/15/2013	Link Medical Products Pty Ltd	Australia	http://apps.tga.gov.au/PROD/SARA/arn-detail.aspx?k=RC-2013-RN-01226-1	RC-2013-RN-01226-1
Pegaspargase Oncaspar	11/1/2013	Sigma-Tau Pharmaceuticals	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-736-2014
Recombivax HB	6/26/2013	Merck	USA	http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm359493.htm	B-0625-14
Cefazolin	5/30/2013	Sandoz	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-597-2013
Vancomycin Hydrochloride	2/7/2013	Pharmaceutical Partners of Canada	Canada	http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/23809r-eng.php	*
Cyanocobalamin	9/27/2012	Fresenius Kabi	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-0297-2015
Cyanocobalamin Injection	4/2/2012	American Regent	USA	http://www.fda.gov/Safety/Recalls/ucm298545.htm	*
Midazolam/Heparin/Ketorolac Trometharnine/Ondansetron/Diazepam	7/8/2011	Hospira	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm282859.htm	*

The process of restoring the production after such a breakage takes 8 hours i.e., the downtime for the vial breakage is 8 hours. The downtime is high as the leakage or biohazard needs to be cleaned off from the production machinery and then re-sterilize the entire process using VHP (vaporized hydrogen peroxide). Therefore, the overhead production cost to fill the vaccine orders and clean the broken vials are also extremely high. The manufacturing method of the product that is filled in the vials are discussed later in this paper. The business loss and product loss associated with all the above-mentioned points requires a in-depth analysis of the root cause of the vial breakage inside a fill/finish process of a pharmaceutical company.

2 COMPANY OVERVIEWS

The pharmaceutical manufacturing company is based in the United States of America in the state of Illinois, which has been at the cutting edge of biotherapeutics production for over 100 years. The company is one of the greatest and fastest in developing protein biotherapeutics on the planet with the presence in 30 nations utilizing 16,000 employees. The Company distributes the pharmaceutical products to patients in more than 60 countries. Their substantial markets include North America, Europe, Asia, and Australia. The Company offers the broadest scope of plasma-derived vaccines in the protein biotherapeutics industry. The company utilizes the latest production techniques available to meet or surpass rigid international safety and quality standards.

2.1 Albuminex Product Concentrations (5%, 20%, & 25%)

The product or vaccine that is filled in the vials are the Albuminex – (in three different concentrations 5%, 20%, and 25%) in four different vial sizes (Figure 2.1). The vial composition is discussed later in this paper. The concentration denotes that the vaccine content of Albuminex in mixture with water (i.e., if a product is named as Albuminex 20%, it means that the vial has the vaccine concentration of 20% and water concentration of 80%). Human albumin stands for the greater part of the protein in the plasma and speaks to about 10% of protein synthesis activity by the liver. (2020, June 2) [2]"Albumin is a protein created by the liver that flows in plasma (the fluid segment of blood)."(2020, June 2) [2]

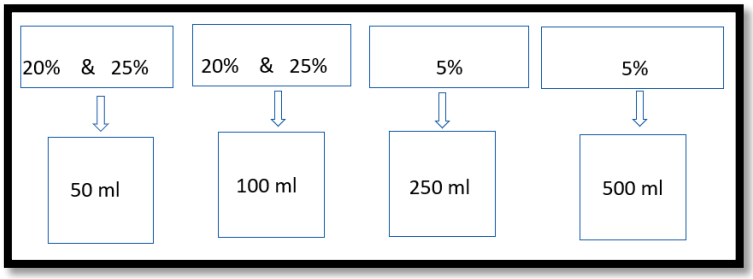


Figure 2.1: Product Concentrations Filled In Different Vial Size

Albumin stabilizes circulating blood volume and is a carrier of all nutrients, minerals enzymes, medicinal products, and toxins. “Albuminex works by expanding plasma volume or levels of albumin in the blood.” (2020, June 2) [2]Albumin is used to supplant blood volume loss coming about because of burn injury or a physical injury that causes blood loss. It acts as an antioxidant agent too. This medication is additionally used to treat low albumin levels brought about by medical procedure, dialysis, stomach contaminations, pancreatitis, respiratory trouble, and other many different conditions.

2.2 How Albuminex Is Manufactured?

Albumins consist of plasma proteins derived from human blood. Generally, “Albumin (Human) 25%, 20% and 5% solution are a sterile aqueous solution for intravenous administration containing the albumin part of human blood.”(2020, September 2)[3] The plasma donation of various blood donors is collected, and the vaccine is manufactured from those donations. Alcohol fractionation is used and once the product is received after donation, it is heated for 10 hours at 60°C for inactivation of any microbial or fungus if any are present. The alcohol fractionation process eliminates any potentially dangerous viruses that may be present. Moreover, heat treatment at 60°C for a time of 10 hours effectively inactivates viruses.

2.3 What if its Contaminated?

The vials can easily get contaminated through if any crack develops during the filling process or if its already present in it inherently. The crack allows for the microbial organisms such as bacteria or fungi to develop in the filled solution. Contaminations may also occur through delamination (discussed further in vial anatomy). Since Albuminex is intravenously administered, if there are any contaminants those particles directly enter into the blood stream. Injectable items require security from infectious organism presence since they evade a substantial portion of the human body's physical immune system (skin, mucous films, and so forth), allowing quick and complete dispersion of infectious pollution into a patient's blood circulation. This will lead to bacteraemia, fungemia, sepsis, coma or even death.

3 PROBLEM STATEMENT

3.1 DMAIC Approach

The DMAIC method is a problem-solving strategy used to find different root causes. DMAIC can also be known as Define, Measure, Analyse, Improve and Control. The letters in the abbreviation address the five stages that make up the Process. This research uses this method to find the root causes leading to the vial breakage in the fill/finish department. The following table (Table II) shows the various parts of the research being categorized into one of the five stages such as Define, Measure, Analyse, Improve and Control.

A small description of the five stages is given below.

Define: This phase defines the problem with adversity involved.

Measure: This phase quantifies the problem and collects data associated with it.

Analyse: This phase analyses the collected data to find root causes by conducting different experiments and uses software to validate the found root cause

Improve: This phase proposes solutions to solve the root causes and verify the improvement

Control: This phase verifies the sustenance of the applied solution

TABLE II: DMAIC CLASSIFICATION OF RESEARCH PHASES

	DMAIC				
	Define	Measure	Analyse	Improve	Control
Introduction	↔				
Company Overview					
Problem Statement					
Process Mapping		↔			
Data Collection					
Research Questions			↔		
Root Cause analysis					
Analysis					
Results and Discussion				↔	

3.2 Problem Statement

The entire process of filling the vaccine in vial takes place in an isolated environment known as RABS (Restricted Access Barrier System). The isolated environment gives a controlled atmospheric condition such as pressure, temperature. One of the problems faced by the Fill/Finish Department of the Biotherapeutics Manufacturing Facility is the vial breakage during the filling operations of those vaccines. The aim of this research is identifying the root causes leading to the breakage of the vial during the fill/finish operation.

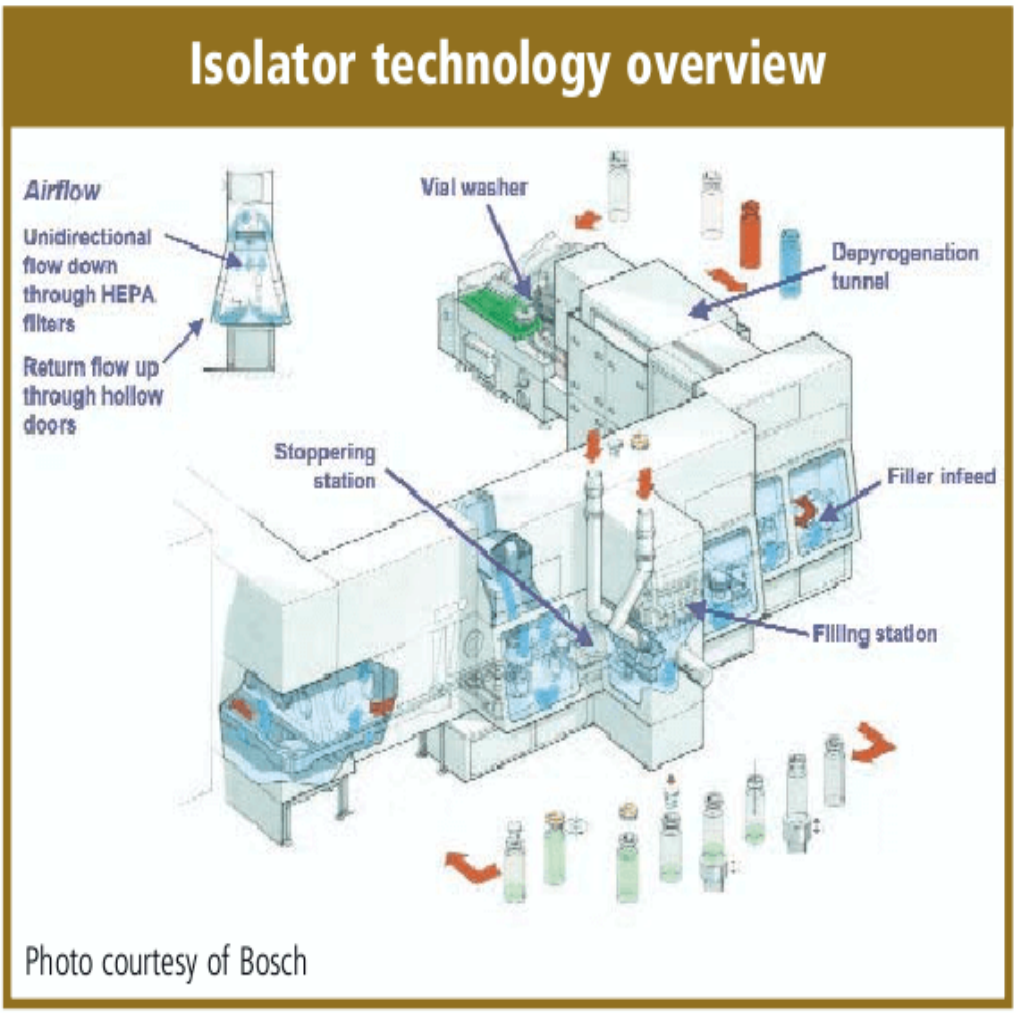


Fig 3.1: Isolator Technology (source- Isolator Technology. (2020, January) [27]

3.3 Adverse Effects

A case of vial crack which is produced from one of the manufacturing facilities of a leading pharmaceutical company in 1996 led to recall of those vaccines produced at that facility. Recalling that this ha event occurred during the year of 1996 when there was less advancement in technology with regard to the tracking of the shipped vials. Also, the occurrence rate of the container having cracks are underrepresented decreasing the likelihood of investigation and identification. Moreover, the symptoms associated with fever, sepsis coincide with the symptoms that arise when a contaminated vaccine has been administered (Schaut et al., 2017) [1]. The poor tracking of distributed medications and the patient's response to a potentially contaminated vaccine added more severity to the vial cracking issue. The crack occurrence was as high as 1.5% within a single lot when investigated. (Wang et al., 2000) [4]. Although automated methods and sophisticated quality processes are now in place to detect a cracked vial product after the filling process, still cracks occur before the filling process which leaves a small space for the defect to escape to the customer again.

4 PROCESS MAPPING

The process mapping starts right from the place where the vials are received in the production facility to the place where the filled vials are received as final output. First, the incoming quality inspection procedure of the vials are explained through the (**Figure 4.1)** The second flow chart shows (**Figure 4.2.1 & Figure 4.2.2)** the process mapping (i.e., from the process of integrating the vials into the production line to the point in a process where the filled vials are received as final output).

4.1.1 Incoming Quality Inspection

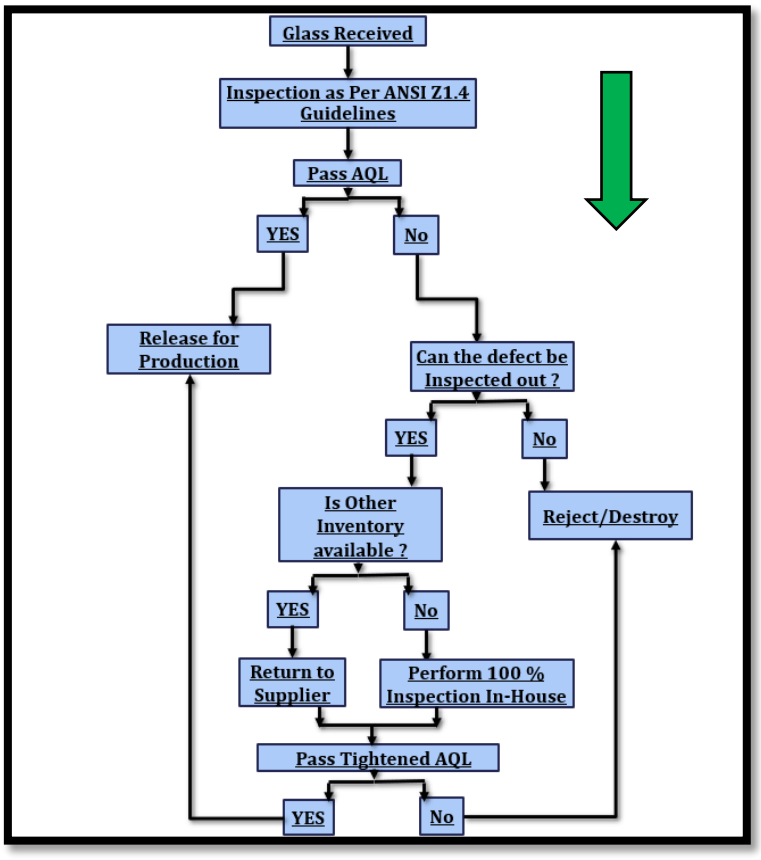


Figure 4.1: Incoming Quality Inspection Flowchart

The above flow figure explains the incoming quality inspection procedure in how the vials are inspected before they are received in the production facility. The vials are inspected according to the inspection guidelines ANSI Z1.4. As per the guidelines ASQ.(2018, January 10) [4], it is an inspection

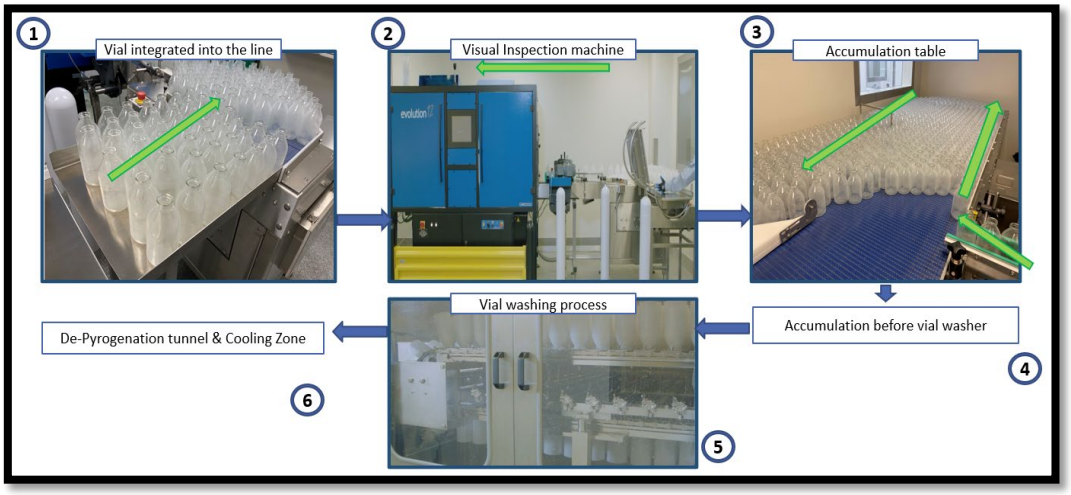
by attributes through sampling systems and tables. It is an acceptance quality control system which is used to determine the sampling size from a given lot size. The inspection for non-conformities per 100 units are provided in the form of normal, reduced, and tightened designs. The number of samples to be withdrawn for inspection is done as per the ANSI/ASQ Z1.4 standards. The type II vials are inspected under a tightened inspection plan for visual defects. For inspection, the samples are withdrawn from each pallet or Pre-Delivery Samples (PDS) and then the entire main shipment represented by the PDS is accepted or rejected. The samples are examined for dimensional and visual inspection. The dimensional inspection procedure ensure dimensions are within the minimum and maximum dimensions per the specification using suitable fixed gauges or callipers. In the visual inspection method, the visual defects are identified according to the standard glassware inspection report (a list of glass defects, defect classification as major or minor and then the defect description).

If any questionable visual or dimensional defect is present, it would be rejected in the inspection process. The glassware associated with the failed samples will also be rejected. Using the above **Figure 4.1**, the quality management team will decide as to whether to destroy the subject glass, require 100% inspection by the manufacturer or perform 100% inspection by the organization itself. The last option would be exercised only if the product is in jeopardy. In total as per the standard operating procedure defined by the company, glass can be inspected only twice (i.e., during the initial incoming PDS inspection and during subsequent 100% resort). After the tightened Accepted Quality Level (AQL), if still the inspection fails then the entire lot is rejected or destroyed.

