Implementation of Automated Visual Inspection Machines
in Biopharmaceutical Industry

by

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Sc.B. Mechanical Engineering, Massachusetts Institute of Technology, 2013

Submitted to the MIT Sloan School of Management and Department of Mechanical Engineering
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ABSTRACT

Currently, manual visual inspection is the gold standard for the required visual inspection of particulate matter in parenteral medicines. Automated visual inspection machines offer an opportunity for Amgen to improve efficiency, rate and consistency, while reducing its equipment footprint. However, the implementation of automated visual inspection poses challenges that need to be resolved. This thesis identified and developed solutions to three execution pain points: (1) low detection rates of dense particles in products; (2) misuse of automated inspection machines for product impact testing; and (3) ambiguous understanding of cost drivers when selecting an inspection method.

The pain points mentioned above were addressed separately. First, experiments with modified plunger surfaces were conducted to determine their effectiveness at agitating dense particles into solution where the particles could then be easily detected. Second, embedded sensors were identified as the sensor of choice to measure the mechanical stress history of products passing through an automated visual inspection machine. Experiments were designed to test the effectiveness of accelerometers to replace the limited range of gyroscopes' rotational velocity measurements. Third, a cost benefit analysis model was created that used discounted cash flows to calculate the net present cost of selecting automated visual inspection or manual visual inspection.

The results of these three work streams were promising. First, the experiments with modified plunger surfaces showed up to a 97% success rate of agitating particles into solution compared to an 11% success rate for the original plunger design. Second, experiments on accelerometers in embedded sensors showed that the accelerometers could measure centripetal acceleration that related to rotational velocity. A linear regression model was developed to relate accelerometer readings to rotational velocity within an accuracy of 50RPM. Lastly, the cost benefit analysis model confirmed expected drivers regarding the favorability of different inspection methods. The model also showed that automated visual inspection is the cheaper method of inspection, even with conservative estimates of cost of capital and false eject rates. A follow-up effort is necessary to achieve a more streamlined implementation of automated visual inspection machines throughout Amgen's manufacturing network.

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1 Background

This chapter provides a brief introduction to the biotechnology industry focusing on protein therapeutics. Additionally, this chapter will provide some background on Amgen, one of the leading companies in protein therapeutics. Lastly, a short introduction to visual inspection of injectable medication will be provided.

1.1 Biotechnology Industry Overview

Biotechnology or biotech is the utilization of biology to turn raw materials into useful products. The basic use of biotech has existed for centuries, with some of its earliest uses including the manipulation of yeast to brew alcoholic beverages like beer and wine. Discovery of the three-dimensional structure of DNA in 1953 was a major breakthrough in the biotechnology industry. Around the same time, Dr. Jonas Salk in 1955 produced the first polio vaccine through the use of mammalian cells (monkey kidney cells) [1]. This was the first use of mammalian cells to produce a vaccine. In 1970, restriction enzymes were discovered that provided a way to cut DNA into segments. This allowed researchers to isolate sections of DNA that were responsible for expressing proteins of interest. DNA ligase, which has the ability to link different fragments of DNA, was discovered in 1972. An understanding of DNA structure and the ability to cut (using restriction enzymes) and paste (using DNA ligase) was pivotal to the advancement of biotechnology as we know it today. Recently, CRISPR (clustered regularly interspaced short palindromic repeats) , utilized by bacteria for defending themselves against viruses, has been engineered for various purposes, in human cells and other eukaryotes. With this technology one can precisely alter the genomes of various organisms for numerous purpose. This opens up the possibility of treating humans with genetic diseases.

1.2 Amgen background

Amgen is one of the world's leading biologics manufacturing companies with a market cap of $117 billion [2]. In 2018, Amgen earned $23.7 billion in revenue and $8.4 billion in net profit [3]. Amgen was established in April 8, 1980 in Thousand Oaks, California by venture capitalists

William K. (Bill) Bowes and associates. Amgen, then called AMGen (Applied Molecular Genetics Inc.), explored different ways to apply genetic techniques commercially. Early experiments included cloning luciferase (the light source for fireflies) and producing indigo dye from engineered E. coli[4]. Amgen eventually decided to focus on developing protein therapeutic medicines to treat and cure diseases in humans. Amgen's first breakthrough drug was EPOGEN ™, which was created in 1983 and later obtained FDA approval for use in humans in 1989. NEUPOGEN™, Amgen's second blockbuster drug, was developed and got FDA approval in 1985. Currently, Amgen manufactures and sells nineteen products, including two biosimilars (KANJINTI™ and AMGEVIVA™)[5] [3]. The products span six therapeutic areas, including cardiovascular disease, oncology, bone health, neuroscience, nephrology and inflammation [5]. In addition to products already on the market, Amgen has 35 drugs in different stages of development[6].

Amgen is still headquartered in Thousand Oaks, California and has expanded to facilities in nine United States cities and fifty-five countries outside the United States. This adds up to approximately 20,000 staff worldwide [5]. In addition to its own network of manufacturing facilities, Amgen also works with contract manufacturing organizations all around the world. This extensive manufacturing network has enabled Amgen to supply millions of patients in approximately 100 countries[5].

1.3 Biotechnology in Pharmaceutical Industry

Medicine is a therapeutic substance that can be used to treat, prevent or cure a disease. The most common medicines used are chemical compounds, like aspirin. These medicines are usually referred to as small molecule, because they are not as large and complex in structure when compared with proteins. Small molecule drugs are produced by chemists in laboratories using chemical reactions. They are usually taken orally in liquid or solid form.

Biotechnology medicines are large molecules that are similar or identical to proteins or other complicated molecules that are necessary for the healthy functioning of the human body. Large molecule drugs have higher molecular weight and are very complicated in structure compared to

small molecules. The size, level of complexity of structure and delicacy of biotechnology medicines make them extremely difficult, if not impossible, to make from chemical reactions in a laboratory, like in the case of small molecules. Large molecule medicines have to be manufactured inside living organisms. The ability to alter the DNA structure of living cells using restriction enzyme and DNA ligase allows scientists to control the structure and composition of therapeutic substances produced by these cells.

Biotechnology medicines are developed by first identifying the gene of interest in DNA. The gene is then cut out from DNA using restriction enzyme. The gene is then placed into a vector like plasmids or bacteriophage with the help of DNA ligase. The vector is then used to carry the DNA into a host cell, which could be a bacterium like E coli or into mammalian cells like hamster cells. These cells are grown in a nourishing culture and are induced to produce the desired protein from the gene. The last step requires extracting the protein and preparing for use in patients.

Biotechnology medicines cannot be taken by patients the same way as small molecules. While small molecules are usually taken orally, biologics cannot be taken that way. The large and complicated molecular structure of biologics can be broken-down and/or altered by the digestive processes occurring in the alimentary canal. This means that all biotechnology medicines are parenteral drugs (administered or occurring elsewhere in the body than the mouth and alimentary canal). Injection is the most common way of administering parenteral drugs. This causes challenges as injections have higher requirements for quality as they bypass immune system mechanisms present in the digestive system.

1.4 Biopharmaceutical Manufacturing Process

As mentioned in section 1.3 above, identification and isolation of the target gene are very important to starting the development of a new biotechnology medicine. Once the gene has been identified, the biologic can be manufactured commercially. Biopharmaceutical manufacturing processes have four keys steps:

1. Creation of master cell line
2. Production of biologic

3. Isolation and Purification
4. Formulation, Filling and Finishing

1.4.1 Creation of Master Cell Line

The gene needed for the production of biotechnology medicine is introduced into cells. This process happens in laboratory controlled conditions. A small number of cells are genetically modified at first and tested to ensure that the target gene was successfully transferred. These cells are placed in petri dishes or flasks that contain a culture of nutrients. The cells that have the gene become part of the master cell line that is used as the starting point for the mass production of the biotechnology medicine.

1.4.2 Production of Biologic

Some cells are taken from the master cell line into a small bioreactor. The conditions in the culture are precisely controlled to ensure the rapid growth of the cells. The cells start off in small bioreactors and are progressively moved into larger and larger bioreactors as the number of cells grow. The initial bioreactors could be a couple of liters in volume and the final bioreactors could be up to 20,000 liters in volume. During this growth period the cells are induced to produce the target protein. The conditions in the bioreactor, like pH, temperature, oxygen concentration and nutrient concentration are constantly monitored. These conditions not only allow for the rapid growth and production of biotechnology medicines, but also prevent the growth of unwanted organisms, like yeast or bacteria, that would spoil the product.

1.4.3 Isolation and Purification

After the optimum concentration of the target protein in the bioreactor is achieved, the product has to be extracted. The desired biologic product is isolated from the cells and growth media. The isolated proteins undergo filtration techniques designed specifically to isolate and purify the protein based on its specific characteristics, like molecular weight and electric charge. The isolated proteins are then placed into bags or bulk frozen to be transferred to the next step of the process.

1.4.4 Formulation, Filling and Finishing

The purified proteins obtained after the Isolation and Purification step cannot be used directly in humans yet. The Formulation, Filling and Finishing step ensures the safety and effectiveness of biotechnology medicines during their storage, distribution and administration[7]. Proteins in biopharmaceuticals are not optimized for vitro (in glass) processes, but rather they are optimized for vivo (within living organism) biological processes[7]. The vivo processes determine how effective the protein is as medicine. During the formulation step, excipients are added to improve the stability of large molecule drugs towards vitro processes and conditions the drugs are exposed to before administration. Additionally, the formulation step includes dilution of the product to the right concentration for it to be administered.

After the formulation step, the mixture is filtered again before filling occurs. Typically, automated filling machines are used to fill drug containers. Accurately controlling the fill volume is important to ensure patients receive the right amount of dosage of drugs. Filling is conducted in clean rooms to reduce the chance of contamination of the product by particles and/or pathogens. Containers are usually sealed immediately after filling to prevent contamination during distribution.

Finishing is the final step of the process. Sealed containers are visually inspected to ensure that they meet quality standards. Potential defects are particles in the solution, cracks and issues with the seals. Defect free products are then labeled with the appropriate information that is specific to the region where the medicine will be sold. The labeled products are then packaged to protect them from damage caused by ambient stresses, like temperature and mechanical shock that could damage the protein or the drug container. Figure 1.1 below outlines the sequence of steps during Formulation, Fill and Finishing for vials. This project will focus on the visual inspection for particles sealed products.

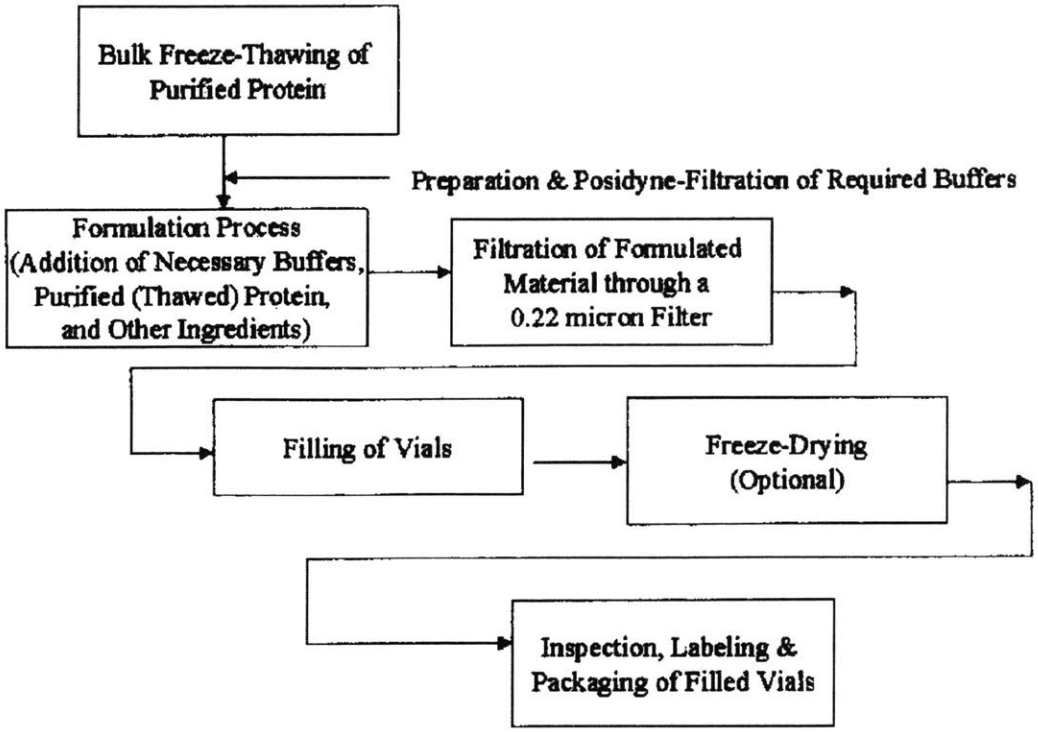

Figure 1.1: Diagram of the sequence of formulation, fill and finishing steps for vials[7]

1.5 Visual Inspection at Amgen

Inspection of products before they are shipped to patients is an important step in the manufacturing process to ensure quality products reach customers. There are a number of visual inspection quality checks performed on drugs, including plunger level and label checks, but this thesis is going to focus only on detecting unwanted particles in medicines. Inspection of visible particulates in parenteral drugs is required by law and is regulated by Chapter 790 of the United States Pharmacopeia (USP). Particulate matter is defined in the USP <788> (Particulate matter in injections) is "extraneous mobile undissolved particles, other than bubbles, unintentionally present in solutions." Examples of such particles include fibers, glass and metal that are introduced into the medication during the manufacturing process. 100% visual inspection is required for all the units. Visual inspection is done to demonstrate that the drug products are "essentially free of visible particles" [8]. The use of the term "essentially free of visible particles" hints toward the probabilistic nature of detecting the particles in the drugs. The probability of detecting defects

depends on a number of environmental factors, like light intensity, so the USP has provided additional information on the inspection environment and process. The requirements are as follows:

- Minimum illumination intensity has to be between 2000 and 3750 lux
- Drugs have to be viewed against a white background and against a black background
- No magnification
- Five seconds viewing against each background
- Swirl and/or invert product ensuring no bubbles are produced
- No labels and the container's outside surface has to be washed and dried

In order to satisfy the USP requirements of "essentially free of visible particles," the pharmaceutical industry uses three methods of inspection: manual visual inspection, semi-automated visual inspection and automated visual inspection. Amgen utilizes all three of these inspection methods across their manufacturing network.

Aside from regulatory requirements, inspection reduces the risk of sending bad products to patients that could result in negative outcomes. Inspection also provides a way for Amgen to determine if the manufacturing process is in control and identify, through root cause analysis, how improvements can be made to the process.

1.5.1 Manual Visual Inspection

The USP defines the requirements for visually inspecting parenteral drugs from the perspective of a human operator manually looking at the product with no magnification. This makes manual visual inspection the industry standard that the other two methods are compared against. Trained inspectors sit in inspection booths like the one shown in figure 1.2.

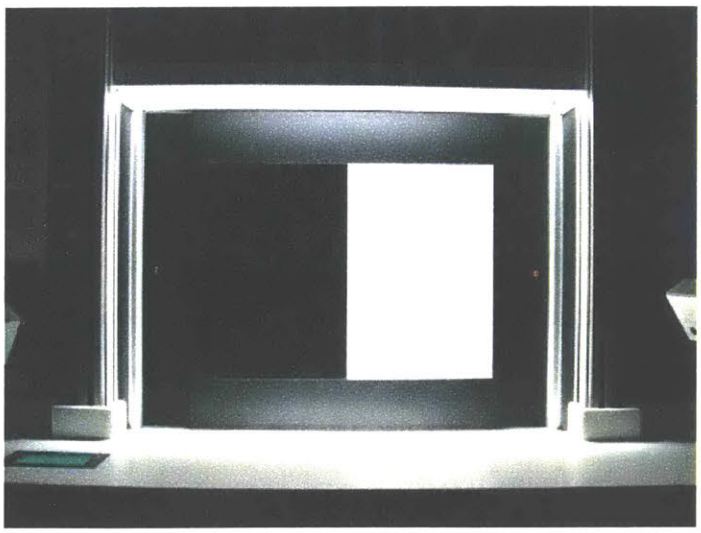

Figure 1.2: Illuminated manual visual inspection booth

Figure 1.3 shows an illuminated visual inspection booth with the black and white backgrounds, which are used to improve contrast to detect light reflecting and light absorbing particles respectively.

The booths are illuminated either from the top or top and bottom, and have black background and white background. The operator manually picks up the product and gently swirls and/or inverts the container in front of each of the backgrounds. While doing this, the operator inspects the product in order to detect any particles and other defects in the product. The operator has to at view each product against each background for at least five seconds to meet the minimum requirements, but in practice operators take longer to ensure that they are adequately identifying defects.

Unfortunately, visual inspection does not gurantee 100% detection of all defects. The chances of the operator detecting particles depend on the following factors:

- Illumination (intensity and glare)
- Contrast (white and black backgrounds)
- Duration of inspection
- Agitation (mobility of particles)
- Number of particles
- Product type (color, density, etc.)

- Container type (thickness, tranparency etc.)
- Particle size

The effect of particle size on the probability of detection has been the subject of many studies. Because of the variation in the results of these studies, it is difficult to define what is the "minimum visible" particle size that should be detected in visual inspections. Figure 1.4 below shows how the probability of detecting particles varies with particle size in six different studies. Generally, as particles get bigger, the probability of detecting them increases, but different studies do not agree on what the detection probability is for any particle size. For example, the probability of detection for a 100 micron paticle varies from 20% to 70%.

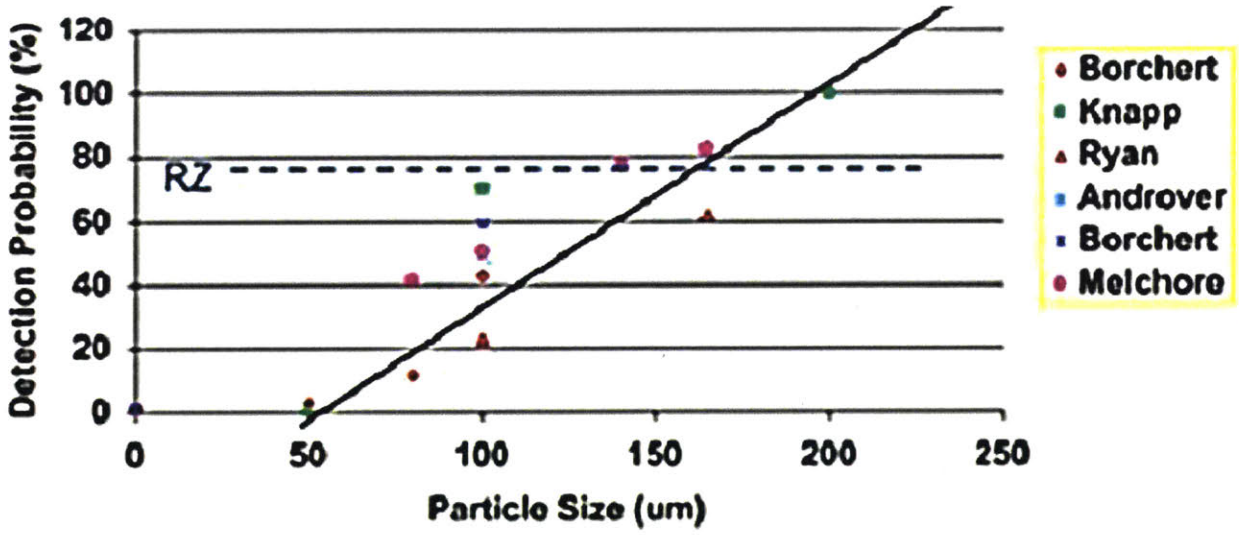

Figure 1.3: Manual visual inspection performance by particle size and study [9]

Because of the probabalistic nature of the manual visual inspection and the variation in inspector performance, an additional post 100% visual inspection quality check is required for all parenteral drugs. Samples from the inspected products are inspected again by quality control to ensure that the inspection process is effectively detecting defective products within Acceptable Quality Limits (AQL). Additionally, products that are determined to be defective by inspectors are also reinspected if the rejection rate goes above product specific acceptable levels. If the defect rate is truly high, destructive forensic analysis may be performed to understand the root cause of the increase in defects. This serves as a way to verify that the manufacturing process is still under control.