4.1.2 Filling Process

Once the inspections are carried out and the vials are deemed good they go through a set of processes before getting filled with the pharmaceutical product. Note the following process flow charts in figures.

Figures 4.2.1 & 4.2.2 will give a better understanding of the aseptic filling process.



Figures 4.2.1: Process Flow

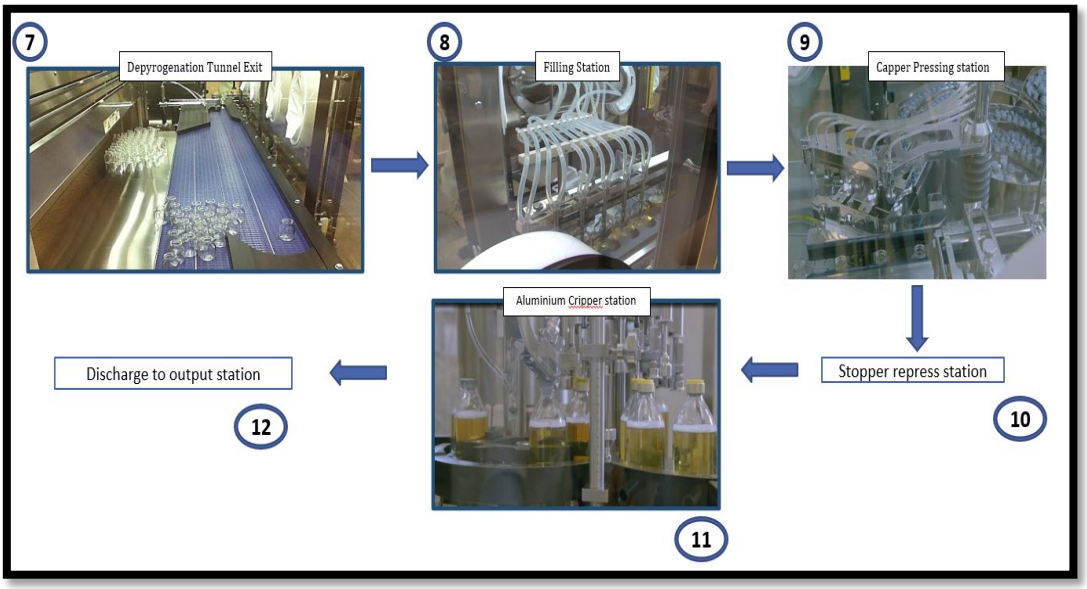


Figure 4.2.2: Process Flow

4.1.3 Integration of Vials into the Line

The type II vials are unpacked from the cart and then the packing is removed to load the vials onto the turn table. The vials are loaded into the turn table in an inverted position. The turn table is turned upside down to bring the vials into the correct position. They are pushed using nylon pushers into the conveyor belt of the visual inspection machine. The vials are of varied sizes which are 50 ml, 100 ml, 250 ml, and 500 ml. The conveyor speed is set for different vial sizes has been detailed in the following table (Table III).

TABLE III: CONVEYOR SPEED TABLE FOR DIFFERENT VIAL SIZE

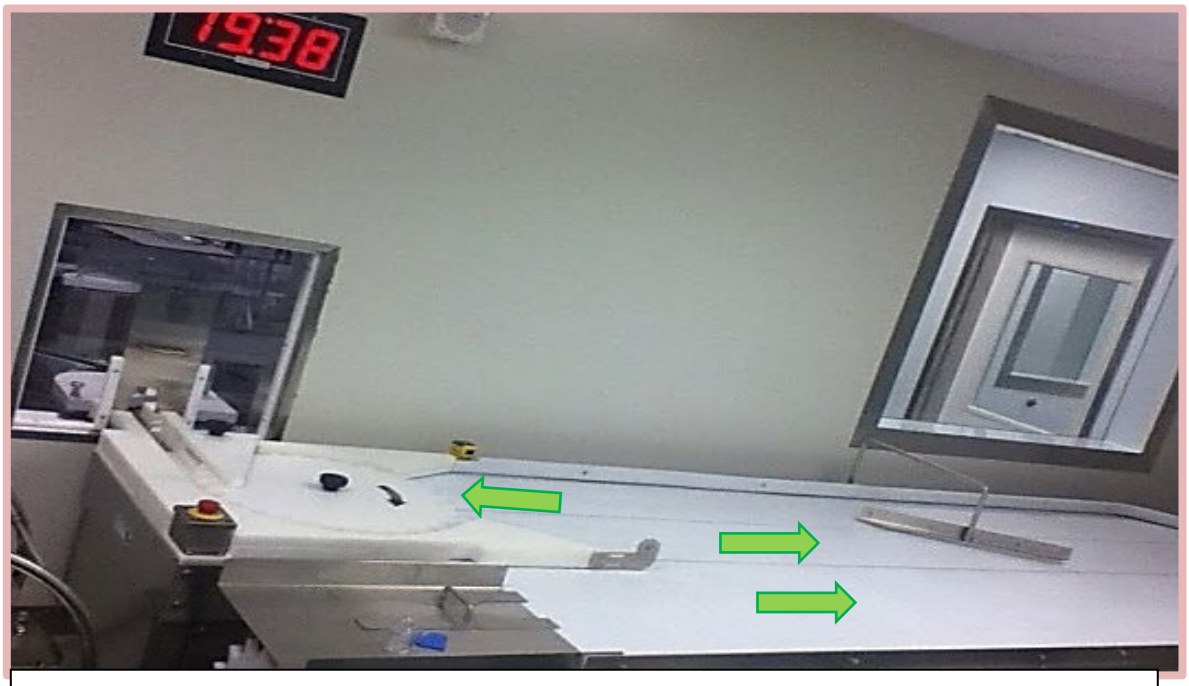
Empty Vial Inspection Conveyor Various Speeds				
	50 ml	**100 ml**	**250 ml**	**500 ml**
Visual Inspection Machine				
Conveyor 1-1	38	38	35	37
Conveyor 1-2	40	40	45	42
Conveyor 1-3	38	38	35	33
Accumulation Table				
Conveyor 2-1	40	40	30	42
Conveyor 2-2	40	40	30	25
Conveyor 2-3	40	40	35	25
All units in Feet/Min				
Star Wheel Speed (RPM)	6	6	5	5

4.1.4 Visual Inspection Machine

The vials are manually loaded into a turn table and are pushed into an infeed bi-flow accumulation table. There two inspection machines are placed in series. Conveyor known as skids, carry the vials which runs through the inspection machines. The first inspection machine consists of 12 cameras, with each of them being a static camera connected to an industrial computer. Two lights sources which can be adjusted electronically illuminate the vials passing through the machine. The first inspection machine checks for defects in the side wall of the vials. Rejected vials are discharged using compressed air (i.e., a pneumatic rejector to an attached rejection bin). Vials which are good passes through the second inspection machine which is connected in series to the first inspection machine. The second inspection machine checks for defects such as defects in the bottom and top finish regions of the vials. The inspection station in the second inspection machine consists of a camera, an LED light source, a cell, and a step-by-step motor. All this equipment is connected to an industrial PC which provides an image analysis and a user interface. Rejected vials again are discharged using compressed air (i.e., a pneumatic rejector to an attached rejection bin). Good Vials are automatically discharged to an outfeed bi-flow accumulation table to await transfer to the downstream vial washer.

4.1.5 Accumulation Table

The accumulation table has the vials which has been discharged from the empty vial inspection machine via conveyor belts**.** The accumulation table has a 3-belt conveyor system. The three belts are placed adjacent to each other with each having a direction of its own. All these conveyor belts are placed in a closed nylon boundary table to prevent any contact with metal.



Empty Vial Bi-Flow Table in Empty Vial Inspection Room

Figure 4.3: Bi-Flo Accumulation Table

The vials are tightly packed in the accumulation table as it can be seen visibly from the step 3 of **Figure 4.2.1**. The vials which are tightly packed together moves onto the conveyor belt to reach the star wheel at the end of the conveyor. The star wheels which are at the end of the conveyor has pockets which extracts the vial from the conveyor and holds them in the pockets. The star wheels with the vials in the pocket revolve and deliver the vials to the next stage. This process of extracting the vials from the conveyor belt is known as back pressure. Varied sizes of vials have different speed which can be referred from the Table 4.1.

4.1.6 Pre-Vial Washer

The vials from the accumulation table travel through the star wheel and reaches the pre-vial washing stage through infeed belt and reach the buffer belt. Here the vials wait in a single row before being taken into the vial washing machine. The vials in a single row are pushed towards the vial washer carrier pockets. The number of rows in this stage differs based on the size of the vials.

4.1.7 Vial Washer

The fully automated vial washing machine is designed to clean 50 ml, 100 ml, 250 ml, and 500 ml vials. As the vials reach a transfer unit via infeed belts and pushes the vials to the infeed belt which then transports the vials to the inclined elevator. The inclined elevator transports the vials to the transport system. Then the vials are pushed into the vial washer carrier pockets. From here, the pockets hold the vial in an inverted position so that the washer sprays the Water For injection (WFI) into the vials. WFI should be sterile as per the regulatory requirements from the United States Pharmacopoeia XXIV. WFI should be free of all contaminants like microbial living organisms, dissolved gases, metals, electrolytes, and other particulate matter (Li, L et al., 2006) [6].

The transport system carries the vials to the individual stations and to the discharge. The stations are divided into various zones. The water that is used in zone 1 is supplied by recirculation tank 1, this water is not reused after zone 1 and its drained. The water that is used in zone 2 is supplied by recirculation tank 2. This water is collected in recirculation tank 1 and then it is heated up again and supplied to the stations of zone 1. In zone 3, WFI is used. This water is collected in the recirculation tank 2 and then it is heated again and supplied to the stations of zone 2. The carrier pockets of the transport system carry the vials with their opening facing downward to the induvial cleaning stations and to the discharge. At each stage vials are cleaned inside and outside. The outside rinsing is performed by spraying and blowing pipes. The inside rinsing is performed by spraying and blowing pipes with mounted spraying or blowing nozzles. The slide plate takes the vials over from the carrier pockets and then the vials are pushed onto the tunnel belt of the de-pyrogenation tunnel. Blowing

nozzles that generate an airflow pushes the vials in the carrier pockets into the direction of the discharge.

4.1.8 De-Pyrogenation Tunnel & Cooling Zone

The vials must be eliminated of any pyrogens if present, through a process known as de-pyrogenation. Otherwise called bacterial endotoxins, pyrogens are metabolic results of either living or non-living micro-organisms. The expression "pyrogen" (i.e., fever-creating agent) comes from the way that if a parenteral item containing pyrogens is infused into a patient, a quick ascent in internal heat level happens after an inactive time of around 60 minutes, trailed by chills, headache, and discomfort. Sterilization and de-pyrogenation can be accomplished by physical methods such as heat by creating a tunnel of hot temperature. Hot temperate air is blown through the tunnel (Li, L et al., 2006) [6]. The following image shows the schematic of a typical de-pyrogenation tunnel.

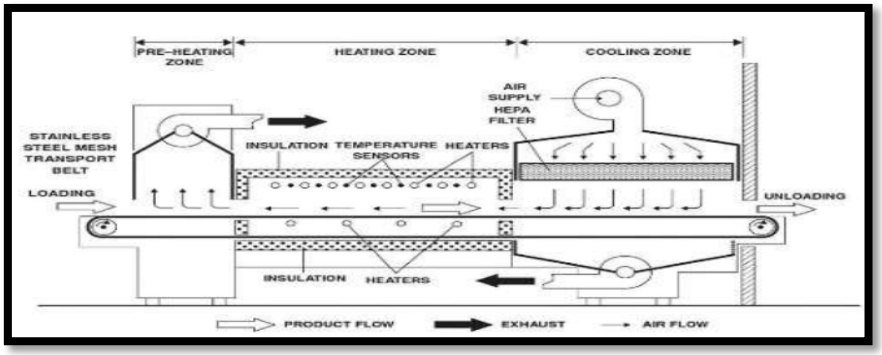


Figure 4.4: De-pyrogenation Tunnel Image (source – Akers. (2010) [7])

A standard de-pyrogenation tunnel consists of a High Efficiency Particulate Air (HEPA) and pre-filter. Like all other filters, the HEPA filter is a kind of filter which can prevent entry of substances, such as incoming air molecules. “It can remove up to air particle sizes of 0.3 microns (µm), the diameter of 0.3 microns reacts to the most pessimistic scenario; the most penetrating particle size (MPPS).” EPA. (2020, May 3)[8] Particles that are bigger or more modest are caught with higher effectiveness. “In the pharmaceutical industry, de-pyrogenation and washing, in addition to disinfection of vials, is regularly performed during drug manufacturing to guarantee that vials are adequately cleaned and

sterile at the specific time and spot when being filled with a sterile drug product solution. (Ditter et al., 2017)″

The de-pyrogenation tunnel design allows for the processing of 50 ml, 100 ml, 250 ml, and 500 ml. As seen from Table IV, the tunnel speed and temperature has been set and validated for all the vial sizes such as 50 ml, 100 ml, 250 ml, and 500 ml. The tunnel consists of four zones, including: Infeed zone, Heating Zone, Cool Zone 1, and Cool Zone 2. The vials are transported from the upstream vial washing machine onto the tunnel belt of the sterilizing tunnel where the vials are transported through the tunnel zones. The de-pyrogenation tunnel is integrated with the upstream vial washing machine and it is automated. As vials are washed on the vial washer, they are automatically fed onto the conveyor belt of the tunnel. The infeed zone sets up a barrier towards the ambience. A filtered air which runs through a prefilter and HEPA- Filter) is showered over the vials. In the heating zone the vials are de-pyrogenated by hot purified air.

TABLE IV:DE-PYROGENATION TUNNEL BELT SPEEDS AND TEMPERATURE FOR ALL VIAL SIZE

De-Pyrogenation Tunnel Belt Speed and Temperature			
Vial Size	**50 ml**	**High**	**Low**
50 ml	**Temperature**	325 ºC	315 ºC
	Belt Speed	291 mm/min	273 mm/min
100 ml	**Temperature**	325 ºC	315 ºC
	Belt Speed	207 mm/min	195 mm/min
250 ml	**Temperature**	315 ºC	305 ºC
	Belt Speed	159 mm/min	149 mm/min
500 ml	**Temperature**	320 ºC	310 ºC
	Belt Speed	172 mm/min	162 mm/min

A fan circulates the air inside the heating zone and directs it to the vials via the HEPA filter. In the cooling zone, the vials are cooled down to the required temperature with purified air of 20 degree Celsius). A fan circulates the air inside the cooling zone and directs it to the vials via the HEPA filter. At the end of the infeed zone the sensor detects the first row of the vials. The tunnel belt stops, and the

infeed gate of the heating zone (Gate 2) and opens automatically to the height that is specified for the vial size. The tunnel bet runs with 80% of its normal operating speed until the sensor of the third gate detects the first row of the vials. The third gate which is at the end of the heating zone is automatically opened. While gate 3 is opening, the tunnel belt stops. When the correct height of the vial is reached, the tunnel belt runs again with normal operating speed and the vials are transported on into the cooling zone. When the first row of vials has reached the end of cooling zone, the tunnel belt is stopped, and the tunnel discharge gate (gate 4) opens automatically to the correct height. The tunnel belt then automatically transports the vials out of the cooling zone and transfers them to the downstream filling and closing machine. The automatic pressure balance system maintains a positive pressure between the tunnel heating zone and the infeed zone. This system uses a variable speed exhaust fan to maintain the differential pressure. The transition from a hot zone to cooling zone occurs very slowly as the tunnel belt conveyor speed is slow. For example, from Table IV it is evident that the speed of 500 ml vial is 172mm/min. The cooling zones must be sterilized prior to processing the vials.

4.1.9 De-Pyrogenation Tunnel Exit

The transition of the sterilizing de-pyrogenation tunnel to the infeed of the filling and closing machine must be sealed and separated. To separate the cooling zone from the filling and closing machine, the tunnel exit door is automatically closed, and its inflatable gasket is blown up before the sterilization starts. The vials are slowly pushed from the tunnel exit to the infeed belt of the filling stations. The vials are transported onto bi-flow belt and on into the infeed of the filling and closing machine. These belts take the vials from the de-pyrogenation tunnel exit to the filling stations.

4.1.10 Filling Station

The de-pyrogenated vials are pushed from the upstream de-pyrogenation tunnel onto the Bi-Flow-Belt. The Bi-Flow-Belt transports the vials to the infeed star wheel via the infeed transport belt. The segment wheel accepts the vial from the infeed star wheel and transfers them to the rake transport of the vial filler.

Figure 4.5: Filling station (source -Manufacturing Process.(2019, May 10) [10])

The transport rake transfers the vials to the ionization station, filling station and stopper insertion station. The machine has a stoppering station and a secondary stoppering station. The empty vials are weighed by the tare weigher of the In-Process-Control. The time/pressure filling system fills the vials via filling needles. The filled vials are weighed by the gross weigher of the in-process-control. If the filled vials after the weighing process have any deviations from a standard filled vial, they are marked for rejection discharge.