Visual inspectors have to undergo qualification in order to limit the variation within inspectors and reduce the variability associated with having human inspectors. Inspectors must pass an eye exam before training. Most pharmaceutical companies require 20/20 near focus vision and passing color blindness test [9]. Inspectors are taught the importance of detecting defects and trained on the standard operating procedure for inspecting each specific product, given the variation of defects in products. A typical inspector has an eight hour shift and is allowed to take multiple eye rest breaks throughout the day to reduce eye fatigue. Inspectors typically have to demonstrate patience and ability to perform tedious work for long periods without losing focus[9].

Trainees are given a series of defect test sets that contain a wide range of defects that inspectors are expected to catch as part of the training process. Once a trainee has completed training they are given a "challenge set" of containers that has a mixture of characterized defects (created in a lab to specific size and material requirements) and good containers. The trainees have to demonstrate an ability to identify and characterize defects to an acceptable level before being qualified. Because of the probabalistic nature of detection of defects, a baseline for acceptable performance has to be established with trained inspectors. Containers that are rejected less than 30% of the time are "Acceptable," ones that are rejected more than 30% of the time but less than 70% of the time are "Grey Zone," and containers that are rejected 70% of the time are "Rejects" [9]. Qualified inspectors must be able to detect the "Rejects" in the challenge set to an acceptable level. Containers in "Acceptable" and "Grey Zone" that are rejected by inspectors are called false rejects as these were considered acceptable products. The level of allowable false rejects is a business decision, as this is lost revenue that the company could have earned but does not affect the quality of products that reach the patients. Companies typically use the allowable false rejects as a buffer to ensure the "Rejects" are detected [9]. After inspectors are qualified, they are required to perform requalification that includes eye tests and tests with challenge sets at a predefined cadence.

1.5.2 Semi-Automated Visual Inspection

Semi-automated visual inspection is somewhere between manual visual inspection and automated visual inspection. Just like in manual visual inspection, it relies on a human inspector to make the

decision of accepting or rejecting a product. However, semi-automated inspection operators don't manually handle the product—instead, a machine passes the product in front of the inspector. This allows for the product's handling and inspection time to be consistent across units. Also, semi-automated machines offer additional optional features that help reduce inspection time, like lighting configurations, and rotation of product. Semi-automated inspection machines can inspect up to 6,000 units per hour[10]. In order for semi-automated machines to be qualified to inspect products, studies have to be conducted to demonstrate that the detection probability is either equal to or better than manual visual inspection. An example of a semi-automated inspection machine is shown in figure 1.5. Semi-automated inspection was not a focus of this project.

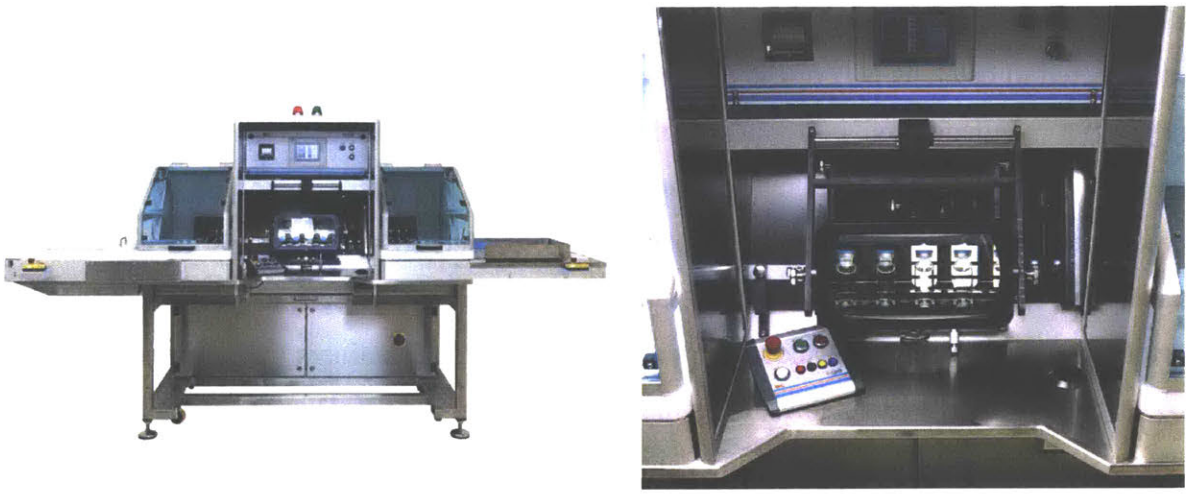

Figure 1.4: Semi-automated visual inspection machine

1.5.3 Automated Visual Inspection

Automated visual inspection is the last of the three non-destructive methods used for inspection of parenteral drugs. As the name suggests, the machine performs the handling and detection of defects without the intervention of humans. Automated machines utilize software and a number of technologies to detect particle defects, including visual cameras, laser sensors, light resistance, opt-eletronic method and static division (SD) sensors[10] [11]. Technology development in computer vision is showing potential to improve detection and characterization of particles.

Static Division (SD) sensors date back to the 1970s and remain a common method of detecting particles.The figure 1.6 below shows the basic setup of the system. Light from a light source is

passed through a condenser lens and the product. The emerging light is detected by a single array of diode "bits" that measure the light intensity and converts it into an electric signal. To distinguish between particles that are inside the product and those on the outside, the unit is spun to high rotation speeds above 1,500 RPM and then abrubtly stopped. This results in particles on the outside of the product stopping while particles in the solution continue to move, because of the inertia of the liquid. Particles are detected by observing the change in light intensity as particles move within the solution, creating a moving shadow. Figure 1.6 shows an example of how three different "bits" in the diode array respond to a particle moving in solution. By setting the right sensitivity threshold, particle defects can be detected.

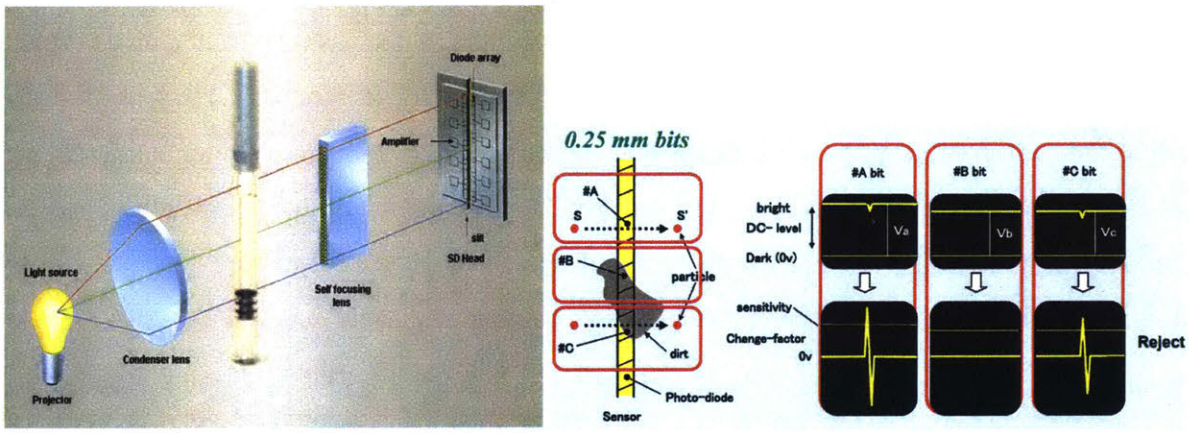

Figure 1.5: Static Division (SD) sensor particle detection operation [12]

Cameras in automated visual inspection machines also take advatange of the same spin and stop sequence used with SD sensors to identify particles in the product. Each camera can take up to 24 images of the product just after stopping rotation and use image processing software to identify particles that are still moving in the solution [12] [13]. Figure 1.7 below shows how the system works. Automated visual inspection machines typically consist of as many as 15 inspection stations with different technologies to detect different types of defects in the product [10].

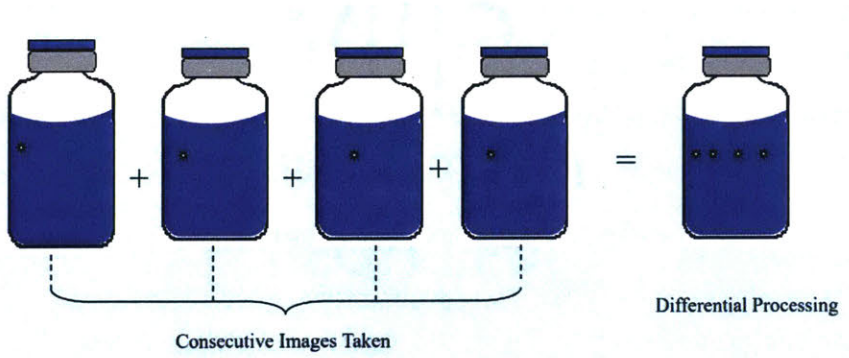

Figure 1.7: Particle detection using image process software [12]

Products that are suspected to contain particles by automated visual machines, or "ejects," are sent to be reinspected by manual operators. This is because automated inspection machines typically have a high false eject rate[11]. The high eject rate is caused by vibrations, variations of ambient lighting, and differences in transperancies and dimensional tolerances of the container[9]. High eject rates are also a result of having high sensitivity in the machine settings, which is necessary to reduce the probability of bad products being accepted. Ejected units are inspected by two different inspectors before they can be accepted as being particle free.

Automated visual inspection is the fastest of the three inspection methods, with rates as high as 36,000 units per hour[13] [10]. Automated visual inspection machines offer a very consistent defect detection rate that is not affected by operator fatigue. However, procurement and qualification of automated visual inspection machines is resource intensive. Also, it takes a long time to get the fine-tuning of detection software and hardware settings to an acceptable balance between false rejects and false accepts. As with semi-automated inspection machines, automated inspection machines have to be proven to detect defects with a probability that is at least equal to that of manual inspection. Table 1.1, shows a summary of the pros and cons of automated visual inspection and manual visual inspection.

Table 1.1: Pros and cons of manual and automated visual inspection

	Manual visual inspection	Automated visual inspection
Pro	• Flexible • Shorter per SKU qualification process • Low capital requirements • Rapid training	• Consistent inspection performance • High inspection rate (36,000 units/hr) • Can be validated • Smaller per inspected unit footprint
Con	• Low inspection rate • Inconsistent performance across inspector and time • Can not be validated • Ergonomic issues • Higher safety concerns • Higher per inspected unit footprint	• Higher capital cost • Longer per SKU qualification process • Prone to container damage • High maintance cost

1.6 Strategic significance of Automated Visual Inspection for Amgen

Manual visual inspection is the current gold standard in the pharmaceutical industry. This may change in the future with the advent of technology, product changes and changes to regulations. This section will explore how automated visual inspection could be used at Amgen as a strategic advantage.

1.6.1 Regulatory Uncertainty

As discussed in section 1.3, United States Pharmacopeia (USP) regulates the inspection of particles in parenteral drugs. The current requirements for inspection are defined according to human visual ability. With the advent in technology, there is a regulatory compliance risk that inspection requirements will be tightened to a detection probability greater than those of human inspectors.

The current requirements for visual inspections do not take into account the nature of the particles in the solution. Particles can be made of different material and so have different effects on the patient's body[14] [15]. For example, particles created by protein aggregation can trigger immune responses in patients [7]. Particle type characterization might eventually become required as regulations start to take a patient risk based approach to inspection. Products with particles that have a high risk of causing negative patient outcomes should be rejected, while products with inert particles or beneficial particles could be allowed to reach patients.

Additionally, regulators like the FDA have already developed frameworks for inspecting sub-visible particles in parenteral drugs [16, p. 4]. These frameworks are currently non-binding recommendations, but could very well become requirements in the future. This could present a tough challenge for Amgen to make all inspections automated, or at the very least, manual with magnification, in order to detect the sub-visible particles.

1.6.2 Competitive Advantage on Quality

Delivery of high quality product is very important in the pharmaceutical industry. Companies can be held accountable for negative impacts their products cause as a result of lapses in quality. One recent example is Johnson & Johnson, which was ordered to pay $4.69 billion to 22 women over allegations that their products gave them ovarian cancer[17]. Rulings like these not only cause financial distress for companies, but can also cause long term damage to the brand of the company. Most importantly, quality issues can hurt patients that Amgen strives to serve. Executing an automated visual inspection could reduce the risk associated with variability in human inspections.

Amgen has the potential to use the quality of its products to differentiate itself from other pharmaceutical companies. The U.S. Congress passed the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, allowing for shorter FDA approval processes for biological products that are biosimilar or interchangeable with FDA-approved biological product[18]. This means that product differentiation is becoming more important as biosimilars, which are typically lower cost than original drugs enter the market. Amgen can differentiate its products through quality. Automated visual inspection machines offer consistency across all inspected products that can provide reliable quality to patients.

1.6.3 Operational and Efficiency Improvements

Automated visual inspection machines offer potential operational and efficiency improvements. The high inspection rates offered by automated inspection machines would allow Amgen to respond quicker to changes in customer demands for products, and so require less inventory to be stored to meet these fluctuations. Implementation of automated techniques to identify the nature of the particles in the products would provide good feedback to upstream manufacturing processes to more quickly identify and fix issues that might be impacting product quality and potentially product supply. A tighter control on the manufacturing process will lead to an increase in manufacturing efficiencies as less products will be rejected as defects.

2 Project introduction

The development of recombinant DNA technology in the late 1970s spurred the growth of biotechnology, revolutionizing medical treatment as we know it today[7]. However, the protein nature of these drugs means that they can not be take orally, as the digestive system can break them down into their constituent amino acids, rendering them ineffective. In order to deliver the medication in its effective state, protein based drugs are usually administered as injections to patients. Injections bypass a number of the human immune system defense mechanisms and so it is important to ensure that the drugs are not contaminated. During the biopharmaceutical manufaturing process, unintended particles could be introduced into the product. These particles could be aggregated proteins, glass, metal, rubber, fibers, cotton, silicone oil and rubber [15] [7] [14]. These particles, depending on their size and material, can cause mechanical pulmonary artery obstructions, injection site reactions, negative impacts on organ function, immune responses and blood clotting disorders [14], [7], [15]. There are reported cases where particles have even led to patient deaths[19].

A number of mechanisms are employed throughout the biomanufacturing process to exclude particles from the final product. These include filtration, using clean rooms and washing product containers right before filling [7], [15]. Even with all these processes in place to limit the chances of particles in the final product, final 100% visual inspection is still necessary and required by law according to Chapter 790 of the United States Pharmacopeia (USP). This ensures that all the defects that could have been introduced during manufacturing, are identified and removed before they leave the manufacturing facility.

Manual visual inspection is the standard for final product inspection in the biopharmaceutical industry. All other methods, automated visual inspection and semi-automated visial inspection, have to be shown to detect defects with a probability equal to or better than that of manual visual inspection. Automated visual inspection and semi-automated inspection both offer advantages over manual visual inspection, including improved inspection rates and greater sensitivity to particles in parenteral drugs. This project will only focus on automated inspection machines.

Amgen currently utilizes a mix of manual, semi-automated and automated visual inspections, both at its internal manufacturing sites and contract manufaturing sites. There is an internal driver within Amgen to improve operational effiencies and product differentiation. One potential way to achieve this goal is by improving its final product inspection capabilities. Automated visual inspection has great potential to boost performance and consistency of final product inspection at Amgen manufacturing sites and at contract manufacturing sites. The focus of this thesis will be to solve some of the challenges that Amgen and the biopharmacuetical industry are facing with implementing automated visual inspection for parenteral drugs.

2.1 Project goals

The goal of this project is to address business and technical challenges Amgen is facing with the implementation of automated visual inspection machines at its internal manufacturing and contract manufacturing sites. After conducting interviews with key stakeholders at Amgen, three challenges were identified to be the focus of this thesis:

1. Detection of dense particles in solution
2. Disruption of automated visual inspection machine processes by product impact testing
3. Lack of a cost model for deciding between automated visual inspection and manual visual inspection

This project aims to develop tools and processes that would make the smooth implementation of automated visual inspection across Amgen's manufacturing network a reality. Additionally, the project aims to develop a better understanding of some of the limitations of automated visual inspection and identify cases where manual visual inspection would be a better fit.

2.2 Project approach

Visual inspection at Amgen involves at least 14 different stakeholder teams. Having a good understanding of the main pain points and getting stakeholder engagement is crucial to the goals of this project. After initial stakeholder meetings, three work streams were identified. The work streams are as follows:

1. Improvement of dense particle detection

2. Elimination of use of automated visual inspection machines for product impact testing
3. Development of a cost model for making decisions between automated visual inspection machines and manual visual inspection machines

These work streams will be dealt with individually in the following chapters. The approach and results for each work stream will be discussed in those chapters.

3 Dense Particle Detection

Particles in parenteral drugs can cause negative patient outcomes. It is important that automated visual inspection machines detect the presence of these particles before they reach patients. This chapter will discuss the techniques used to detect particles using automated visual inspection machines and outline challenges associated with detecting dense particles, like glass and metal in parenteral drugs. The chapter will also cover the development of a patentable technical solution to reduce false accepts during the inspection process. Lastly, this chapter will show results of experiments conducted to test the efficacy of the technical solution.

3.1 Particle detection in automated visual inspection machines

As discussed in Section 1.5.3, automated visual inspection machines utilize a combination of hardware and software to detect particles. Static Division (SD) sensor and video cameras are the popular hardware sensors used to detect particles [10], [13], [20]. Static Division (SD) sensors detect the change in light intensity caused by shadow particles as they move around in solution. Video cameras on the other hand mostly use image processing software to detect particles in solution. In both Static Division and video cameras, the motion of particles in solution helps the automated visual inspection machine differentiate between particles in the product and those on the outside of the container. Particles on the outside of the container do not affect the product quality and so are not rejects. Section 1.5.3 provides a more detailed description of the technique used to differentiate between particles in solution and those on the outside of the container.

Automated visual inspection machines try to get particles into solution to improve their detection. The machines usually rely on spinning the product at a high rotational speed, abruptly stopping the rotation and then inspecting for particles. This process in shown in the figure 3.1 below:

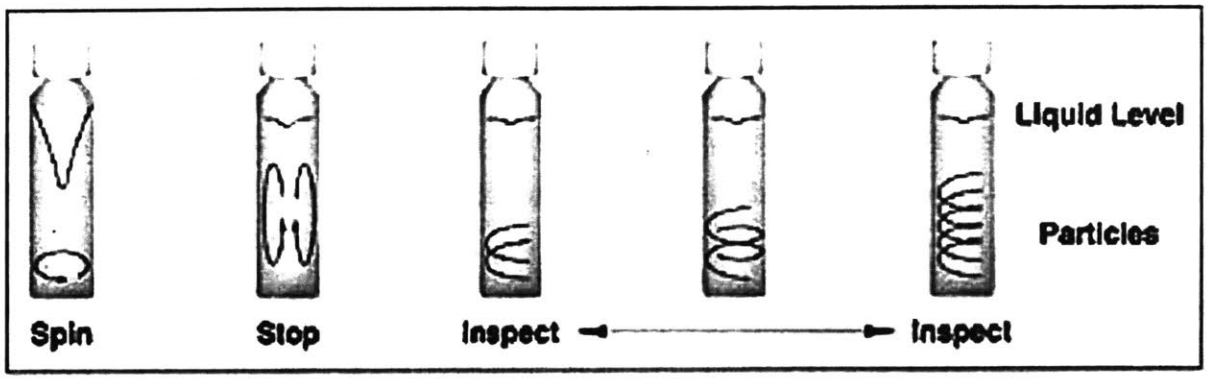

Figure 3.1: Visual inspection machine spin and stop sequence to detect particles [21]

When the product is spun at a high rotational speed, usually above 1,500 rpm, a vortex is created in the liquid. The liquid surface in the rotating product forms a parabola whose shape depends on the rotational speed of the container [22]. When the rotating container is stopped suddenly, the parabolic shape of the liquid collapses, creating eddy fluid flow within the container. This flow causes particles to move around in the product. The motion of particles in solution, as mentioned earlier, helps with distinguishing between particles in product from those on the outside of the container.

Unfortunately, dense particles like glass and metal, are harder to get into solution, and tend to stay at the bottom on the containers where they are harder to detect. Since the lift force generated by the spin and sudden stop process increases with higher spin speeds, higher rotational speeds are needed to get dense particles into solution where they can be detected. However, there is a limit to the rotational speed that can be used in automated inspection machines. The increased mechanical stresses caused by very high rotation speeds may also cause proteins in the drugs to be damaged, rendering the medicine ineffective or causing negative patient outcomes [23].