4.1.11 Stopper Pressing and Repressing Station.

One of the common process used for sealing the vials consists of a moulded rubber stopper having a depending cylindrical nipple portion adapted to be received into the neck portion of the vial to be sealed. The crimper which is an anodized aluminium crimper holds the stopper in sealing engagement to the neck of the vial by with a focal opening which allows the inclusion of a needle through the plug for withdrawal of all or a bit of the substance of the vial. The sealing ring has an aperture which can be initially closed with a tear away member. The vial with filled product is automatically passed under a hopper where a washed and sterilized stopper is inserted. The unit then passes beneath another hopper where the anodized aluminium sealing ring is added, and the unit is next passed to a crimping stage where the seal is completed. (Hershberg and Wolkoff, 1969) [11]

Vials which are filled in the filling station are transported to the capper pressing station by the transport rake. At the stopper insertion the filled vials are closed when a stopper is inserted. The stoppers are

fed to the stopper insertion station in correct position via a sorting and feeding device. The infeed belt transports the vials to the transport screw. The Transport wheel transports the vials to the infeed wheel crimping station via vacuum wheel 1. The in-feed wheel crimping station transports the vials to the crimping cap feeding track and then onto the crimping station. The capping skid has three cameras. cameras 1 & 2 check the stopper position and the stopper height. Camera 3 checks the printing image on the crimping cap. There are two photo eyes that verify and count the discharge vial count. The vial pulls off the crimping caps from the crimping cap feed track. As sorting and feeding devices transport the crimping caps to the feeding track in correct position. The crimping station seals the vials with crimping caps. The processed vials are transported to the vacuum wheel 2 via the discharge wheel crimping station. Incorrectly processed vials are discharged into the tray of the rejection unit via vacuum wheel 2. Correctly processed vials are transferred to the discharge belts of the outfeed via vacuum wheel 3. The printer in the vial capping skid, prints the batch number and a serialized vial number on each individual cap. Vials with incorrect printing images, incorrect stopper positions and stopper heights are diverted to the rejection tray.

4.1.12 Discharge to Output Station

The vacuum wheel at the discharge accepts the filled and closed vials from the rake transport. The vials that have been correctly processed are transported to the outfeed. Vials that have been incorrectly processed are discharged at the rejection.

5 RESEARCH QUESTION AND APPROACH

5.1 Research Questions

The Thesis goal is translated into primary and secondary research questions. The primary research question (PRQ) is "*What are all the causes of vial breakages on the filling line?*"

This research question is solved in a step-by-step manner which involves investigating various aspects of the processes and supporting processes leading to the problem. Investigating the following secondary research questions (SRQ) will pave the way to the answer for the primary research question.

SRQ1: "*Does the visual inspection machine have the rejection rate within target."*

SRQ2: "*What impact does the vial colliding with each other have on cracking?"*

5.2 Research Approach

The research structure below shows the direction in which the research would go ahead to answer the secondary research questions 1 & 2.

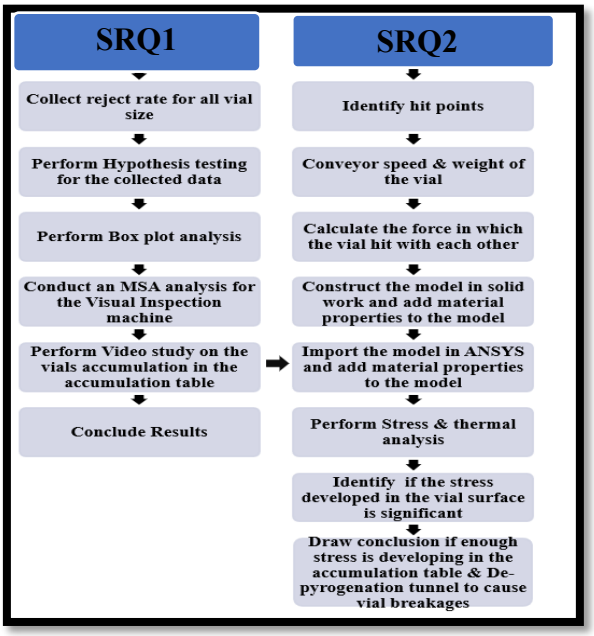


Figure 5.1: Research Structure

The research can be split into two parts respectively for the two secondary research questions. In the first part of the research, the primarily step is analyzing the visual inspection machine by analyzing the rejection rate data using statistical methods such as hypothesis testing, box plot analysis, Measurement System Analysis. This part 1 of the research will answer the secondary research question 1 of "*Does the visual inspection machine have the rejection rate within target."*

The second part is identifying the hit point or the exposure points where the vials hit with each other in the fill/finish process. After identifying the exposure points using a video study, then the speed of the conveyor and weight of the vial are used to find the force with which the vials collide with each other. Multiple runs are simulated in stress analysis software such as Ansys to find if the hit points or exposure points are building up enough stress or strain to start micro surface deformation. This part 2 of the research will answer the secondary research question 2 of "*What impact does the vial colliding with each other have on cracking?"* Researching to find the answers to the secondary research questions 1 & 2 will lead the way to answering the primary research question of "*What are all the causes of vial breakages on the filling line?*"

6 ROOT CAUSE ANALYSIS

6.1 Scope of the Root Causes

The root cause under investigation has its own boundaries. The following are the criteria based on which the facts have been excluded and included for the research.

6.1.1 Exclusion Criteria

Primarily, the vial design has been excluded from one of root causes for the crack phenomenon in the filling process. The vials that are used in the filling of Albuminex filling process is the Type 2 vials (explained later in this paper). Before getting into the Type 2 vial properties, let us see why glass vials are used in this particular process instead of polymer or plastic vials. There might be a thinking from consumers as to why plastic bottles not used in place of glass vials. In fact, the plastic bottles do not have the issue of breakage or crack occurrence which might prevent the contamination of the vials. When it comes to choosing the plastic that is right for the pharmaceutical application, the facts that should be put in consideration are the type of material used and the manufacturing method used to manufacture the bottle. The product that is filled here is Albuminex which is also known as Albumin. It is used in the treatment of symptoms related to trauma of haemorrhagic shock patients and burn patients. Due to the concerns for the presence of the hepatitis virus, these albumins are treated with heat in the form of an aqueous albumin solution. Normally, Albumin preparation is filled into the conventional glass vial and they are hermetically sealed by rubber plug (Figure 6.1).

Figure 6.1: Capper Seating in Opening of the Glass Vial (Source: Heuft.(2020) [12])

Hermetic sealing is done for creating an airtight container which prevents any material in the container from being exposed to the outer environment or contaminations. The albumin is filled in glass vials and then sealed hermetically, the entire process is done in a closed environment to prevent contamination. Recently there have been attempts to fill the albumin in plastic vessels but this has failed because the hermetical sealing of rubber plug in the plastic vial has caused heating which resulted in thermal denaturing of the albumin. (Hershberg and Wolkoff, 1969) [11]

One of the significant properties of the albumin is the physical instability of their solutions and their tendency to revert to a solid or semi-solid state. This change of irreversible coagulation or alteration of the protein shape can be brought by the application of heat or external stress. Due to this the albumin will lose its physical properties which characterizes them as Albumin. This phenomenon is known as denaturization (Bancroft and Rutzler, 1969) [13].

All though plastic bottles are cheap compared to glass bottles, other factors such as finished plastic bottles have not proved convincing enough to be used in place of glass vials for intravenously administered vaccines. For example, the uneven sealing surface such as found in Figure 6.2.

Figure 6.2: Uneven Surface on the Plastic Vial Opening (Source: (2020, July 20) [14])

If the vial has an uneven top, it results in an improper seal and increases the chance of product contamination.

As one of the exclusion criteria, plastic is not used will not be discussed. The next exclusion criteria for this research is that the research is focussed only on identifying the root cause of breakage or crack

that happens with the fill/finish assembly line. It does not include factors that are contributing for the crack of the vials outside the fill/finish assembly line such as mishandling of the storage cart of filled vials.

6.1.2 Inclusion Criteria

The Inclusion criteria includes all the facts and data associated within the fill/finish process starting from the point where the empty vials are integrated into the line to the point where the filled vials are discharged as final output. All vial material properties associated with Soda lime Silica glass is included. (Refer Table VII)

7 DATA COLLECTION

The data collection starts from the collection of the vial dimensions and their material properties.

7.1 Vial Anatomy

The vials that are used in this filling process are of four different vial sizes such as 50 ml, 100 ml, 250 ml and 500 ml. Find the various parts of the vial labelled with common locations. The body, heel, & footprint are the regions in which the maximum number of 90% of cracks (deformation) are introduced.

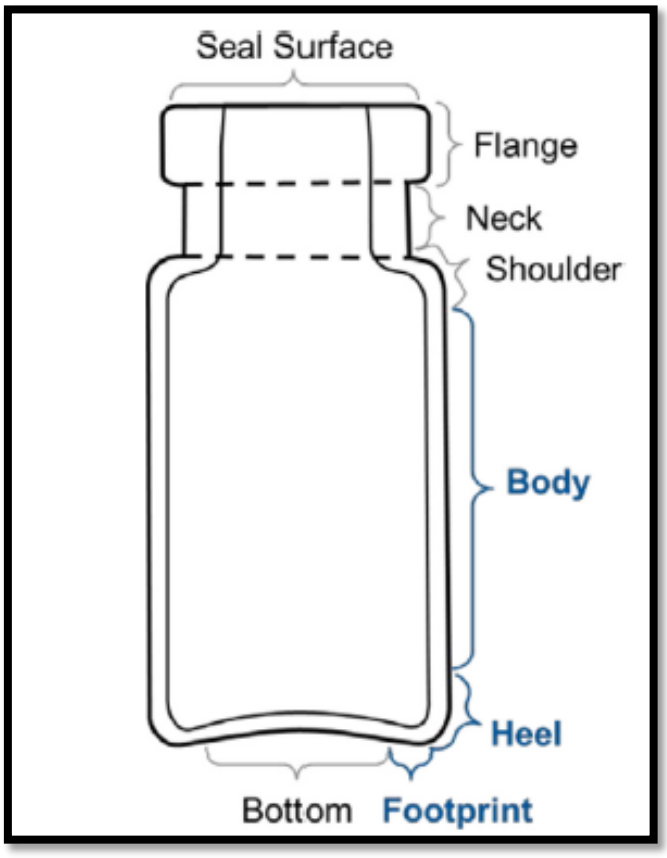


Figure 7.1: Glass Vial Anatomy Image (Source: (Schaut et al., 2017))

50 ml:

The 50 ml vials have a hazy appearance due to the treatment process of type 2 material manufacturing process. This vial size has a standard ISO(International Organization for Standardization)finish of 32 mm. The 50 ml vial has a practical fill capacity of 68 ml with tolerance of ± 5 ml overflow. The weight of the 50 ml vial is 55.00g. The 50 ml vials have an expiration date of 5 years from the date of manufacture. The following model was constructed in solid works using the given dimensions below the model.

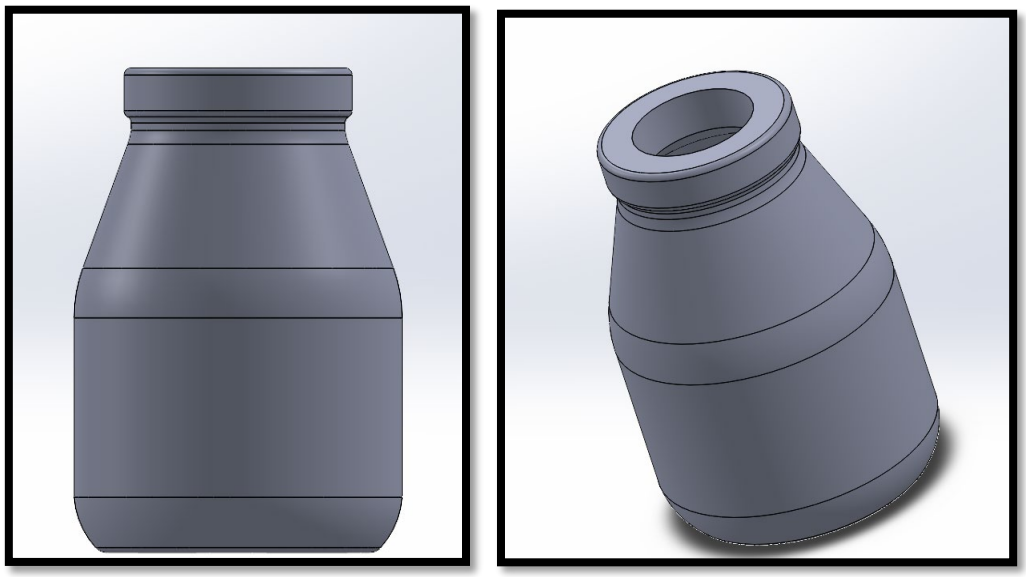


Figure 7.2: 50 ml vial designed using Solid Works.

Following are the vial dimensions:

Bottom outer Diameter: 46 ± 0.8 mm **Bottom inside Diameter:** 37 mm

Bottle height: 68±0.7 mm **Top diameter:** 32±0.3 mm

Minimum Wall Thickness Body: 0.8128 mm

Minimum Wall Thickness Bottom:1.4986 mm

100 ml:

The 100 ml vials have a hazy appearance due to the treatment process of type 2 material manufacturing process. This vial size has a standard ISO(International Organization for Standardization)finish of 32 mm. The 100 ml vial has a practical fill capacity of 128 ml with tolerance of ± 5 ml overflow. The weight of the 100 ml vial is 87.00g. The 100 ml vials have an expiration date of 5 years from the date of manufacture.

Figure 7.3: 100 ml vial designed using Solid Works.

Following are the vial dimensions:

Bottom outer Diameter: 49 ± 0.8 mm **Bottom inside Diameter:** 39 mm

Bottle height: 104±0.8 mm **Top diameter:** 32±0.3 mm

Minimum Wall Thickness Body: 0.8128 mm

Minimum Wall Thickness Bottom:1.4986 mm

250 ml:

The 250 ml vials have a hazy appearance due to the treatment process of type 2 material manufacturing process. This vial size has a standard ISO(International Organization for Standardization)finish 0f 32 mm. The 250 ml vial has a practical fill capacity of 308 ml with tolerance of ± 8 ml overflow. The weight of the 250 ml vial is 170.00g. The 250 ml vials have an expiration date of 5 years from the date of manufacture.

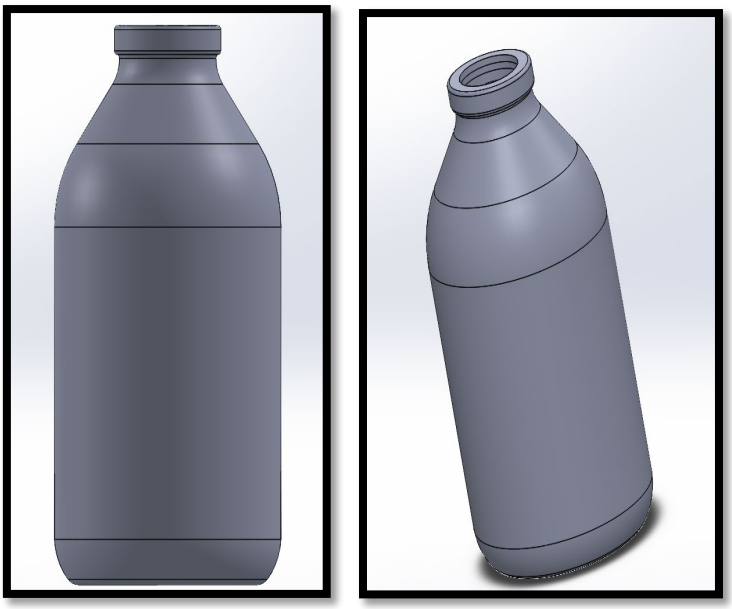


Figure 7.4: 250 ml vial designed using Solid Works.

Following are the vial dimensions:

Bottom outer Diameter: 66.0 ± 1.2 mm **Bottom inside Diameter:** 54 mm

Bottle height: 136.0±1.2 mm **Top diameter:** 32±0.3 mm

Minimum Wall Thickness Body: 0.8128 mm

Minimum Wall Thickness Bottom:1.4986 mm

500 ml:

The 500 ml vials have a hazy appearance due to the treatment process of type 2 material manufacturing process. This vial size has a standard ISO(International Organization for Standardization)finish of 32 mm. The 500 ml vial has a practical fill capacity of 598 ml with tolerance of ± 8 ml overflow. The weight of the 500 ml vial is 220.00g. The 500 ml vials have an expiration date of 5 years from the date of manufacture.