3.2 Improved Dense Particle Detection

As explained in section 3.1 above, getting dense particles into solution where they can be detected is difficult, because of the potential damage to protein molecules from high rotational speeds. This

section will discuss an idea for improving suspension of dense particles in solution through modification of plunger surfaces.

3.2.1 Hypothesis

Modified plunger surfaces can increase the turbulent flow in spinning drug product. The turbulent flow caused by the features on the plunger will lift dense particles into solution where they can be more readily detected by automated visual inspection machines.

The figure 3.2 below illustrates how the surface features would create a fluid streamline that could lift the particles into solution. Introducing surface features will alter the fluid streamlines close to the plunger surface, potentially lifting particles into solution

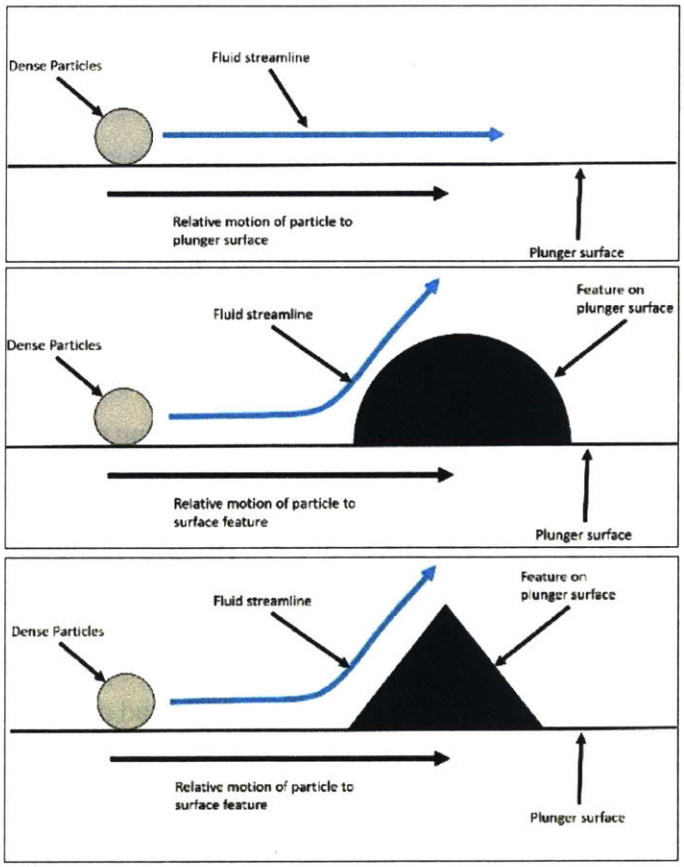

Figure 3.2: Fluid streamlines under different surface features

3.2.2 Potential benefits

If the hypothesis that creating features on the plunger surfaces can lift up dense particles holds true, there are a number of potential benefits to automated visual inspection. Firstly, dense particles moving around in solution can be more easily detected by current automated particle detection techniques than if they were at the bottom of containers. Secondly, the dense particles moving in solution can be differentiated from stationery non-contaminant particles on the outside surface of the product container. Thirdly, there is the potential to reduce the rotational speed that is needed for reliable inspection of particles in drugs. Lower rotational speeds have two potential benefits—reduced risk of damaging proteins from high elongational stresses and decreased wear on automated inspection machines' mechanical components.

3.2.3 Materials

Experiments were conducted using syringes. Syringes were chosen for this experiment over vials, because it was easier to modify the surface of plungers in syringes compared to altering the bottom of vials. A standard 1 ml syringe made of Crystal Zenith™ was chosen for the experiment, because Crystal Zenith™ is clear and more breakage resistant than glass syringes.

Protein based parenteral drugs are sensitive to ambient conditions and have to be maintained within a controlled environment. This poses a challenge when conducting experiments as the product can easily degrade while performing tests. A mimic solution for one of Amgen's products was used for the experiments. The mimic solution shares similar physical attributes to the pharmaceutical product, like viscosity and surface tension, but is more stable in standard room conditions than the drug. This means that mimic solutions can be used to replicate the physical behavior of the product during experiments. The mimic solution used for experiments had a viscosity of 9.2 cP, density of 1.043 g/cm^3 and surface tension of 51.69 mN/m.

The plungers for the syringes were fabricated using a Form 2 stereolithography (SLA) 3-D printer, with 50-micron layer thickness (axis resolution) and 140-micron laser spot size [24]. Formlabs Flexible resin was used as the material, because its flexibility formed a good seal while still being hard enough to retain its shape during testing. Plungers with different diameters were printed to

find the right fit that allowed easy insertion into the syringe and ensuring that it was an integral unit.

Glass spheres were chosen to be the particles in the experiments. The glass spheres had a density of 2.4-2.6 g/cm^3, about 2.3-2.5 times denser than the mimic solution. The particles had a diameter of 400 microns (22-micron standard deviation and 5.5% coefficient of variation) and were clearly visible to the naked eye. The density and size of the glass spheres make them difficult to suspend into solution. The glass spheres represented one of the more challenging particles for automated visual inspection machines to detect.

3.2.4 Experiment procedure

The first step to performing the experiment was the assembly of the syringe and plungers. Original plungers were used as the control to test the efficacy of the modified plungers. The assembly process had to replicate the conditions that were in a typical 1 ml syringe product. 1 ml of mimic solution was carefully measured and introduced into clean syringes. Great care was taken to avoid the creation of bubbles that could look similar to the glass spheres during the testing. After the mimic solution was added to the syringe, one glass sphere was added to each syringe.

Pressure inside the syringe after assembly of the syringe and plunger is another variable that could affect the results of the experiments. Air compressed during the assembly process can push back the plunger resulting in a bigger air pocket in the experimental sample than would be expected in commercial product. The figure 3.3 below shows the assembly process of the syringes and plungers. The coffee stirrer acts as a flexible hollow tube that allows air to escape while the plunger is being pushed into the syringe by the piston. The plunger depth into the syringe stayed at the same level as that of commercially produced 1 ml syringes of the product.

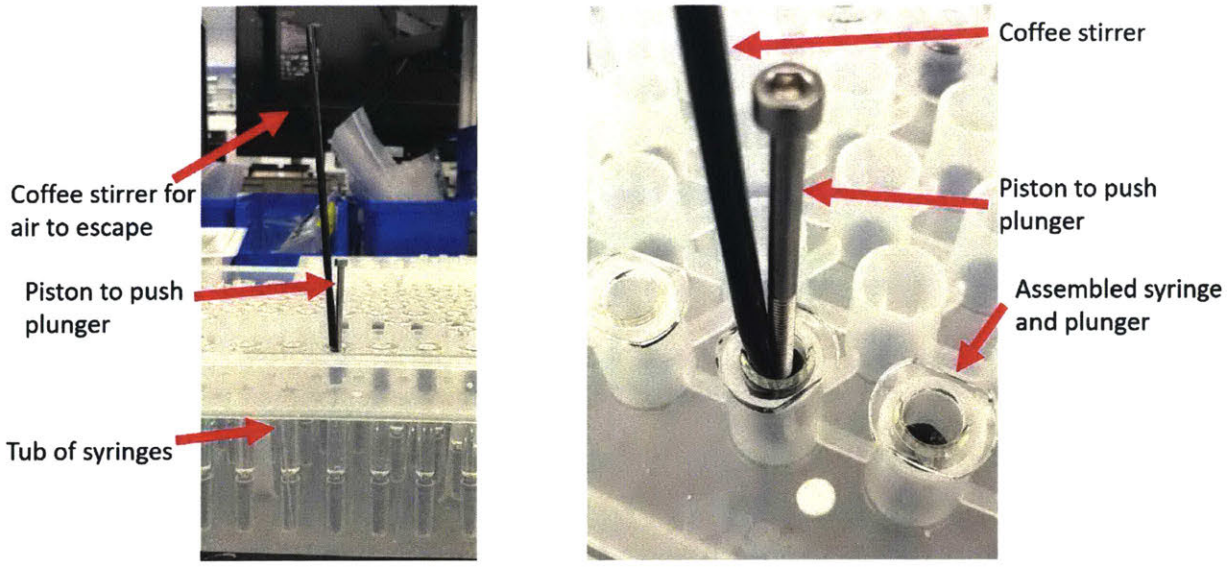

Figure 3.3: Syringe sample assembly process

Assembly process of syringe and plunger is in figure 3.3. The picture on the left shows the zoomed in version of the picture on the right. The coffee stirrer allows air to escape while the plunger is pushed into the syringe.

An Amgen SpinCam was used as the test setup. The Amgen SpinCam consists of a camera to take pictures of the product, an electric motor to spin the product and red LED lights to provide illumination for the experiment. The setup is designed to replicate conditions in an automated visual inspection machine. The figure 3.4 below shows the setup.

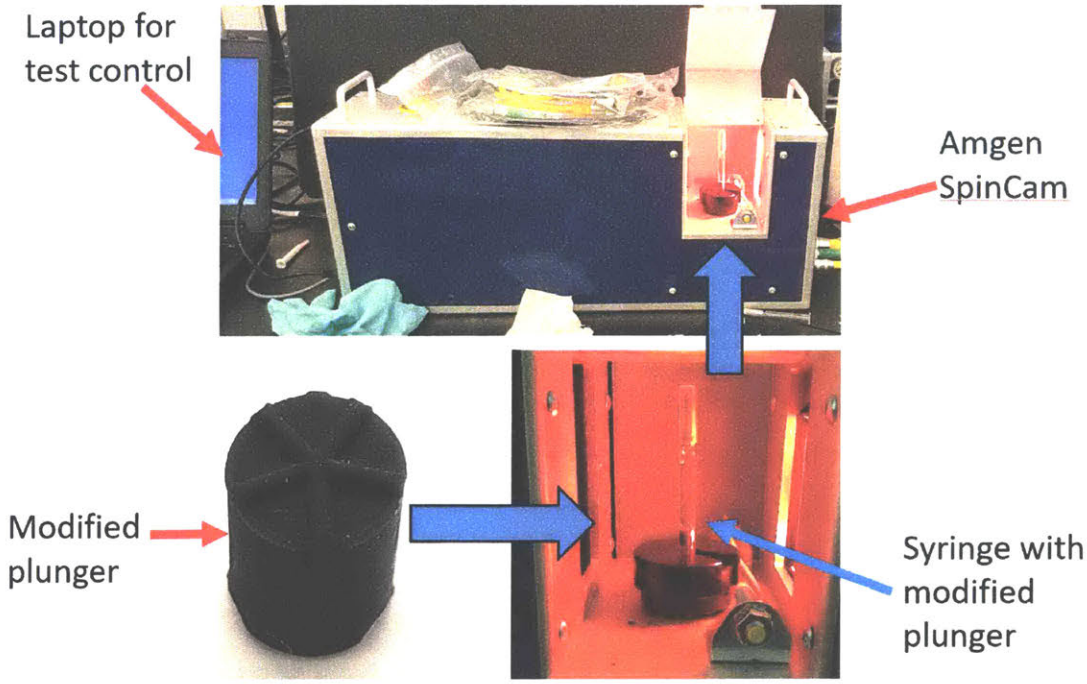

Figure 3.4: Experimental set up, showing plunger surface, syringe and SpinCam

The spin charateristics, acceleration, rotational speed and duration of spin are all controlled via Amgen proprietary software on a laptop that connects to the SpinCam. 3,500 revolutions per minute was used for all the experiments. The syringes were rotated for three seconds before being abruptly stopped. Pictures were taken while the syringes were spinning and for a second after the spinning stops. The exposure of the camera allowed for glass platicles to be observed as white streaks as they move through solution.

After the experiments, the acquired images were analyzed using ImageJ software from the U.S. National Institutes of Health (NIH) image processing software[25]. ImageJ was used to count the number of pixels between the top of the plunger surface to the midpoint of the white streak of the glass particles. The pixel count was coverted into length units by measuring features of a known height as a reference. One pixel corresponded to 20.7 μm ± 0.6 μm.

3.2.5 Experiment Variables

The original plungers were used as controls for the experiments. The surface of the plungers was modified to see how surface features affected the agitation of dense particles—glass spheres in these experiments—into solution. The plunger surface features were all ribs that varied in shape, number of features and size of features.

3.2.5.1 Shape variation of ribs

Two different shapes were used in the experiments, half cylinder and wedge profiles as shown in figure 3.2. The features stretched from the edge of the plunger to the middle of the plunger. The wedge and half cylinder profiles are chosen because of their symmetry. This allows them to have the same effect regardless of the direction of spin of the product. Profiles with steeper angles of attack were not chosen because of the risk of causing cavitation and bubbles that could damage proteins.

3.2.5.2 Feature size

Another variable that was tested is the effect of changing the size of the features. For this variation, only half cylinder profiles were used. The feature sizes were varied from 250 microns to 1,250 microns in increments of 250 microns. This meant there were five different sizes of the half cylinder profiles.

3.2.5.3 Number of feature variation

The number of features was also varied. Modified plungers were created with one, two and five features. This full variation was only done on half cylinder profiles. Wedge profiles only had experiments with two and five features. The figure 3.5 below shows the arrangement of features on the surface of the plungers. Figure 3.6 below shows plunger surfaces with a varying number of features and varying heights.

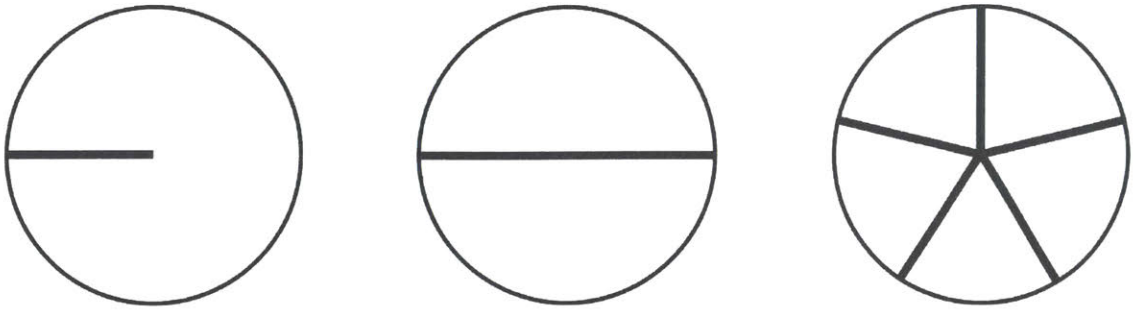

Figure 3.5: From left to right, one feature, two feature and 5 feature arrangement on plunger surface

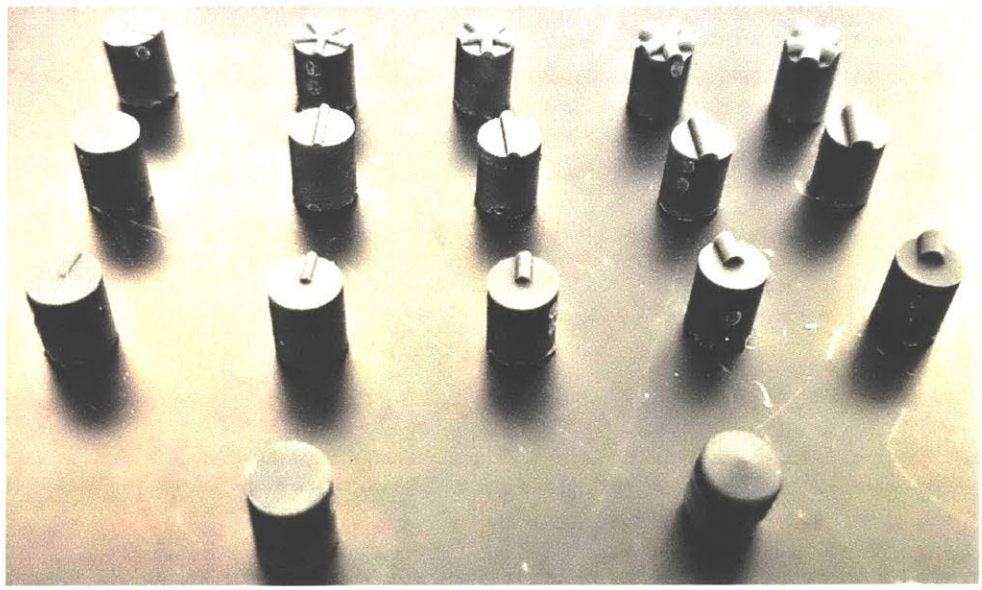

Figure 3.6: Plungers with modified surfaces. Feature size is increasing from left to right

3.2.5.4 Angle of attack variation

The last variable in the surface features was the angle of attack. This was varied on the wedge profile as a varying angle of attack was not applicable to the half cylinder profile. The angles of attack tested were 30 degrees, 45 degrees and 60 degrees. The height of the features was maintained constant at 1 mm for the different angles of attack. Most of the angles of attack were only tested with two features. The 45-degree angle of attack was also tested at 500 microns and five features.

3.2.5.5 Flat or no feature

Original plunger surfaces are very smooth and have a low coefficient of friction compared to the 3-D printed plungers. A difference in agitation of particles into solution could very well be caused by the difference. To test this potential, flat plunger samples with no features were also created. This allowed for the verification that the surface features influenced the particle suspension rather than the change in surface roughness. Flat plungers did however differ from original plunger surfaces that are slightly conical in shape. The figure 3.7 below shows a side by side comparison of the flat plunger surface versus original plunger. The plunger on the right is the original plunger shape.

Figure 3.7: Flat plunger on the left and original plunger on the right

3.2.6 Results

There are a high number of variations in surface features that were tested during experiments. The experiments were conducted in two phases: (1) picking the best features and (2) verifying the significance of results. The results from the different phases will be discussed separately below.

3.2.6.1 Best Features

The best feature selection involved making one sample of each variation. Each sample was tested at least three times in the experimental setup. The effectiveness in agitating particles into solution was measured using the ImageJ software. The results summarized below are grouped into the

number of features for the half cylinder features and according to angle of attack for the wedge-shaped features

Half-cylinder Five Features

The 1250μm and 1000μm features showed very inconsistent suspension of the glass particles. The 1250μm and 1000μm samples resulted in zero out of three trials, and one out of three trials were successful in getting particles into solution respectively. The remaining samples with 250μm, 500μm and 750μm were successful in suspending particles in all three trials. The particles were on average raised to 535μm, 1099μm and 651μm by the 250μm, 500μm and 750μm features respectively. Therefore, out of the five feature samples, 500μm was the best feature in terms of consistency and height the particles were lifted into the solution.

Half-cylinder Two Features

Only 250μm and 1250μm samples had all three trials resulting in suspension of particles. The average heights measured during those trials were 473μm and 666μm, for the 250μm and 1250μm samples respectively. The 500μm sample was accidentally tested five times instead of the usual three times. Three of the experiments resulted in suspensions, with an average of 1122μm, but the experiments that resulted in no suspensions dropped the average to 677μm. Even with the zeros, the 500μm sample still had the highest average height achieved by the glass particle in the solution. The 750μm and 1000μm samples had the least number of successful suspensions, with two and zero out of three respectively. The 750 sample had an average particle height of 244μm.

Half-cylinder One Feature

Only 250μm sample had a 100% success rate in getting particles into the solution with an average height of 507μm. 1250μm sample had the next best performance, with a two out of three success rate and an average of 349μm. Both 750μm and 1000μm samples had only one success and an average particle height of 154μm and 161μm. The 500μm sample was the only one that was not successful in all of its three experiments.

Half-cylinder Summary

One feature samples had the lowest success rate at agitating particles into solution with 8 out of the 15 trials (53%) successful. Five feature and two feature had 5 out of 15 trials (67%) and 6 out of 17 trials (65%) being unsuccessful. From these results, the five feature design is the best. Across the different feature number and feature height combinations, five feature and 500μm has a 100% success rate of suspending the glass particles, and also has the highest average particles height. This combination was best in the experiments conducted. However, further tests are needed to verify the significance.

Two Feature Wedge

Only two feature wedge-shaped units were tested during the initial phase of the experiments. All the wedges had a height of 1000μm, but varied in angles of attack. The angles of attack tested were 30-degree, 45-degree and 60-degree. All three samples were tested four times. The 45-degree angle of attack sample was the only one with 100% successful suspension of particles. It had glass particles reach 658μm on average. The 30-degree sample had the next best success rate with three out of four (75%) successful suspensions and an average height of 304μm. 60-degree proved to be the least successful in the four experiments, only suspending particles twice (50%) and having an average particle height of 324μm. Since the 45-degree angle of attack was the most successful among the wedge-shaped features, it was used for the next round of experiments to verify the significance of the result.