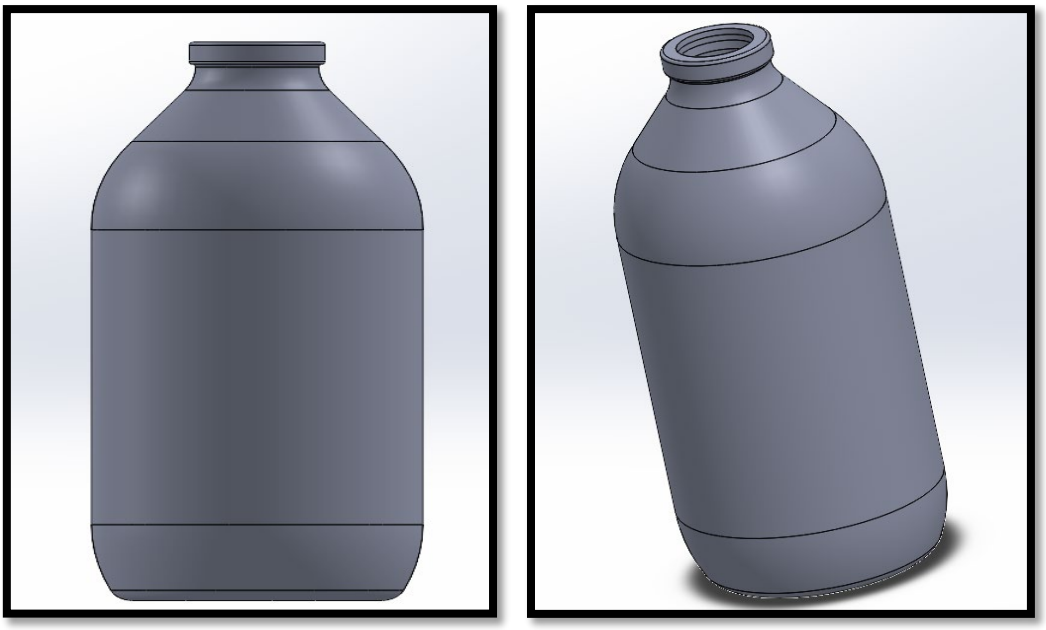


Figure 7.5: 500 ml vial designed using Solid Works.

Following are the vial dimensions:

Bottom outer Diameter: 78.0 ± 1.4 mm **Bottom inside Diameter:** 59.5 mm

Bottle height: 177.0±1.4 mm **Top diameter:** 32±0.3 mm

Minimum Wall Thickness Body: 0.8128 mm

Minimum Wall Thickness Bottom:1.4986 mm

7.2 Material Properties:

The vial type used in this filling process is the type 2 vials. The type 2 vials are usually made up of soda-lime silica glass. As discussed in the earlier chapter in determining why these specific materials are used in these glass vials for the albumin filling process. Since plastic vials are not used in the filling process in the exclusion criteria session, the discussion will identify two specific properties that decided the usage of type 2 vials for the filling process.

7.3 Delamination

The shedding of glass particles from the glass surface is known as delamination. This occurs usually due to the leeching, corrosion, and weathering reactions. These particles originate from the interior surface of the vials because of the leaching of modifier ions into the solution that is being filled. These particles are usually in the range of 1 nm to 2 μm with a width of 50 μm. Glass containers or glass vials used for storing pharmaceutical compositions possess good chemical durability and low thermal expansion. The most used vials are made of boro-silicate glass (type 1 vials). This boro-silicate glass is found to have a phase separation due to exposure of the glass elevated temperature which is used for reforming the glass into container shape.(W.P. Schaut et al., 2016) [15]. The delamination process has caused multiple recall of drug products over the past. The US Food and Drug Administration (FDA) has issued an advisory. The advisory(W.P. Schaut et al., 2016) [15] states “that there is a presence of glass particulates in injectable drugs. The advisory particularly states that there is potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic and other vascular events and subcutaneously led to the development of foreign body granuloma, local injections site reactions and increased immunogenicity”. These factors led the pharmaceutical drug manufacturers to move towards the type 2 vials which is the soda lime silica glass. Soda lime silica glass is a silica glass which contains sodium oxide, alkaline metal oxides and chiefly alkaline earth oxide. Soda lime silica glass possesses good hydrolytic resistance with treatment of inward surface. Type 2 glass vials are used for parenteral and non-parenteral uses which has properties of acidic and

neutral aqueous products (Watkins et al., 2014) [16].One of the most important properties which led to the choice of type 2 vials (soda lime silica glass) are the hydrolytic resistance property.

7.4 Hydrolytic Resistance

The delamination of glass contact surface due to the hydrolytic instability (i.e., glass corrosion which occurs during the beginning phases of delamination) can modify the active pharmaceutical ingredient (API) of solution through its chemical stability (Watkins et al., 2014) [16]. The hydrolytic resistance of the vials can be defined as the ability of the glass to maintain its stability when it is in contact with the pharmaceutical solution. "The hydrolytic resistance test, when used as the sole measure of potential drug-container compatibility, is not reliable" (Bohrer et al., 2004) [17]. There are various tests to decide the glass type (Table **V**) and to decide the hydrolytic resistance of the internal surface of the glass

TABLE V: DETERMINATION OF GLASS TYPES (**Source:** (Watkins et al., 2014) [16]

Container Type	Test	Reason
I, II, III	*Glass Grains Test*	Distinguishes Type I borosilicate glass from Type II and III soda-lime-silica glass

Type 2 vials have high hydrolytic resistance ability which make them suitable for parenteral drug applications. The other properties of type 2 vials composition can be distinguished by the name "13-17% Nao (the "soda"), 5-10% CaO (the "lime"), and 70-75% SiO2 (the "glass")" (Ashby, 2012) [18]. The Table VI gives all the other material properties associated with the type 2 vials (soda lime silica glass).

TABLE VI :SODA LIME SILICA GLASS MATERIAL PROPERTIES (source: (Ashby, 2012) [18])

Composition

73% SiO_2/1% Al_2O_3/17% Na_2O/4% MgO/5% CaO

General properties				
Density	2,440	–	2,490	kg/m^3
Price	0.8	–	1.7	USD/kg
Mechanical properties				
Young's modulus	68	–	72	GPa
Yield strength (elastic limit)	30	–	35	MPa
Tensile strength	31	–	35	MPa
Elongation	0			%
Hardness—Vickers	439	–	484	HV
Fatigue strength at 10^7 cycles	29.4	–	32.5	MPa
Fracture toughness	0.55	–	0.7	$MPa \cdot m^{1/2}$
Thermal properties				
Maximum service temperature	443	–	673	K
Thermal conductor or insulator?	Poor insulator			
Thermal conductivity	0.7	–	1.3	$W/m \cdot K$
Specific heat capacity	850	–	950	$J/kg \cdot K$
Thermal expansion coefficient	9.1	–	9.5	µstrain/°C
Electrical properties				
Electrical conductor or insulator?	Good insulator			
Electrical resistivity	7.94×10^{17}	–	7.94×10^{18}	$\mu ohm \cdot cm$
Dielectric constant	7	–	7.6	
Dissipation factor	0.007	–	0.01	
Dielectric strength	12	–	14	10^6 V/m

7.5 Manufacturing Method

The type 2 vials known as the soda lime silica glass is usually made up of 70% sand alongside a particular combination of soda ash, limestone, and regular substances. At the start of the process, the raw materials are gauged and blended. The molten form which has a temperature of about 1500°C is derived from the furnace through the raw materials. The glass melt is removed and poured into the forming equipment. "The type 2 vials are the shaped vials. Gobs of molten glass are conveyed to the moulds of the machine. The vials are shaped either by (blow and blow process) or by an (press and blow process)". (Susanne Hibler and D. H. G., 2010) [19]

Blow & Blow Process:

In this process, pressurized air is used to frame the gob into a parison after which the neck finish and a uniform shape is created. The parison is then flipped/turned and then air is blowed into it to gain the desired shape. (Refer Figure 7.6)

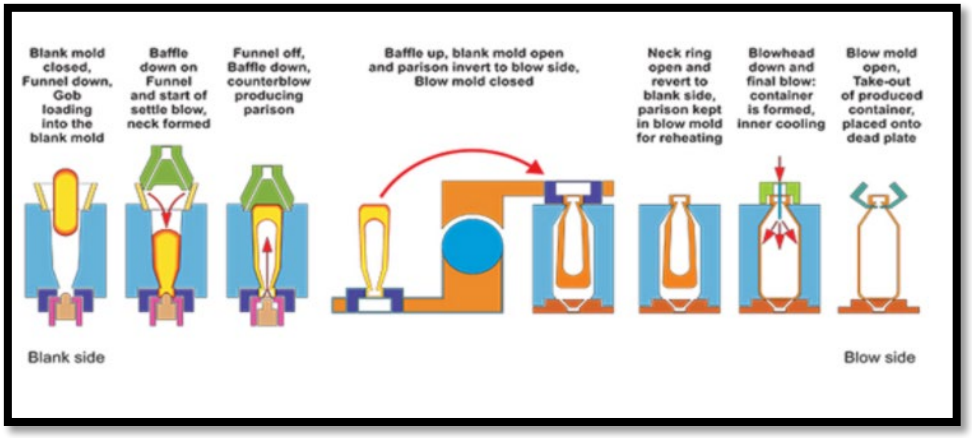


Figure 7.6: Blow & Blow Process source (2020, January)[20]

Press & Blow Process:

In this process, the plunger is inserted into the mould and then air is blown to form the gob into parison (Refer Figure 7.7).

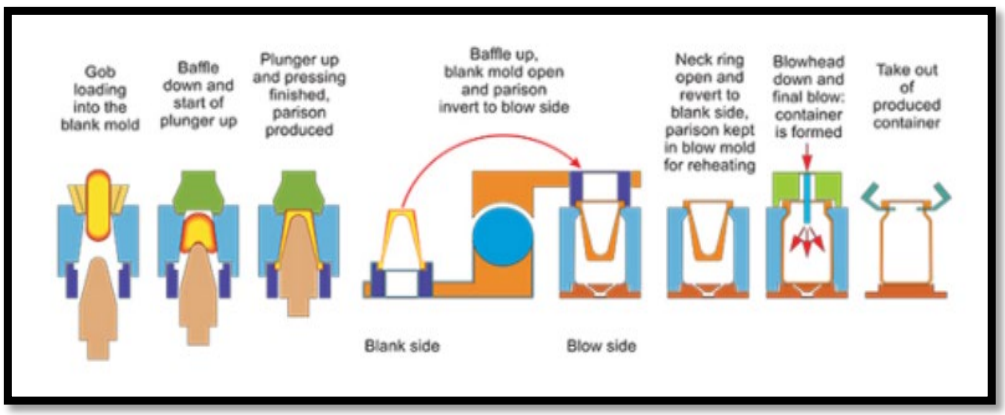


Figure 7.7: Press & Blow Process source (2020, January) [20]

After the blowing process, the vials are loaded into the annealing oven, where their temperature is reduced to 1500° F which is then gradually reduced to below 900° F. This process relieves the inherent

stress if present in the vials. Without this process, the containers would easily shatter. Optical inspections are utilized at the end of the processes so that the quality of the vial produced is ensured.

7.6 Defect Occurring Spot

The vial breakage in the filling line happens at different spots. Primarily there are two locations.

1) The first location is the de-pyrogenation tunnel exit where the cracked vials are spotted. The cracked vials are spotted at the zone when the vial comes out of the de-pyrogenation tunnel and the vials which are cracked are clearly visible here.
2) The second location is the capper pressing station. The breakage happens during the pressing operation of the rubber capper into the vial.

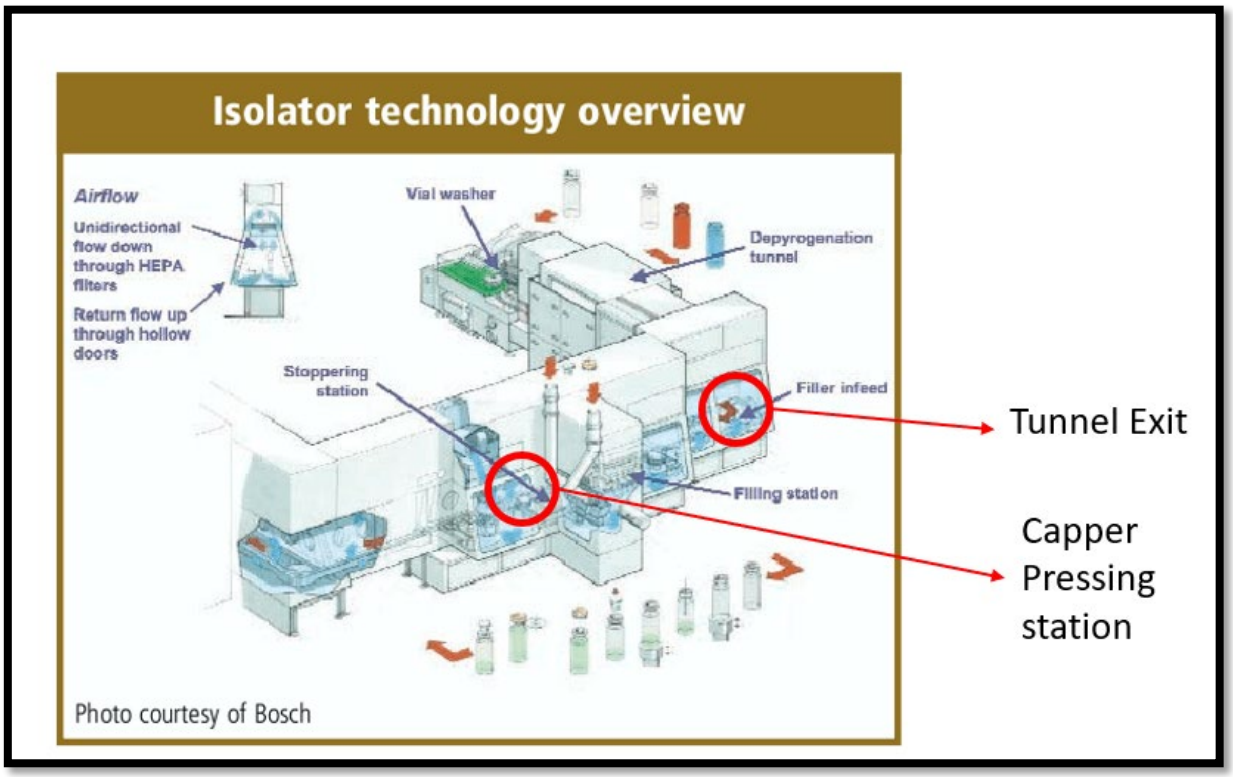


Figure 7.8: Isolator Technology (source -Isolator Technology. (2020, January) [27])

These two locations are where most of the cracked vials and vial breakages occur. To investigate the cracking phenomenon, let us analyze the starting point of the fill/finish process which is the visual inspection machine.

8 ANALYSIS

8.1 Visual Inspection Machine

The visual inspection machine system has been already explained under the process mapping category. The visual inspection machine inspects the vials for any cosmetic defects like scratches, blisters, and cracks. There are two inspection machines connected in series (Figure 8.1), the first one checks the side walls for any defects and the second inspection machine check for the top and bottom finish.

Fig 8.1: Visual Inspection Machine (VIM) (source –Visual Inspection Machine. (2019, January) [21])

The inspection machine checks for the defects and reports the reject rate. The inspection machine checks for various defects as seen from the (Figure 8.2 & 8.3)

Figure 8.2: VIM different Defects(source – Visual Inspection Machine. (2019, January) [21])

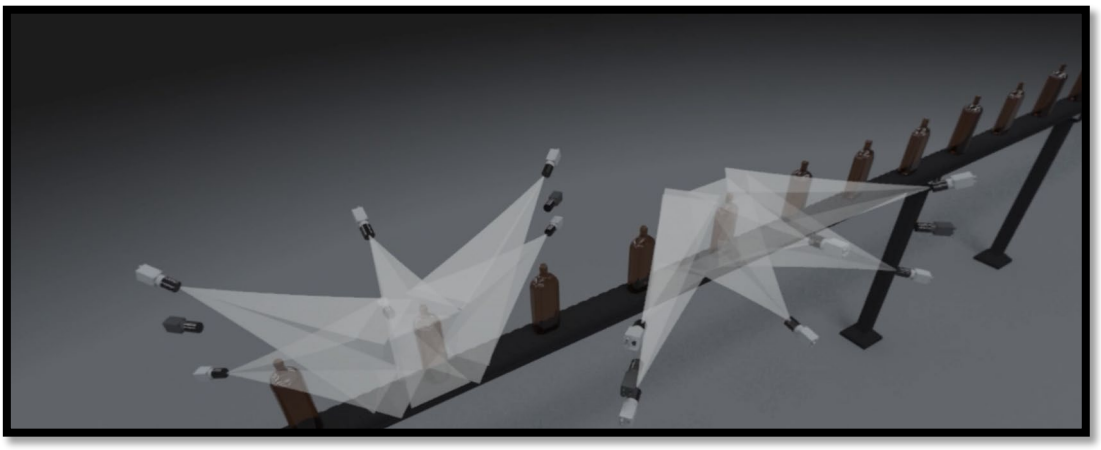


Figure 8.3: VIM working (source – Visual Inspection Machine. (2019, January) [21])

The rejection rate for the machine is calculated as follows.

Total Rejects used: “X”.

Total Inspected: “Y.”