Flat Surface

The flat nature of the plunger made the glass particle visible, even without spinning. Therefore, in all four experiments, the glass particle was observable. However, the surface of the plunger also had bubbles, which could either obscure the glass particle or cause false rejects if the bubbles were categorized as particles. Only two of the experiments (50%) resulted in the glass particles lifting the surface significantly. The average maximum height in the two successful experiments was 211μm. This height allowed glass particles to be distinguished from bubbles that would float all the way to the meniscus if they separated from the plunger surface.

3.2.6.2 Features Selected for Round Two Experiments

As discussed above, five features did better than two and one feature samples at agitating particles into solution. Also, 500μm high features were better at suspending particles than the other feature heights. Lastly, when analyzing different angles of attack, 45-degree samples performed the best. To test the significance of these results, five feature and 500μm high features of both the half cylinder and 45-degree wedge were used in the next round of experiments. For these experiments, seven samples each of the original plunger, half cylinder and 45-degree wedge were tested 10 times each. This mean that there were 70 data points for each of the three types of samples.

Second Round Experiment Results

The results from the 70 experiments are summarized in table 3.1 below. The wedge and half-cylinder had a higher success rate at agitating particles into solution, with an 89% and 97% success rate respectively, compared to only an 11% success rate with the original plunger design. The wedge plunger had the highest average height of the particles, just beating the half-cylinder by 41μm. The difference in height between wedge and half-cylinder is insignificant, as the standard deviation of these measurements of 611μm and 690μm respectively, are more than 10 times the 41μm difference. It would be safe to assume that it is the result of natural variation.

The high standard deviation of the heights of the particle is most probably due to the variation of the position of the glass ball relative to the features. One would expect that a glass particle closer to the feature would experience the greatest lift as the relative velocity between the particle and feature would be high when the glass particle hits the feature. Particles further away from the feature would be accelerated by interacting with the flat surface of the plunger first, so by the time they reach the feature the relative velocity would be lower.

Another explanation for the high variation could be attributed to vibrations in the system when the syringes are being rotated. High vibration would cause the particles to be shaken to higher heights. Vibration of the syringe however cannot be used to explain the variation in the success rates. Assuming chance of vibration to be uniformly distributed across the three types of samples, the success rates would be closer in value. The assumption of uniform distribution of vibration across tests is supported by the similar standard deviations for the wedge and half-cylinder.

Table 3.1: Results of suspension experiments

Feature	Average Particle Height (μm)	Standard Deviation (μm)	# of Suspensions	# Failed Suspensions	% Success
Original	79.1	266	8	62	11%
Wedge	908	611	62	8	89%
Half-cylinder	867	690	68	2	97%

Getting particles into solution consistently to allow for the reliable detection of dense particles is the most important metric. The 500μm, five feature and half-cylinder design does this the most consistently at a success rate of 97%. Therefore, it is the best surface modification that was tested during these experiments.

3.2.7 Discussion

The sections above outline experiments that were done to test the hypothesis that surface features on plunger surfaces can get dense particles into solution where they can be easily detected by automated visual inspection machines. The experiments showed that modifications to the plunger surfaces did improve the rate that particles were successfully agitated into solution. Modified plungers show great promise for improving the detection rates of dense particles using automated visual inspection machines. However, there is more work that is needed to ensure that modified plungers find their way into common use with parenteral drugs in automated visual inspection. Section 3.2.8 below discusses these steps in detail.

3.2.8 Future work

Additional work needs to be done before surface modified plungers can be used in the pharmaceutical industry. The work that needs to be done can be broken down into three main work streams: (1) technical and patent filing, (2) product impact and (3) business implications.

3.2.8.1 Technical work

Future technical work includes performing additional experiments to test the hypothesis even further. The experimental setup used in these experiments suffered from vibration. The next iteration of the experiments would include reduction in vibration to allow for a more accurate measurement of the effects of the surface features. In the current experimental setup, the top of the syringe is unconstrained, allowing the tip of the syringe to wobble side to side. Fitting an appropriate bearing that restricts this vibration while allowing the sample to rotate freely and reduce vibration significantly.

The experiments in this chapter only tested a subset of possible feature shapes. Also, only 400μm glass spheres are tested. There are many other particle sizes and materials that fall under the dense particle category, like steel. More experiments are still needed to test the different surface feature shapes and their effects for not only dense particles, but for other particles as well. This would confirm that there are no unexpected adverse effects to the detection rates of other particulate matter.

3.2.8.2 Product Impact

The experiments conducted tested the agitation of particles into solution, but not the impact caused by adding features to plunger surfaces. There is a possibility that the features are causing vertices as the liquid rushes past them, especially during the initial acceleration to the rotational speed and the sudden brake at the end of the rotation cycle. These vertices can cause bubbles and high energy pockets in the vicinity of the features. Air/fluid interfaces are known to cause aggregation of proteins into visible and sub-visible particles that can cause negative outcomes in patients[23], [26], [27]. Because of the adverse effects of protein aggregates, their presence could lead to the rejection of the product.

No bubble formation was observed using the mimic solution during the experiments. However, tests with the real product would need to be conducted to ensure the product would not get damaged during actual production. The experiments would involve real product and tests to determine the threshold of rotational speed where protein aggregation occurs. Once the rotational

speed is assessed, a maximum speed for spinning the product would be set that includes a safety margin to mitigate risk of damaging the product.

The plunger serves an important job in administering medicine to a patient. The design changes to the surface must be tested to ensure that they don't affect the purpose of the plunger in the syringe assembly. The current conical design of the plunger surface might allow for the efficient administration of all the medicine in the syringe. Additional studies have to be conducted to test this with the new plunger surface designs.

3.2.8.3 Business Implication

Changing the design of the plunger involves working through the business and regulatory implications. The first that comes to mind is the impact on manufacturing costs. Syringes used in the pharmaceutical industry are very standardized in terms of design for the same volume. If Amgen were to implement the modified plunger surfaces, the plungers would cost more because they would have to be custom made.

Additionally, the change in plunger design could impact Amgen's supply chain network. Manufacturers currently making plungers for Amgen might not be able to produce the modified plungers and Amgen would have to change suppliers. Also, the limitation of manufacturers that could make the modified plunger surfaces may place Amgen at risk if they over rely on very few manufacturers. Manufacturers willing to produce the modified plungers might require Amgen to sign exclusive agreements before vendors invest resources to develop the equipment and processes necessary to deliver quality plungers. These agreements could result in Amgen having lower negotiating power when establishing pricing.

Changing the plunger design would also involve managing interests of all the stakeholders. This would involve developing a clear business case so that both the internal and external stakeholders understand the change and the impact of the change. For example, Amgen inspection and procurement teams would not experience the same impact from this change. As discussed in the previous paragraph, customization of the plunger surface means that the procurement team might

need to change their sourcing strategy and the costs could go up. This could lead to negative performance metrics for the procurement and increased cost of goods. Meanwhile, the improved dense particle detection rates caused by the modifications to the plunger surfaces would reflect positively on the inspection team performance. For internal stakeholders, a three-lens analysis would be necessary to understand the political, cultural and structural power within Amgen. After understanding these three lenses, a change management strategy would be developed to ensure the success of the initiative to change the plunger design.

In addition to internal stakeholders, Amgen would need to manage external stakeholders, like patients, investors and doctors. The impact to external stakeholders must be clearly understood, including how the change is perceived. Unambiguous communication of the benefits and mitigation plan for the drawbacks of the new design are important. The new design can be used as a competitive advantage and be protected through a patent. If communication is well executed it can result in increased demand for Amgen's products, because of the increase in quality. The intellectual property of the design can be licensed out to suppliers leading to improved relationships. Also, investors may acknowledge the value of intellectual property if well communicated, which could lead to an increase in share price.

There are a number of business implications outlined above, both positive and negative. The final decision to proceed with executing the new design of the plunger will rely on the careful evaluation of the pros and cons of the decision. If the decision is made to proceed with this idea, effective internal and external change management is needed to realize the intended benefits and minimize the impediments.

4 Product Impact Analysis

Product impact analysis is an important step during the qualification of equipment before it can be used in the manufacturing processes of pharmaceuticals. Product impact analysis confirms that the equipment is not damaging the product during production. Regulatory authorities in the pharmaceutical industry have very strict guidelines on the qualification process for not only the impact of the equipment on product quality, but also for performance metrics like accuracy. This chapter will focus on the product impact analysis of automated visual inspection machines. It will look at technological solutions for improving the current process of impact testing.

4.1 Background

As mentioned in chapter 1, biotechnology medicines consist of proteins that have large and complicated molecular structures. These proteins can be damaged by light intensity, elevated temperatures, mechanical shock and exposure to air-water interfaces, causing particles or protein aggregation to occur [7], [23], [26]–[28]. The resulting protein aggregation can cause negative outcomes in patients, including triggering an immune response [7], [14], [15], [19]. Automated visual machines expose drug products to light, temperature increases and mechanical stresses. The accurate control of the level of stress that automated visual machines place on products is important to ensure products are not damaged and inspection performance is maintained.

4.2 Problem Statement

Mechanical stresses, as discussed in chapter 3, can agitate particles into solution where they can be more easily detected. Unfortunately, high mechanical stresses can damage the product. The fine tuning of hardware and software settings for automated visual inspection machines is a fine balance between improving detection efficiency and not degrading the product during inspection.

Light exposure of products is well understood and can be measured using cameras already in the automated visual inspection machines or through compact light sensors. Also, temperature

increase as a result of the inspection process can be easily measured using infrared sensors that detect the temperature of products as they come out of automated visual inspection machines. However, measuring the full mechanical stress history of the product as it passes through an automated inspection machine is more challenging.

Because light exposure and temperature increase can be accurately measured for the automated inspection machines, tests for acceptable levels of these parameters can be conducted independent of the machine. This means that experiments can be conducted separate from the machine and guidelines can be developed for what the acceptable levels of light exposure and temperature elevation are. Technicians fine tuning machine settings that affect the temperature and light exposure of the automated visual inspection machines can more quickly come to the right value. Since the mechanical stress history of the product as it passes through the machine is unknown, technicians have to fine tune these settings using trial and error.