Reject Rate (% Rejected) = ((“X”/”Y”) *100)

The allowable rejection rate for the machine has been defined as 30%. So, the machine inspects and reject the vials if the rejection rate is within 30%, if the reject rate exceeds 30% then the defective vial lot is replaced with a new vial lot. The defective vial lot will go under a material review request. The rejection rate is calculated for the campaign that is being followed.

A campaign is defined as the period in which the Albuminex (say a concentration of 5%) is filled. Campaign can be regarded as a batch of production. Maximum of three shifts of filling is allowed for a campaign. A shift of production or filling is eight hours. So, the rejection rate reported is for the campaign or also known as a batch of production.

To verify the rejection rate is within the specified limits, the rejection rate of different batches for two years has been taken and hypothesis testing is done. This test is done to prove/disprove if the rejection rate is scientifically within or above the allowable limits.

8.2 Hypothesis Testing:

A hypothesis test is a rule that specifies if to accept or reject a claim based on the data collected about the population. Sample data collected from the population usually acts an evidence for this test. A hypothesis test conducts or tests two hypotheses about a population. The first is the null hypothesis and the second is the alternate hypothesis. Generally, the null hypothesis is the problem or subject being investigated. The alternative hypothesis is the statement that we want to test based on the evidence provided by the population or sample data.

The test is usually determining whether to fail to reject or reject null hypothesis. A P-value can be used to conclude to "reject the null hypothesis or fail to reject the null hypothesis." A P-value is probability statistics which when less than the significance value (α) rejects the null hypothesis. Significance value is the confidence level that a particular event is going to take place. Let us apply the hypothesis testing as a case scenario to the problem.

Problem Statement:

The vial cracks in the filling line in various locations of the filling line. The vial goes through the aseptic processes (washing, de-pyrogenation, and filling line). Before this process, each vial is examined through a visual inspection machine. The inspection machine checks for cosmetic defects like blisters, scuffs, and cracks if any are present and rejects them accordingly. After the inspection process, the vials deemed good for production are stored in the accumulation table before it is passed to the aseptic processes.

The allowable rejection rate for the inspection machine is 30% of each vial lot. If the rejection exceeds 30%, then the production must stop and remove the defective lot and then integrate a new set of vials into the line. Rejection rates for the past two years has been taken.

The following are the Null and Alternate Hypotheses:

Null Hypothesis: The rejection rate (P_R) in the visual inspection machine is within target.

$$Ho: P_R \leq 30.$$

Alternate Hypothesis: The rejection rate (P_R) in the visual inspection machine is not within target.

$$H_a: P_R > 30$$

The significance level (α) is taken as 95 % for this problem which is.

$$1- \alpha=0.95$$
$$\alpha= 0. 05$$

The rejection rate for the past two years (Table VII) have been noted and feed into Minitab for further analyzing.

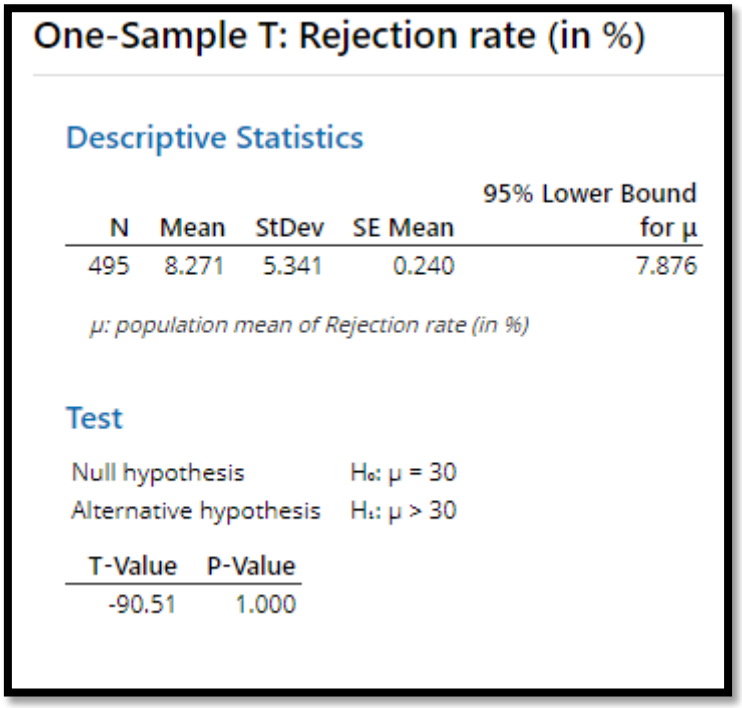
TABLE VII: REJECTION RATE FOR 50 ML VIAL SIZE

AlBurx percentage (Campaign)	Vial Size	Rejection rate (%)
20	50	5
20	50	12
20	50	7.6
20	50	13.1
20	50	13.4
20	50	11
20	50	13
20	50	12
20	50	6
20	50	11.3
20	50	7
20	50	7
20	50	8
20	50	12
20	50	14
20	50	16
20	50	17
20	50	16
20	50	18.2
20	50	16.4
20	50	13
20	50	14
20	50	13
20	50	4.8
20	50	3.5

The table (Table VIII) above is an example of the data that was collected for two years. The above collected data is collected for all vessel sizes of 50 ml,100 ml, 250 ml, & 500 ml. The collected data was entered into Minitab software for statistical analysis and Hypothesis testing.

Results from Minitab:

The following test is the One sample T-Test that was performed in the Minitab software. One Sample T-Test is used since the standard deviation of the entire population is unknown (i.e., rejection rates for the past two years has been taken and not the whole period right from when the machine has been commissioned).



One-Sample T: Rejection rate (in %)

Descriptive Statistics

N	Mean	StDev	SE Mean	95% Lower Bound for μ
495	8.271	5.341	0.240	7.876

μ: population mean of Rejection rate (in %)

Test

Null hypothesis	H_0: μ = 30
Alternative hypothesis	H_1: μ > 30

T-Value	P-Value
-90.51	1.000

Figure 8.4: Minitab results: One Sample T-test

Based on the hypothesis testing results (One Sample-T test) using Minitab, following are the inferences determined from the analysis. The P-Value observed from the above test is 1.000 which is greater than the α (0.05), 1) Since the P-Value is greater then α (significance level), fail to reject null hypothesis. The Inspection machine rejection rate is within the limits which means that there is no abnormal rejection of vials or the vial rejection rate distribution is well within the specified rejection rate limit of 30%. Also, the rejection rate data was input into Box plot application of Minitab software (Figure 8.5)

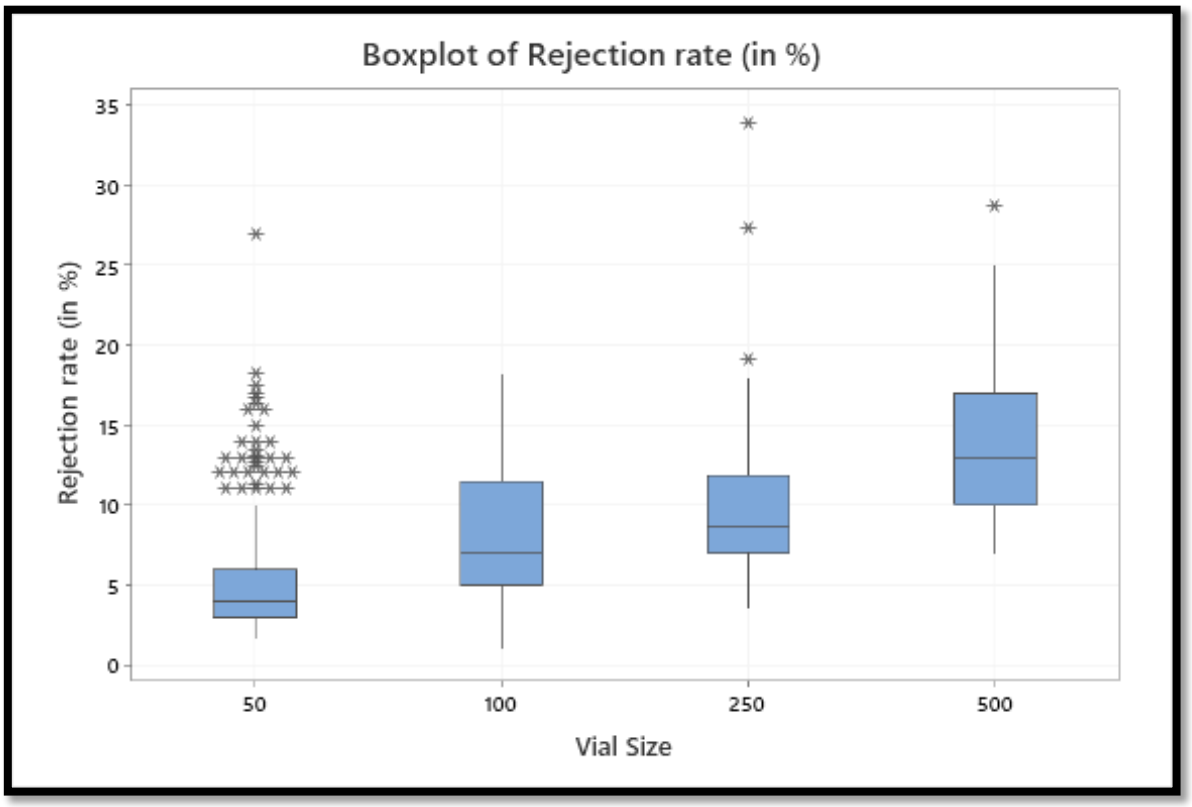


Figure 8.5: Minitab results: Box Plot

The Box Plot represents the interquartile range box with the middle representing the 50% of the data and the lines extending from the box are known as whiskers represents the top and bottom 25% of the data. The 50 ml vial has the distribution of the rejection rate in the range of 3% to 6%. The 100 ml vial has the distribution of the rejection rate in the range of 5% to 11%. The 250 ml vial has the distribution of the rejection rate in the range of 7% to 12%. The 500 ml vial has the distribution of the rejection rate in the range of 10% to 16%. Box Plot for the rejection rates for different vial sizes concluded the following.

1) The rejection rate increases as the vial sizes increases. As seen from the above box plot the rejection rate for 500 ml has been distributed around (10 -16%), while the rejection rate for 50 ml has been distributed around (3 - 6%)

2) The rejection rates for the 50 ml vial size are erratic and has many outliers meaning that the distribution is not uniform for the 50 ml sizes while the rejection rates for other vial sizes have the

rejection rates distributed around a certain value with less or no outliers in their rejection rate data distribution.

8.3 One way-ANOVA Testing

ANOVA known as the Analysis of Variance, is an estimation procedure which is used to analyze the differences among the means in a sample. In our case, ANOVA is used to analyze the difference among the means of the rejection rates of all the vial sizes such as 50 ml, 100 ml, 250 ml, and 500 ml.

The One-way ANOVA is used to decide if there are any significant differences between the means of the independent variable (vial size). This is used to determine if the effect of an independent variable (Vial Size) affects the dependant variable which is the rejection rate.

The rejection rate data which is collected for a time of two years is fed into the one-way ANOVA analysis testing tool of the Minitab software, following are the interpretations:

STEP 1: Determining whether the differences group means are statistically significant.

Method

Null hypothesis	All means are equal
Alternative hypothesis	Not all means are equal
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Figure 8.6.1: Minitab results: One Way ANOVA test

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Vial Size	3	4152	1383.91	68.35	0.000
Error	491	9941	20.25		
Total	494	14093			

Figure 8.6.2: Minitab results: One Way ANOVA test

To decide if the differences between the means of the rejection rates of different vial sizes are statistically significant, the P-Value is compared with the significance level.

The decision of if to fail to reject the null hypothesis or to reject the null hypothesis. The significance level as decided from the hypothesis testing is α (0.05). As per the results from Minitab in Figure 8.6.2, the P-value is equal to 0.000 which is very low compared to the significance level α (0.05). According to the rule of thumb the null hypothesis is rejected since the significance level is less compared to the P-value and it can be concluded that the difference between the means have statistical significance meaning that the vial sizes such as 50 ml, 100 ml, 250 ml, and 500 ml each have a different rejection rate.

STEP 2: Examine the group means:

The following interval plot shows the mean and confidence interval for each vials size. The dot stands for a sample mean. The plots in Figure 8.6.3, displays that the 50 ml vials has the lowest mean, and the 500 ml vials has the highest mean.

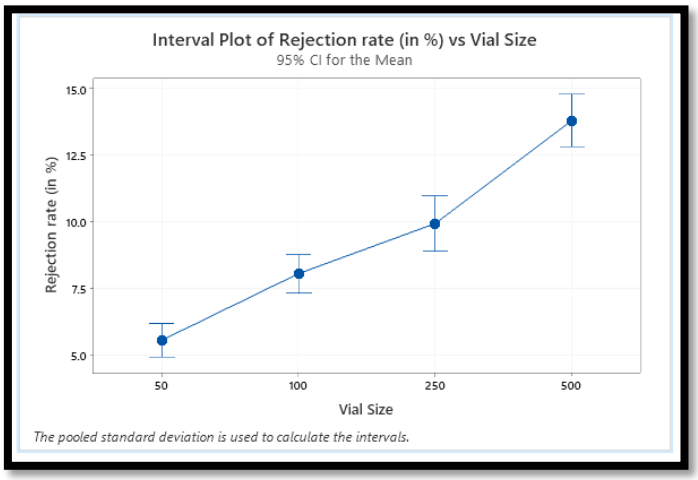
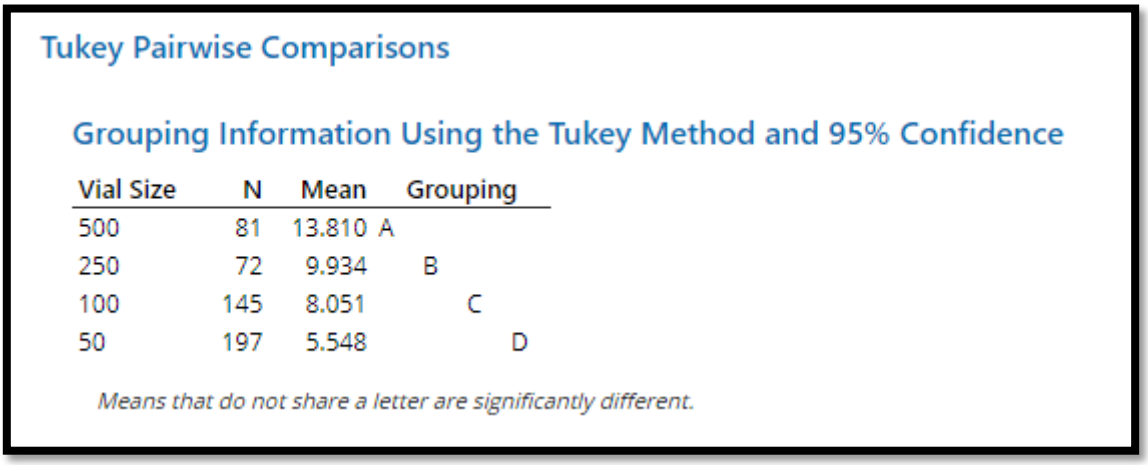


Figure 8.6.3: Interval Plot of Rejection Rates of Different Vial Sizes

STEP 3: Compare the group means:

Since the P-value of one-way ANOVA is less than the significance level, it is known that the group means are different, but the pairs of which groups is not known. So, the following results are derived which will show if there is any significance of the mean difference between the specific pairs of vial sizes. For this analysis, the tukey pairwise comparison is used.



Tukey Pairwise Comparisons

Grouping Information Using the Tukey Method and 95% Confidence

Vial Size	N	Mean	Grouping		
500	81	13.810	A		
250	72	9.934		B	
100	145	8.051			C
50	197	5.548			D

Means that do not share a letter are significantly different.

Figure 8.6.4: Grouping Information for Different Vial Sizes

From the group information table which uses the tukey pairwise comparison, the rejection rate means of vial which do not share a letter with other vial sizes are significantly different. So, the vials 50 ml, 100 ml, 250 ml, and 500 ml each have a different rejection rate mean associated with them.

8.4 MSA Measurement System Analysis

Measurement System Analysis is characterized as an experimental and numerical technique for deciding the measure of variability that exists within a measurement process. Variation in the measurement process can straightforwardly add to process variability. MSA is used to confirm the measurement system for use by assessing the precision, accuracy, and dependability. (Measurement System Analysis. (2020) [22].We are testing the visual inspection machine as that is the source of variation which is clear from the hypothesis testing and box plot results. Upon statistically verifying

the rejection rates, now it was necessary to conduct an experimental analysis to verify the repeatability of the visual inspection machine.

To conduct the experiment, 60 sample of vials with 30 defective vials and 30 good vials were taken. They were fed into the visual inspection machine to check if they were being correctly inspected and sent to the accumulation table or if they have been marked and rejected if they have any defects. The following analysis have been completed, based on the results from the experiment done on the visual inspection machine.

Sensitivity vs Specificity

This test is done to check if the test measures what it is supposed to measure. It is also known to check the accuracy of the test. Some basic terminologies are the four terms used in this test, they are True Positive, false positive, false negative and true negative. The following figure contains the definition for the terms.

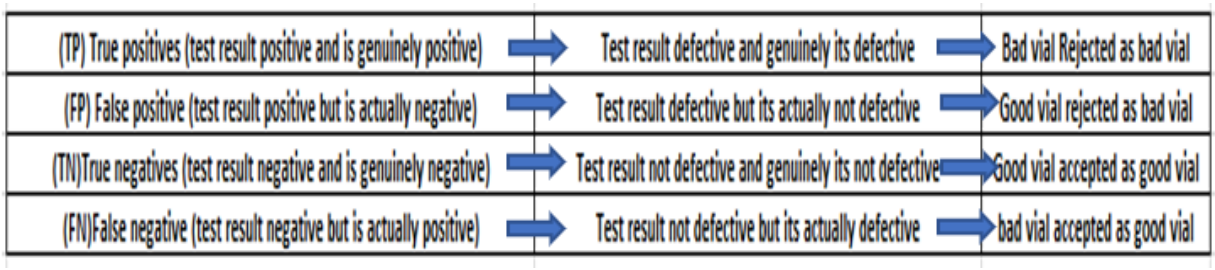


Figure 8.7: Sensitivity vs Specificity definition Terms

TABLE VIII: SENSITIVITY VS SPECIFICITY TEST RESULTS

		Genuinely Positive		Genuinely Negative	Total
Test Positive	**TP**	**15**	**FP**	**0**	**15**
Test Negative	**FN**	**15**	**TN**	**30**	**45**
Total		**30**		**30**	**60**

Referring Table VIII, In the first row Test Positive and first column Genuinely Positive, the values entered as in the test of how many times the bad vial were rejected correctly in other words, the test is positive, and the bad vials are rejected as bad vial by visual inspection machine. These are the true positives (TP). In the first row Test Positive and second column Genuinely Negative, the values entered as in the test of how many times the good vials were rejected. In other words, the test is positive, and the good vials are rejected as bad vials by the visual inspection machine. These are false positives (FP). In second row Test Negative and first column Genuinely Positive, the values entered as in the test of how many times the bad vials were accepted as good vials by the visual inspection machine. The inspection machine had wrongly labeled a bad vial as a good vial. These are false negatives (FN). In second row Test Negative and second column Genuinely Negative, the values entered as in the test, how many times the good vials were accepted as good vials by the visual inspection machine. These are true negatives (TN).

Test positive	a (TP)	b (FP)
Test negative	c (FN)	d (TN)
	Sensitivity: a/ (a+c)	Specificity: d/ (b+d)

TP: True positive, FP: False positive, FN: False negative, TN: True negative

Figure 8.8: Sensitivity vs Specificity table (source (R. Parikh et al., 2008) [28])

Sensitivity is the ability of a test to correctly classify a test specimen as defective. It is calculated as follows:

Sensitivity = a / (a+c)

= a (TP) / a+c (TP + FN)

= Probability of being tested positive when a defect is present.

Specificity is the ability of a test to correctly test a sample as defect free. It is calculated as follows:

Specificity = d / (b+d)

= d (TN) / b+d (TN + FP)

= Probability of being tested negative when a defect is absent.

Based on the test result from Table VIII, Sensitivity and Specificity is calculated below

TABLE IX: SENSITIVITY VS SPECIFICITY CALCULATION RESULTS

Sensitivity	TP/(TP+FN)	0.5
Specificity	TN/(TN+FP)	1

Sensitivity calculations show that the visual inspection machine is 50% capable of finding a vial as defective and specificity shows that it is 100% capable of finding a vial as defect free. To evaluate the reliability of the above results, the following are calculated. “Positive Predictive value (PPV) is the probability that a subject/sample that returns a positive outcome is truly positive” and “the Negative Predictive value (PPV) is the probability that a subject/sample that return a negative outcome is truly negative.”

The positive predictive value is decided using the following equation:

PPV = TP/ (TP + FP)

The negative predictive value is decided using the following equation:

NPV = TN/ (TN +FN)

The Sensitivity and Specificity is determined same as the PPV and NPV. Following are the results.

TABLE X: PPV AND NPV CALCULATION RESULTS

PPV-Positive Predictive value	TP/(TP+FP)	1
NPV-Negative Predictive value	TN/(TN+FN)	0.666666667

So, based on the above results the positive predictive value says that it has a chance of a 100% being correct for the test result being positive and the negative predictive value says that it has a chance of only 66% being correct for the test result being negative.

Next the False Discovery Rates (FDR) and False Omission Rate (FOR) are calculated, FDR gives the percentage of positive results that are wrong and FOR gives the percentage of negative results that are wrong. The formula is as follows.

FDR = FP / (FP+TP)

FOR = FN / (FN+TN)

The result are as follows:

TABLE XI: FALSE DISCOVERY RATE & FALSE OMISSION RATE CALCULATION RESULTS

False discovery rate	FP/(FP+TP)	0
False Omission rate	FN/(FN+TN)	0.333333333

Based on FDR results, whatever vials are rejected it is 100% correct and based on FOR whatever the accepted vials are, they are 33% wrong.

8.5 Accumulation Table

The next process that needs to be studied is the Accumulation Table that has the good vials stored in them. The accumulation table stores the good vials and passes them to the vial washers. As mentioned in the process mapping section of the accumulation table, the table has three different belts with different speed (refer Table III). The accumulation table scenario has been simulated using Ansys and solid works.

8.6 Static Stress Analysis of Vials

The aim of the static stress analysis is to check whether the glass vials hitting with one another in the accumulation table is creating stress which in-turn causes micro level deformation in the vial surface or crack initiation in the vials when they are hitting with each other in the accumulation table. The vial surface is affected due to fatigue and the strength of the glass. Scratched glass loses significantly less strength than unscratched glass (Baker T.C and Preston F.W., 1946) [23]. The vials models are constructed using 3D CAD modelling software of Solid Works. These models are constructed in Solid Works CAD modelling software and then imported into the Ansys software which is a primarily stress analysis software. Before heading into the Ansys analysis, what is a Static Stress Analysis? The Static Stress Analysis tool in Ansys is used to calculate the deformation or stress that is created when an object is loaded. In this case, the object is the glass vials. The glass vials are subjected to a force being loaded in the face of the vial. Same way static thermal analysis tool is used which calculate the deformation or stress that is created when an object is thermally loaded. This method will focus on if there is enough stress (crack initiation) is created in the accumulation table due to being hit with one another and the stress that is developed in the de-pyrogenation tunnel is enough to cause deformation.

Figure 8.9.1: 50 ml & 100 ml

Figure 8.9.2: 250 ml & 500 ml

All Materials have a failing tendency (i.e., when they reach a certain number of cycles of loading the material will fail). This is how a Stress-Number of cycles to fail(SN) graph comes into play of the stress analysis.

8.7 SN Curve

Fatigue or endurance limits of certain properties or materials are described using the SN curve. It is plotted between number of cycles to fail and the cyclic stress amplitude. The following figure denotes an SN graph with the number of cycles to fail in the horizontal axis and the stress amplitude of the cycle in the vertical axis. The curves in the graph are decided using the fatigue tests which are performed by applying force in constant amplitude in the form of stress until the test specimen fail.

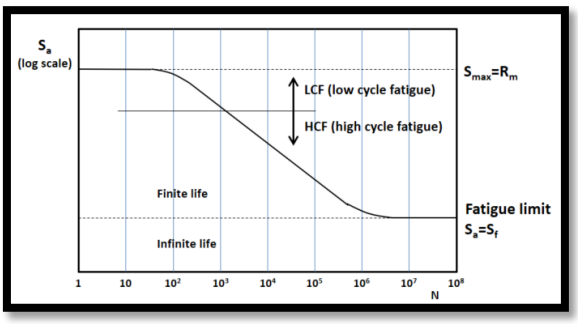


Figure 8.10: SN Curve Example Image (source-Homan, J. (2018, February 20) [24])

The SN curve (Figure 8.11) for the soda lime silica glasses is taken and values are plotted from the graph in a table form. The curve (Figure 8.11) denotes the relationship between the breaking strength and duration of the test. In our case, simply one cycle here means the vials get a one time hit with the other vial. So “x” number of cycles may have breakage at “y” alternating stresses. This table is given below (Table XII).

TABLE XII : TABLE FOR SN CURVE OF SODA LIME GLASS

Cycle (Seconds)	Alternating Stress (MPa)
0.01	137.8952
0.1	103.4214
1	82.73712
10	69.637076
100	62.05284
1000	55.15808
10000	53.779128

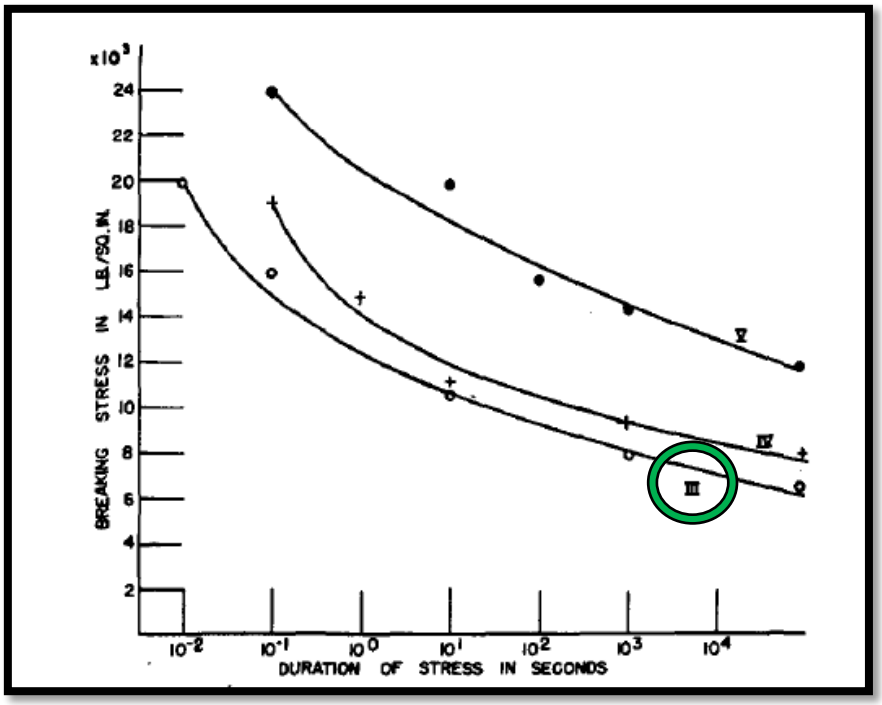


Figure 8.11: III-Denotes SN Curve for Soda Lime Glass –(Baker T.C and Preston F.W., 1946) [23]

8.8 Impact Force Calculation

The accumulation table has three different conveyor belts with three different speeds (Table III). For the impact force calculation, the speed of the conveyor belt which takes the vial and makes an impact with the already present or accumulated vial is used. The following is the table of the impact force calculated for all the vial size.

The Formula used to calculate the impact force(F) is,

F=m*a

m- It is the mass of the vials in Kg.

a- It is the acceleration of the vial when it is hitting the accumulated vial.

1) Initial velocity is taken as zero, as the vial is in idle condition before being pushed into the table. The final velocity is taken from the Table III for respective vial size.
2) The change in time taken is 1 second.

TABLE XIII: IMPACT FORCE CALCULATION FOR ALL VIAL SIZES

Vial Size	Mass (kg)	Acceleration (m/s^2)	Force=mass*acceleration (N)
50 ml	0.055	0.2032	0.011176
100 ml	0.087	0.2032	0.0176784
250 ml	0.17	0.1524	0.025908
500 ml	0.22	0.21336	0.0469392

The force expressed in newton is taken as the force acting on the vial.

8.9 Ansys Analysis of Vials

This study is done for a single vial taking in account all the other properties that single vial goes through such as impact force, temperature the vial model designed in solid works CAD modelling

software is imported into the Ansys analysis software. The vial size that is used here is soda lime silica glass.

The analysis systems (**Figure 8.12)** that are used here is static structural analysis and thermal analysis.The type 2 material (soda lime silica glass) is added to the 3D model of 500 ml vial size under the engineering data.

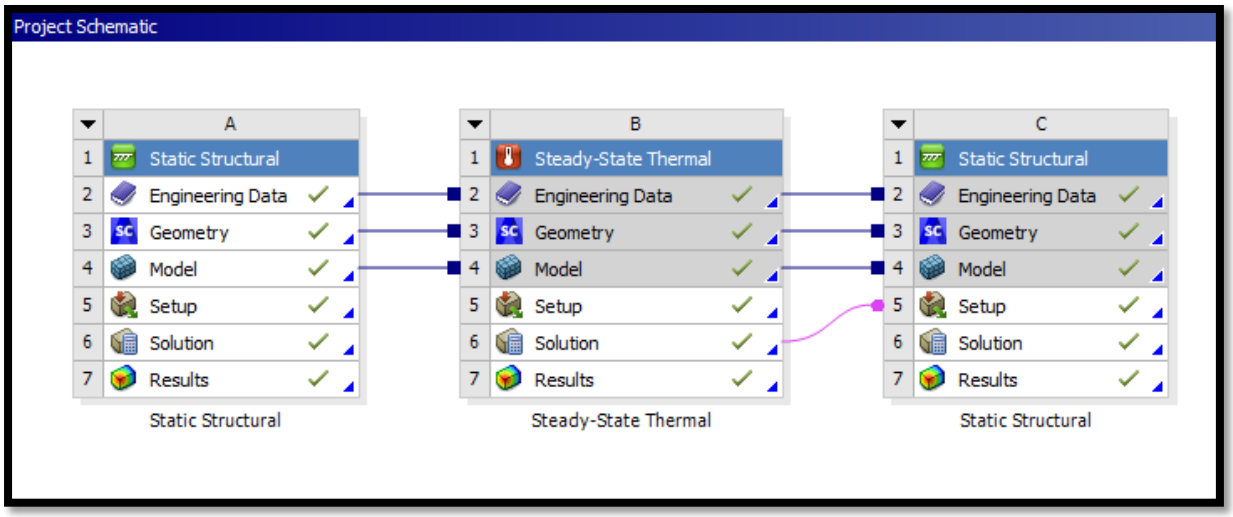


Figure 8.12: Ansys-Project Schematic

SN curve data from the Table XII for the glass vial 3D model is added into the analysis system. The next step is applying the impact force (from Table XIII) to the 3D vials. The impact force is added through choice of nodes in one of the faces of the vial (i.e., in the middle part of the vial body).

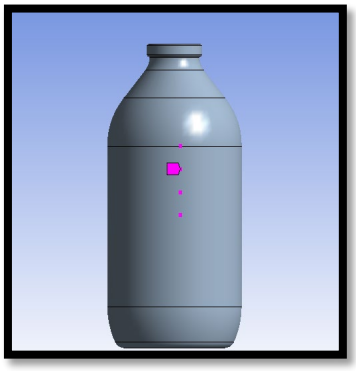


Figure 8.13: Ansys model with force nodes

The force added is perpendicular to the one of the faces of the vial. This is done to simulate the real-life event of vial hitting with each other in the CAD analysis software. The next part is adding the

temperature (Table IV) of the de-pyrogenation tunnel in the Ansys software to simulate the vial reaction with hot temperature environment of the de-pyrogenation tunnel.

The first part of adding force in the Ansys software will simulate and produce the results in the form of stress developed in the vial when they hit with each other while the second part where the temperature is added into Ansys to simulate and produce the results in the form of stress developed in the vial in de-pyrogenation tunnel (i.e., when the vial is subjected to hot temperature environment). Different vial sizes have different temperature in the de-pyrogenation tunnel. This can be referred from the Table IV.

The solution needs to be defined for both the impact force calculated and the vial reaction with hot temperature environment. For both defined conditions, the apt solution is finding the maximum and minimum principal stresses, so that they can be compared with SN curve to find the cycle and corresponding stress they are failing for. "The principal stresses are the maximum and minimum extensional stresses in a stress state at a point. The principal directions are the corresponding directions. (Principle Stresses. (2005)) [25]"

8.10 Comparing the Results with SN Curve

The results from Ansys has been summarized in the following table.

TABLE XIV ANSYS RESULTS

Vial Size (ml)	Mass (kg)	Acceleration (m/s^2)	Force=Mass*Acceleration (N)	De-Pyrogenation Tunnel $^0C(^0F)$	Stress Developed in Accumulation Table (Pa)	Stress developed in De-Pyrogenation Tunnel (MPa)
50	0.055	0.2032	0.011176	325(617)	120-604.8	60-62.8
100	0.087	0.2032	0.0176784	325(617)	256-2307	55-62
250	0.17	0.1524	0.025908	315(599)	166-1215	50-61
500	0.22	0.21336	0.0469392	320(608)	69-1534.9	58-67

The Impact force calculated and the hot temperature in the de-pyrogenation tunnel was input into the Ansys software and the corresponding stress developed in the vials in the accumulation table and stress developed in the vials in the de-pyrogenation table has been derived. Next a comparison of the results of the stress developed in the 500 ml vials in the de-pyrogenation table is presented.

The impact force applied to the bottle implies the real-life situation of the bottle hitting with one another. Based on the results from the static structural analysis of the glass vials, the principal stresses developed in the 500 ml glass vials was in the range of 69-1534.9 pa. On comparing this value with the SN curve **(Figure 8.11),** the stress developed in the 500 ml glass vial in the accumulation table is well below the endurance limit of the soda lime silica glass.

Hence it will take infinite number of cycles for the bottle to develop stress enough to cause breakage or crack.

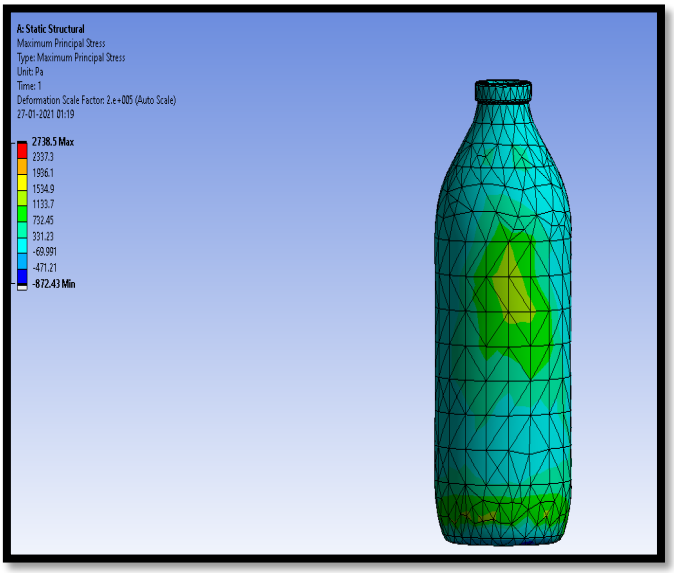


Figure 8.14: Ansys Model with developed Stress in the Body of the Glass Vials

Now the stress developed in the 500 ml glass vial when they are subjected to hot temperature is shown below. The stress develops as an interaction of the glass vial with the hot temperature of 320ºC. (Refer Table IV)

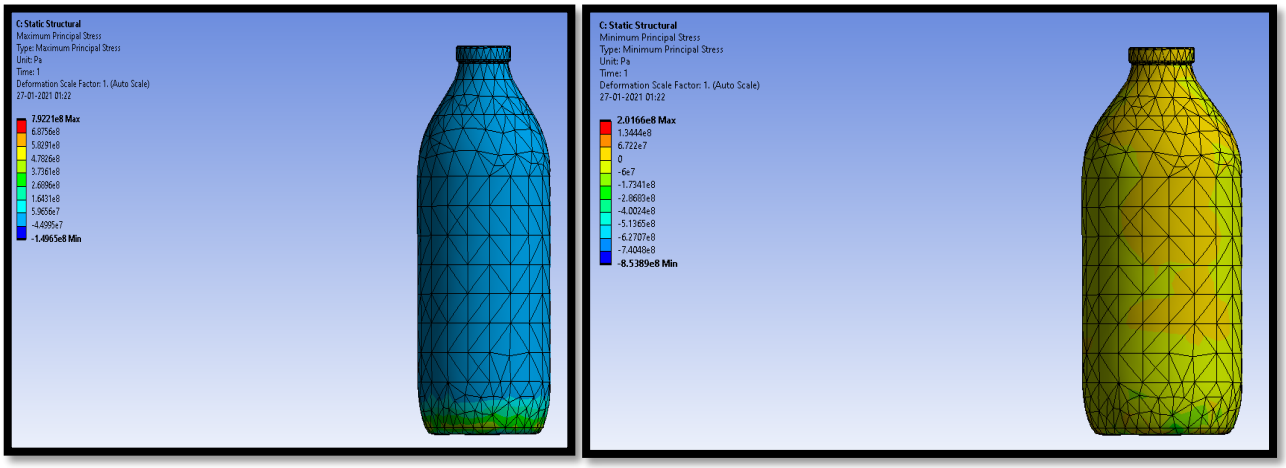


Figure 8.15: Principal Stresses-Maximum and Minimum

When the 500 ml vial undergoes thermal loading, the stress developed in the bottle is 58-67 Mpa. From the SN curve & the Table XIV, the stress developed will fail at 10-100 cycles. It means that if the vials are hit with one another after or during the de-pyrogenation tunnel, then the vials have high chance for the failure to happen which is the cracking or breakage in the vials.

9 RESULTS

The Vial cracking phenomenon is not due to a single root cause but a mixture of different root causes which leads to the cracking. If the cracking was due to one cause, then every vial passing through this process should crack. The results are summarized in the following table, which is explained in the order that has been mentioned in the table below.

TABLE XV: RESULT SUMMARIZATION TABLE

S.no	Analysis Phas	Description	Analysis Description
1	Phase 1	Statistics	Hypothesis testing for the rejection rates of the machine
2	Phase 1	Statistics	One way ANOVA testing for the machine
3	Phase 1	Statistics	MSA Analysis
4	Phase 2	CAD Modelling	ANSYS analysis - Static Structural
5	Phase 2	CAD Modelling	ANSYS analysis - Thermal Structural

The analysis part was divided into two phases Phase 1 and Phase 2. First part of the Phase I of this research focused on the statistical analysis of the empty glass vial visual inspection machine rejection rates. Rejection Rates for the past 2 years has been collected and hypothesis testing is used which showed that the visual inspection machine rejection rate is within the target limits and Box Plots show that the rejection rate increases with the increase of vial size.

The second part of the Phase I of this research was the ANOVA testing for the rejection rates of the empty glass vial visual inspection machine. This testing was done to see if the effect of the vial size was affecting the rejection rate. As seen from the analysis, each vial size had different mean rejection rates **Figure 8.6.4**.

Also, the visual inspection machine was subjected to sensitivity vs specificity analysis to control and judge the measurement process. The sensitivity vs specificity result is summarized below with the inferences column stating the conclusions from the test.

TABLE XVI: MSA RESULT SUMMARIZATION TABLE

S.No	Description	Result	Inferences
1	Sensitivity	50%	50% Capable of Identifying a Vial as Defective
2	Specificity	100%	100% Capable of Identifying a Vial as Defect Free
3	PPV-Positive Predictive Value	100%	If Test Result is Positive, there is a 100% Chance it is Correct.
4	NPV-Negative Predictive Value	0.6666667	If Test Result is Negative then it is a 66% Chance it is Correct.
5	False Discovery Rate	0	Percentage of Postive Results that are Wrong i.e Whatever Rejected is correct
6	False Omission Rate	0.3333333	Percentage of Negative Results that are Wrong i.e Whatever Accepted is 33 % Wrong

Although the above result has a false discovery rate of zero which means that the vials that the machine has been rejecting is correct, the False Omission Rate of 33% is derived which implies that whatever the machine is accepting as good vials are 33% of the time is a wrong decision.

Phase II of this research examined the joint effects of impact force and thermal exposure in the glass vials. A combination of tools was used to find the magnitude of stresses developed in the vials due to the impact force and thermal exposure including numerical methods which show the impact force the vials are subjected to and those calculated values along with the thermal exposure value (in °Celsius) are applied in 3D modeling CAD/Simulation software such as Solid works and Ansys. This Analysis was done for all the vial sizes (50 ml, 100 ml, 250 ml, & 500 ml) that are used in the production facility. The magnitude of stress (Table XIV) which was calculated in the CAD/Simulation software was compared with the SN curve. The stress developed in the accumulation table due to the impact force (from Table XIV) showed that the values were well beyond the endurance limit (from SN curve table values) for the crack to happen there but with multiple hitting in the bottle, the crack initiates at a micro scale.

Now the magnitude of stress that is developed due to the interaction of the vials with the thermal field is developed (Table XIV), which showed that the stress values are closed to the endurance limit (from SN curve table values). Refer below the comparison table.

TABLE XVII: STRESS VALUE AND ENDURANCE LIMITS COMPARED.

Vial Size	Stress Developed in accumulation table (pa)	Stress developed in depyrogenation table (Mpa)
50 ml	120-604.8	60-62.8
100 ml	256-2307	55-62
250 ml	166-1215	50-61
500 ml	69-1534.9	58-67

Cycle (Seconds)	Alternating stress (Mpa)
0.01	137.8952
0.1	103.4214
1	82.73712
10	69.637076
100	62.05284
1000	55.15808
10000	53.779128

The values that are highlighted in green to the right of the table are close to the stress developed in the vials when they go through the de-pyrogenation tunnel. This shows that after getting exposed to such a hot temperature environment, if the vials are subjected to getting hit with each other inside the de-pyrogenation tunnel they are more susceptible to break inside the tunnel itself. For example, if a 500 ml vial which after getting exposed to the de-pyrogenation tunnel, the stress developed in the vial is 50-61 Mpa, if the vials further get hit 10-1000 times with each other inside the tunnel the vials will exceed their endurance limit and will crack. The vial hitting with each other in the tunnel happens as the vial from the washers are pushed into the tunnel using a push bar. If the speed of the vial washers is increased, this will cause the washers to push the vials into the tunnel at high speed. The conveyor speed inside the tunnel is slow, while the incoming vial from the washers are pushed into the tunnel which causes stagnation of the vial in the tunnel entrance causing the hitting of vials with one another. Therefore, most of the broken or cracked vials are found at the tunnel exit as mentioned in the section (7.6).

10 DISCUSSION

Based on the aforementioned results, the corrective actions that are needed to be taken to prevent the vial cracking process will now be discussed. This is done through a project proposal to the company, which the company needs to follow in a step-by-step manner to achieve the results.

The project plan is divided into three levels as Level 1, Level 2 and Level 3.Level 1 Project tasks are easy to implement, Level 2 project tasks have medium level of difficulty and Level 3 project task has the highest difficulty for to implement the project. The phase 1 will be reducing the stress level induced in the vials, while phase 2 will be the corrective action needed to fix the visual inspection machine, phase 3 is the updating of the incoming quality inspection procedure and finally phase 4 is the vial material revisit. Solutions are explained further below for each phase with the result verification steps to ensure that the implemented idea is working.

TABLE XVIII: PROJECT PLAN/PROPOSAL TO THE COMPANY.

Project Plan to Eliminate the Vial Cracking/Breakage						
Level	Task Description	How	Why	Implementation Ease	Task Result	Result Verification
1	Phase 1 –Controlling the Accumulation					
1 (A)	Reduce the hits within De-Pyrogenation Tunnel	Standardize the speed for vial washer	Changing the speed of washers causes the excess of number of vial to be pushed to the tunnel. This increase the hitting of vials inside the tunnel	Medium	No Crack in the vials	Observe if the process is consistent without cracks
1 (B)	Reduce the accumulation of the vials in the accumulation table	Standardize the allowed number of vials which can be present in the accumulation table	Reducing the congestion between the vials will reduced the stress developed in the vials during hitting of vials with one another	Easy	No Crack in the vials	Observe if the process is consistent without cracks
	Phase 2 -Visual Inspection Machine (VIM)					
1(C)	Check Visual Inspection Machine (VIM)	Re-Calibration of the VIM	To make sure that the machine is inspecting correctly or rejecting defective parts	Medium	Eliminate False positives and False negatives of the inspecting vials	Perform MSA analysis periodically
1 (D)	Rejection Rates to be fixed as per the vial size	Identify Average rejection rate for the vial size from past data	Rejection rates should and will vary from vial to vial based on the size.	Easy	More defective parts will be captured by the inspection machine and rejected	
2	Phase 3 -Incoming Quality Procedure					
2 (A)	Incoming Quality inspection procedure to be made more stringent			Hard		
3	Phase 4 -Vial Material Re-Visit					
3 (A)	Revisit Vial supplier process	Supplier process audit	After fixing all the problems within the process and the facility, if still cracks or breakages of the vials are occurring then the product production process itself needs to be audited	Hard	Identify Process in the vial production process which causes the inherent defect in the vials.	49

10.1 Phase 1-Accumulation Table

1(A) Reduce the hits within de-pyrogenation tunnel.

The vials in the de-pyrogenation tunnel hitting with each other causes the vials to crack/break as proved in the Ansys analysis of the vials in thermal field. The main reason for the vials to hit with each other in the de-pyrogenation tunnel is due to congestion created when the vials are pushed from the exit of the vial washer to the entrance of the de-pyrogenation tunnel. The congestion is created because of increasing the speed of the vial washer which causes excess number of vials pushed to the entrance of the de-pyrogenation tunnel, which needs to be standardized for all vial sizes same as the standardized speed of the de-pyrogenation tunnel. If the speed is standardized for the vial washer, then

the congestion would be reduced which will significantly prevent the cracking process from happening.

1(B) Reduce the accumulation of the vials in the accumulation table.

The number of vials stored in the accumulation table must be reduced by introducing the following design to reduce vial to vial hitting in the accumulation table (Image in the right, **Figure 10.1**).

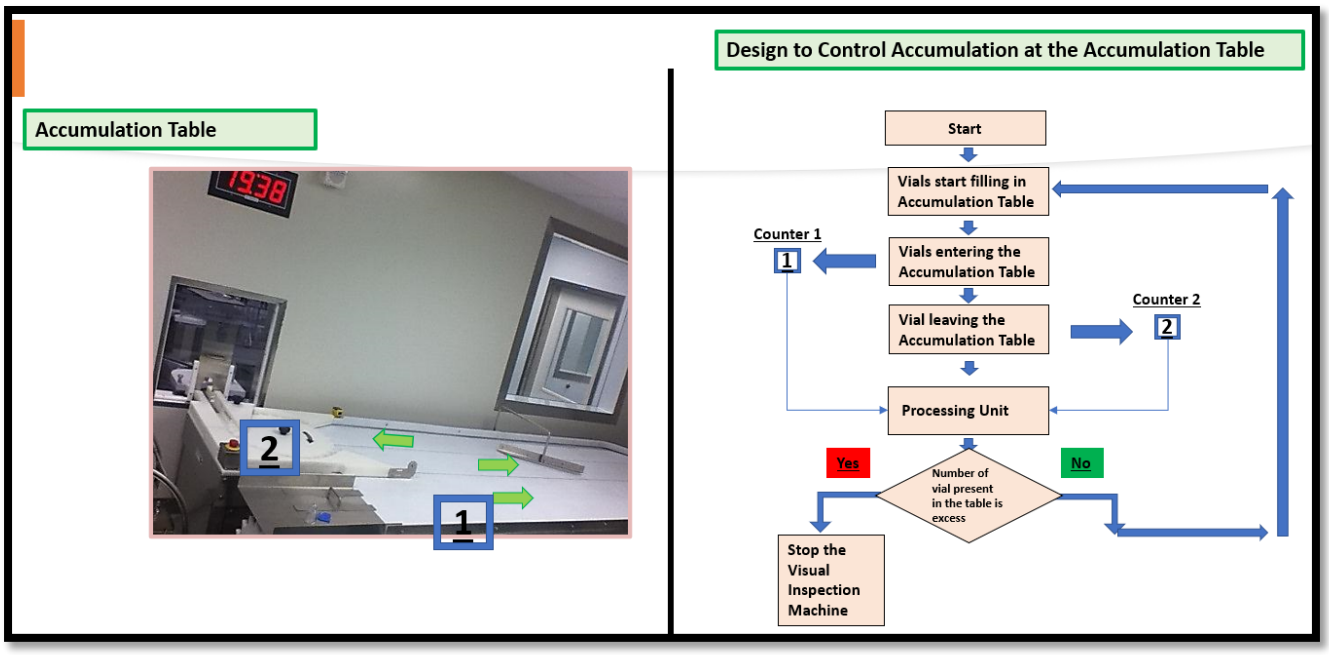


Figure 10.1: Flow diagram of the Design to Control Accumulation.

The above diagram (left) shows the accumulation table with the directions indicated in which the vials move. The counters (sensors) needed to be installed as mentioned in the image in the left. The 1st counter is the one that measures and keeps account of the number of vials entering the system while the 2nd counter will measure and keeps account of the number of vials leaving the system. Both the counters are connected to a processing unit which will keep account of the number of vials are present in the system at a given point of time. The table accumulation capacity for different vial sizes is shown below, it is calculated based on the surface area of the vials and the surface area of the accumulation table. The accumulation capacity shown below happens when there is 100 percentage use of the surface

area of the accumulation table. For example, when there is 100 percent occupancy of the accumulation table by 500 ml vials, the accumulated count is 781 vials.

TABLE XIX: TOTAL NUMBER OF VIALS.

Vial Size (ml)	Vial Bottom Diameter (mm)	Surface Area of Vials (mm^2)	Surface Area of the Accumulation Table(mm^2)	Total Number of Vials
50	46	1661.06	3729275	2245
100	49	1884.79	3729275	1979
250	66	3419.46	3729275	1091
500	78	4775.94	3729275	781

This count needs to be reduced, to reduce the congestion in the accumulation table which will reduce the vial hitting with other vials. This number should be carefully reduced, as the later process like de-pyrogenation tunnel might get starved of vials and cause nonconformities in the process. An effective way of reducing the accumulation count is taking a trial-and-error method to arrive to the exact value. Following example shows that if the accumulation count is reduced to 50% of the original value, the total number of vials at 50% reduced count is 390 vials.

TABLE XX: TOTAL NUMBER OF VIALS AFTER REDUCED CAPACITY.

Vial Size (ml)	Vial Bottom Diameter (mm)	Surface Area of Vials (mm^2)	Surface Area of the Accumulation Table (mm^2)	Total Number of Vials	50% Capacity	25% Capacity
50	46	1661.06	3729275	2245	1123	561
100	49	1884.79	3729275	1979	989	495
250	66	3419.46	3729275	1091	545	273
500	78	4775.94	3729275	781	390	195

For this example, as per the new system, for 500 ml vials the total count that should be present in the table at any point of time should be 390 vials. If the count exceeds the predetermined count of allowable number of vials to be present in the table, then the processing unit will stop the visual inspection machine from processing further units and pushing them to accumulation table.

10.2 Phase 2- Visual Inspection Machine (VIM)

1(C) Check visual inspection machine

The Results from hypothesis testing and MSA analysis are contradictory to each other because the hypothesis testing results show that the machine is rejecting within target (i.e., allowed limit of 30%), the MSA analysis of the attribute agreement shows that the visual inspection machine needs calibration. While the former talked about the rejection limits which is related to the product, the latter talks about the process itself. The results from the sensitivity vs specificity show that the equipment needs re-calibration of parts and processes to prevent false positives (good vial rejected as bad vial) and false negatives (bad vial accepted as good vial).

1(D) Rejection Rates to be fixed as per the vial size.

As per the box plot results from Figure 8.5 and the one-way ANOVA testing from section 8.3 showed that the vial size affects the rejection rate. From the box plot the rejection rate increases as the vial size

increases, which is proved from the mean calculation of ANOVA testing. The ANOVA testing showed that there is a difference in the means of the rejection rate. (refer **Figure 8.6.3**).

These statistical experiments and their results convey the fact that the rejection rate which is currently defined as 30% for all the vial sizes should be eliminated, and the rejection rates should be defined based on the vial size. This ensures that there is no escaping of false positive or false negative vials into the process.

The following are the mean rejection rates for different vial sizes based on the data collected for the past 2 years. The 50 ml vial size has a mean rejection rate of 5.548%, 100 ml vial size has a mean rejection rate of 8.051%, 250 ml vial size has a mean rejection rate of 9.934% and the 500 ml vial size has a mean rejection rate of 13.810%.

TABLE XXI: MEAN REJECTION RATE FOR DIFFERENT VIAL SIZE

Means

Vial Size	N	Mean	StDev	95% CI
50	197	5.548	4.233	(4.918, 6.178)
100	145	8.051	4.417	(7.317, 8.785)
250	72	9.934	5.045	(8.893, 10.976)
500	81	13.810	4.760	(12.828, 14.792)

10.3 Phase 3- Incoming Quality Procedure

2 (A) Incoming Quality inspection procedure to be made more stringent

From Section 4.1, the flow in the inspection procedure has a flaw which says that if the sampling vial does not pass the AQL (Accepted Quality limit), the whole batch of vials undergo further scrutiny to check if it passes the tightened AQL. It is rejected only if it fails in the tightened AQL. In a good system, the vials should be rejected in the first instance they are failed, but the procedure here states that already rejected vials can be made to pass through if it passes the tightened AQL. Although this is a business decision, this must be made more stringent to ensure that there are no defective vials escaping into the system.

10.4 Phase 4- Vial Material Re-Visit

3 (A) Revisit Vial supplier process

After arresting all process bottlenecks and flaws internally, the last step in the project proposal is the auditing of the supplier process. This is done to find the production process of the vials which causes the inherent defects to the vials. It is clear from the box plot that the vials with larger sizes have the higher possibility for jumping into failure zone. This step will be the hardest to implement as it involves the backtracking of the product back to the supplier, studying the process involved in manufacturing vials, shocks involved during the transportation or logistics which will lead to potential root causes of the vial cracks.

11 COST ANALYSIS

It is of utmost importance for calculating the expenses incurred due to the vial breakage issue. The costs due to the vial breakages include the cost of raw materials, cost of operators and indirect costs includes the overhead costs such as utilities, indirect labor costs, repairs, and maintenance. The Table XXII shows the various costs involved in the Fill/Finish department (Sedita, J et al., 2018).

The operational cost is calculated for a year which is further broken down into as cost for a month and then cost for a day and finally operational cost for a shift. The operational costs as shown from the Table XXII for one shift is $16,000. So, when a vial breakage occurs in the fill/finish line the costs associated with one shift such as the costs for the utilities, costs for the labor used for manufacturing the product and the costs for the labor used for the fill/finish line are an economic loss.

This thesis project provides an opportunity for saving costs which totals to $16,000 through the elimination of the vial breakage in the fill/finish manufacturing line.

TABLE XXII: Cost Breakdown for Operational Costs.

		Amount in $	***Amount in $***
Overhead	Repairs & maintenance	707,929	
	Utilities	600,000	
	Indirect labor & corporate overhead (constant)	400,000	
Raw Material and Consumables	Total primary raw material cost (high estimate)	9,000,000	
	Total secondary raw materials (high estimate)	3,737,288	
Direct Labor	Filling	2,004,095	
	Line clearance	478,678	
	Packaging	125,000	
	Total Annual Operating Expense	$17,052,990	
	Total Operating Expense Per Month	$1,421,082.50	**~ $1.4 M**
	Total Operating Expense Per Day	$47,369.42	**~ $47k per day**
	Total Operating Expense Per Shift	$15,789.81	**~$16K per shift**

12 DMAIC CHECK LIST

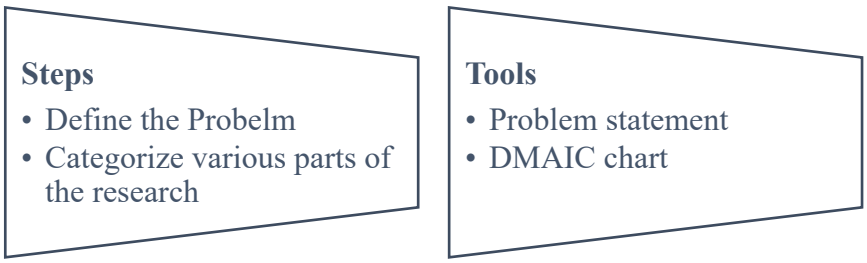
At the starting of this research project, the project was categorized into one of the five phases of the DMAIC approach. The following table gives the check list of the progress of the project.

TABLE XXIII: DMAIC PROGRESS CHECKLIST.

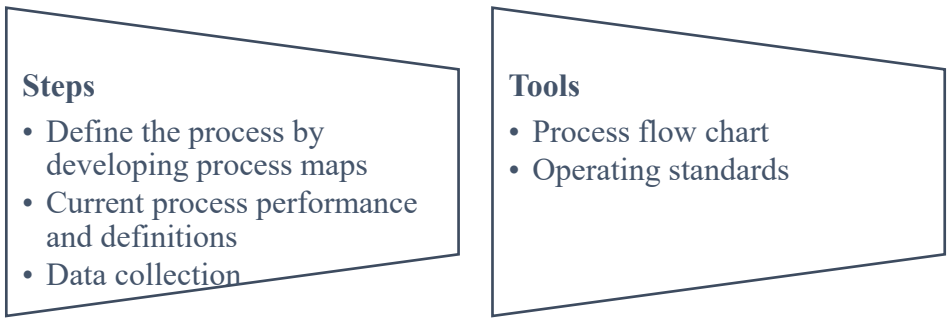
	DMAIC				
	Define	**Measure**	**Analyse**	**Improve**	**Control**
Introduction	✓				
Company Overview					
Problem Statement					
Process Mapping		✓			
Data Collection					
Research Questions			✓		
Root Cause analysis					
Analysis					
Results and Discussion				✓	✓

Individual phases have been explained below with the steps and tools used in each step.

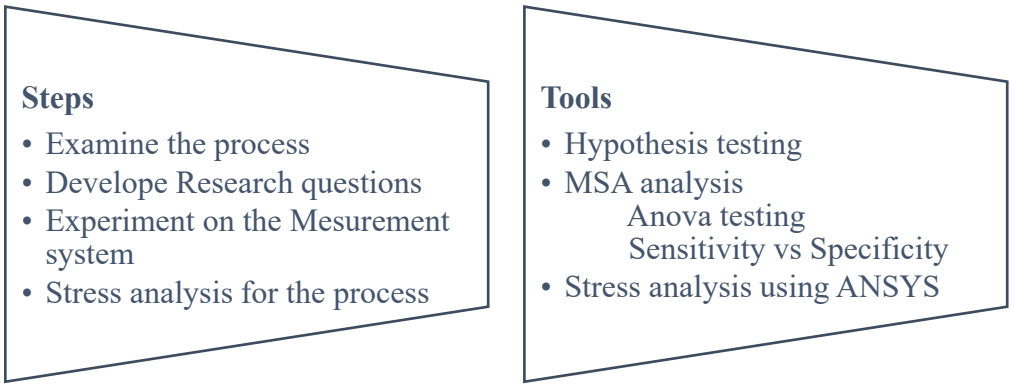
Phase 1: Define.



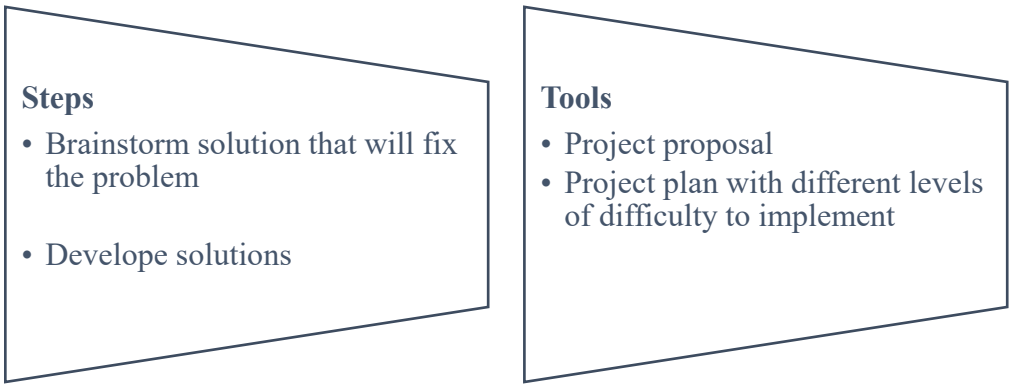
Phase 2: Measure



Phase 3: Analyse.



Phase 4 & 5: Improve & control.



13 CONCLUSIONS

An evaluation of root causes contributing to the Pharmaceutical vial breakage was performed using the problem-solving method of DMAIC. The research questions SQ1: "*Does the visual inspection machine have the rejection rate within target?"* and SQ2: "*What impact does the vial colliding with each other have on cracking?"* were investigated in two phases. Phase 1 used statistical analysis such as hypothesis testing, ANOVA testing, and sensitivity vs. specificity testing to measure the reliability of the visual inspection machine. Although from the hypothesis testing it showed that the process is rejecting the vials within the acceptable quality level of 30%, the ANOVA testing showed that the different vial sizes have different mean rejection rates. Moreover, the specificity vs. sensitivity showed that the false omission rate of 33% meaning that 33% of accepted vials were wrong.

Phase 2 of the research focused on the stress developed due to the impact of vials hitting with each other and the stress developed due to the impact of the vials in de-pyrogenation tunnel (i.e., the application of thermal field on glass vials). CAD modeling such as Solid Works were used to construct the glass vial and the model is used in the stress analysis software such as ANSYS to find the stress developed. In the outcome model, the stress developed in the vials during its movement in accumulation table where the vials hit with each other is calculated, the result showed that the stress level is well below the endurance or fatigue limit of the material directly implying as why there is no cracking or breakage of vials at that spot. Then the stress developed during the interaction of the glass vials with the heat field is found out. The results showed that stress developed in the glass vials is high enough and if further hitting of vials occurs inside the tunnel, then the vial will fail or crack which are clear when they exit out of the tunnel.

The vial hitting with each other in the tunnel occurs when there is a congestion created due to the excess number of vials accumulating at the tunnel entrance. This is possible only when the vial washer speed is increased which will push the washers in excess to the tunnel entrance causing the congestion, due to which the vial hitting with each other happens causing the already developed stress to increase beyond the endurance limit, thus the breakage/cracking of vials. The costs analysis shows that there is

an opportunity to save approximately $16,000 of operational costs involved due to the vial breakage issue.

To conclude, the process analysis of breakage and cracks in pharmaceutical vials using DMAIC problem solving methods provided the following. 1) An opportunity to produce vaccines for rare diseases safely by eliminating the possibility of vial cracking phenomenon. 2) Estimated cost savings of $16,000. Finally, this research concludes with a proposal of a step-by-step project plan with various levels of difficulty indicated by the colour codes, to eliminate the vial cracking phenomenon in the fill/finish process.

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Career Summary: ***Six Sigma-Green belt & VSME/VLFM certified***, Creative, analytical result-oriented Production/Manufacturing Engineer with 4 years of professional experience in Manufacturing, Continuous Improvement projects and supervisory roles.

SKILLS:

• Manufacturing Operations	• TPM (level 1 & 2)	• MS Visio	• CAPA	• MS Office
• 8D	• Lean Manufacturing	• Root cause analysis	• Minitab	• Value stream mapping
• Statistical Quality Control	• FMEA	• Six sigma-DMAIC	• Pareto chart	• Fishbone diagram
• Continuous Process Improvement	• Flow manufacturing-VSME	• Workforce Management	• MS PowerPoint	• Kaizen
• P&ID	• Toyota Production system	• Microsoft Excel	• Why-Why analysis	• 5S

EXPERIENCE:

AlbuRx Manufacturing Engineering Intern, – CSL Behring, Kankakee, US ***May 2020-July 2020***

- Identify root causes leading to the loss of 2000-1300 vials and proposed solutions to eliminate the loss.
- Assist with operations support including process optimization and defect elimination for the AlbuRx Filling department
- Stratified root causes for the non-conformities from given monthly data using Minitab and prepared trend analysis report.
- Conduct FMEA analysis for a bottle neck process and identified significant causes with low RPN which can be easily improved.
- Preparation of PM forms and SAP equipment creation form for the aseptic filling department.

Senior Engineer-Production, – Tractors and farm Equipment ltd (**TAFE**), Madurai, INDIA ***July 2015 – July 2019***

- **Production management**
  - Lead a team of 110 personals for Assembly of Tractors for the Pre-paint Chassis build cells (Cell 1,2,3 and 4WD assembly cells)
  - Responsible for Productivity, Line Efficiency, Line Capacity, Line stoppage, Consumable costs, RFT and DPU are achieved as per Target.
  - Abnormality identification through DWM implementation and support team members through CFT, QCC
  - Responsible for implementing engineering changes note (ECN) in shop floor.
- **Quality Management**
  - Tractor Roll down quality improvements through process adherence and process continuous improvements.
  - Conduct external and internal process audits for assembly process.
  - Quality verification activities for new product implementation (5P sign off)
  - Conducting Root Cause Analysis while implementing process improvement and cost reduction initiatives.
  - Used Six sigma approach to eliminate a defect occurrence by 80 %
- **Lean manufacturing and VSME**
  - Cycle time reduction using VSME resulted in increase of 100 HP tractors production from 2 per day to 8 per day.
  - Driving Rapid Continuous improvement through staff and engineers which generated 150 kaizens in the chassis assembly cells.
  - Line and load balancing, Human Efficiency improvement through VMAP 3and SWC

EDUCATION:

Master of Science - Industrial Engineering, University of Illinois (Chicago)-United States ***Aug 2019 – May 2021(Expected)***
Bachelor of Engineering - Mechanical Engineering, Anna university-India ***Aug 2011 – May 2015***

CAREER PROJECTS:

DPU Defect reduction of brake pedal un-even issue ***June 2018 – Dec 2018***
Skill: - MS Excel, Minitab, MS power point, Six sigma

- 80 % reduction of the number of occurrence (from 90 Occurrence to 27 occurrence)
- Process Capability study conducted for parts analysis & Engineering change note initiated.

Productivity improvement of 100 HP models ***Jan 2018 – May 2018***
Skill: - MS Excel, VSM, VMAP3, SWC, SWCD

- Utilized lean manufacturing tools to identify high cycle time operations.
- Increased the production of 100 HP models from 2 tractors per day to 8 tractors per day.

Enhancing Production Capability of T4 tractors -WINNER LSSEA'17(National level) ***Jan 2017 – Dec 2017***
Skill: - MS Excel, Lean Six sigma, MS Power point

- Cycle time reduction of 5700 sec in offline assembly
- Validated the identified potential causes, given high priority to de-bottle neck the high cycle time operations.
- Ramp up the production of T4 Models from 4 per shift to 10 per shift.

Design of Systematic process layout of engine finishing department-Simpsons & Co Ltd ***Nov 2014 – Dec 2014***
Skill: - MS Excel, Regression analysis, Motion study, time study, string diagram

- Proposed a design for the flow of engines in the engine finishing department, Optimizing operator movement.
- Efficiency, Availability, and overall productivity improvements taken as Targets.
- Estimated process efficiency improvement is 8 % (i.e. from 89 % to 98 %).