This part of the project aims to develop an accurate measurement system for understanding the mechanical stress history of the product as it passes through multiple defect detection stations in an automated visual inspection machine. Once the mechanical history for a particular machine has been understood, an offline robotic system could be created to test the product impact analysis of the machine on specific products without disrupting the use of the machine intended for production purposes.

4.3 Evaluation of solutions

Three mechanical stress measurement solutions were evaluated for their application to the problem. The different solutions had strengths and weaknesses that were evaluated before selecting the final sensor test. The three proposed sensor solutions were:

1. Tachometer
2. Camera measurement
3. Product embedded sensor

4.3.1 Non-contact Tachometer

A non-contact tachometer encoder is an instrument for measuring rotational speed. The sensor consists of a light source (laser) and light intensity detector (photodiode). A reflective strip is attached to the rotating object and then the laser and photodiode are pointed at the object as it rotates. Light from the non-contact encoder reflects off the surface of the rotating object to the photodiode. Since the reflective strip has higher reflectivity compared to the rest of the object, there is an increase in light intensity measured by the photodiode during every revolution the object makes. The software in the tachometer counts the frequency of the spikes in light intensity to calculate the angular velocity.

A non-contact tachometer can be integrated into an automated visual inspection machine to measure the rotation speed of the products as they are inspected. Reflective tape can be placed on products to verify that the machine is accurately spinning products at the set speed. Substitution of regular reflective tape with encoders can increase the level of data that can be measured. Similar to the system that is used in crash tests for cars, rotational velocity and translational velocity can be measured in all 3-dimensions.

4.3.2 Camera Measurement

Automated visual inspection machines utilize multiple cameras to detect different defects. These cameras can also be utilized to measure the mechanical stresses products undergo at the different stations. Containers with biotechnology medicine are not usually filled to the top of the container, and therefore, the solution has a meniscus. The meniscus of a liquid is sensitive to mechanical stresses from movement. Cameras with the aid of software can be used to identify the shape and motions of the meniscus to determine what mechanical stresses the product is experiencing. For example, the meniscus shape gets more parabolic with the increase in rotation velocity.

4.3.3 Product Embedded Sensor

Product embedded sensors was the last solution considered for mapping the mechanical stress profile of a product as it passes through an automated visual inspection machine. Embedded sensors for measuring mechanical stress, like accelerometers and gyroscopes, have existed for many years. With the miniaturization of technology, it has become possible to fit accelerometers and gyroscopes into increasingly tight spaces. Accelerometers and gyroscopes are now small enough to be embedded into biologic size containers, like syringes and vials. Sensors embedded into housings, shaped like drug containers, can be passed through automated visual inspection machines in the same way products are. This would allow measuring the full mechanical history of the product as it passes through the system. Figure 4.1 below is an example of an embedded sensor and a vial that it would replace while passing through an automated inspection machine. The sensor on the left could contain multiple different sensors. This one in particular measures pressure, tilt and spin.

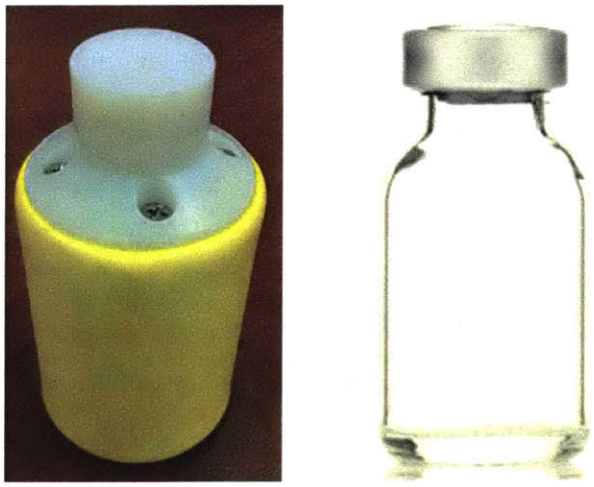

Figure 4.1: Embedded sensor on the left is the same shape as the glass vial on the right

4.3.4 Solution Selection

The three proposed solutions were evaluated qualitatively based on four criteria, namely:

1. Modification needed to existing automated visual inspection machines
2. Completeness of mechanical history measured
3. Compatibility with all Amgen automated visual inspection machines
4. Flexibility - applicability to other formulation, fill and finishing equipment

4.3.4.1 Modification

Understanding the level of modification needed to implement the solution is important. Firstly, major modifications to the machines could void manufacturer warranties of the equipment. Automated inspection machines are multi-million dollar machines and signify a major capital investment. The modifications to the inspection machines have to be minimized when possible. Secondly, the lower the level of modification, the less likely the solution will interfere with the normal operation of equipment. Lastly, little to no modification allow for easier deployment across Amgen's manufacturing network.

Camera measurement and embedded sensor solutions will require no modification to the automated visual inspection machines. Camera measurement will use cameras that already exist in automated inspection machines. Embedded sensors on the other hand just substitute products as they pass through the system. The tachometer involves mounting additional equipment into the automated visual inspection machines. This would be a challenge as space is restricted in the machine to reduce the footprint of inspection machines.

4.3.4.2 Complete Mechanical Stress History

One objective of the sensor is to understand the full mechanical stress history of the product from the moment it is introduced into the system to when it exits the machine. This will provide accurate information for the construction of an offline system that can be used for product impact analysis. Embedded sensors provide the most complete mechanical stress history of the product through the system. Cameras only provide a measurement of the mechanical stresses at inspection stations. There are gaps in the camera's field of view that would that go unmeasured. It is possible for unexpected shocks to products to occur, because of misaligned guide rails that are often adjusted to accommodate different product container sizes. Tachometers provide the least complete mechanical history. The limited amount of space in automated visual inspection machines leaves very few locations that tachometers can be mounted.

4.3.4.3 Compatibility

Automated visual inspection machines are highly customized by the purchaser. Everything from cameras and sensors to product loading and unloading (manual or robotic) are defined by the purchaser before the vendor builds the machine. As such, there is wide variation among the machines in Amgen's manufacturing network. It is important that the solution chosen can be used in most, if not all the automated inspection machines available. Embedded sensors are the most compatible with all the automated inspection machines as they are the same size as products inspected by the machines. Camera measurement is the second most compatible solution. However, not every inspection station in automated inspection machines has a camera, as Static Division (SD) sensors are a popular way of detecting particles. Tachometer is the least compatible of the solutions considered, because the layouts of automated inspection machines vary significantly; therefore, placement of the sensor might not be possible in all automated inspection systems.

4.3.4.4 Flexibility

Product impact analysis is not a challenge that is unique to automated visual inspection machines. Other equipment, like automated filling machines and packing machines can also inflict mechanical stresses on products leading to creation of particles and other defects. Ideally, the sensor solution selected could be applicable to other equipment. Embedded sensors provide the best applicability to other equipment as they have the same shape as the product container. Tachometer provides the next best applicability since the system comes with its own light source. Lastly, the camera has the least applicability, because of the additional requirements for lighting and it is not as compact as the other systems.

4.3.4.5 Final Selection

All the factors listed above were factored into the final decision of the sensor method. The summary of how the different sensor solutions were rated qualitatively is shown in the table 41. below. A one to three integer rating system was used to rate solutions for the four criteria covered above, three being the best rating and one being the worst rating.

Table 4.1: Selection criteria for sensor solution

Sensor Solution	Tachometer	Camera	Embedded sensor
Modification	1	2	3
Stress History	1	2	3
Compatibility	1	2	3
Flexibility	2	1	3
Totals	5	7	12

As can be seen from the table above, the embedded sensors are the best solution for measuring the mechanical stress experienced by products in automated visual inspection machines.

4.4 Solution for Embedded Sensor Challenge

As seen from section 4.3 above, embedded sensors are the best method for mapping out the mechanical stress history of products. The embedded sensors use Micro-Electro-Mechanical Systems (MEMS) to measure rotational and translational accelerations in all three-dimensions. MEMS linear accelerometers on the market can measure up to 500g, which is well above the required acceleration measurement. However, MEMS gyroscopes currently available in sensor embedded drug container shapes only go up to 2000 degrees per second or 333 RPM. This is lower than the typical spinning rate of 1,500 to 3,000 RPM used in automated inspection machines.

4.4.1 Hypothesis

The low measurement ranges for embedded gyroscope sensors, for use in automated visual inspection machines, present a challenge to accurately measure mechanical stresses. It might be possible to use accelerometers to deduce the rotational velocity that containers are subjected to in an inspection machine. Experiments were designed to test out this hypothesis.

4.4.2 Centripetal Acceleration

Accelerometers are used to measure an object's acceleration. To understand how accelerometers could be used for measuring rotational velocity, a relation between acceleration and rotational

velocity had to be found. Fortunately, a well-established formula already existed. Objects that are moving in a circle experience centripetal acceleration that is given by the following equation:

$$a_c = \omega^2 r \tag{4.1}$$

Where a_c is centripetal acceleration in ms^{-2}, ω is the angular velocity in radians per second and r is the radius of rotation in meters.

The radius of rotation in a spinning container can be assumed to be constant. This means if the radius of rotation can be determined, the rotational velocity can be calculated from the accelerometer measurements.

4.4.3 Experiment

An experiment was designed to test whether accelerometers could provide an accurate measurement of rotational velocity at both low and high ranges that are typical in an automated visual inspection machine.

4.4.3.1 Materials

Embedded sensors in the shape of pharmaceutical products are expensive to buy and have a long lead time. A sensor with similar capabilities to what would be used for measuring the mechanical stress of a product in an automated visual inspection machine was selected for the experiments. The selected Slam Stick C sensor had a ±16g DC MEMS three axis accelerometer and a 2,000 degrees per second (333 RPM) three axis gyroscope[29]. This sensor provides measurements in all six degrees of freedom for a rigid body.

4.4.3.2 Method

An experimental setup shown in the figure 4.2 below was built for testing the hypothesis. The setup consists of an electric motor connected to controller software on a laptop. The software and electric motor control the rotational velocity of the Slam Stick sensor as it spins about its vertical axis. The support structure maintains the sensors in position and minimizes the vibration as it is

spinning around, limiting the noise in measurement. The Slam Stick sensor is secured into the structure by friction using a tight fitting custom adapter.

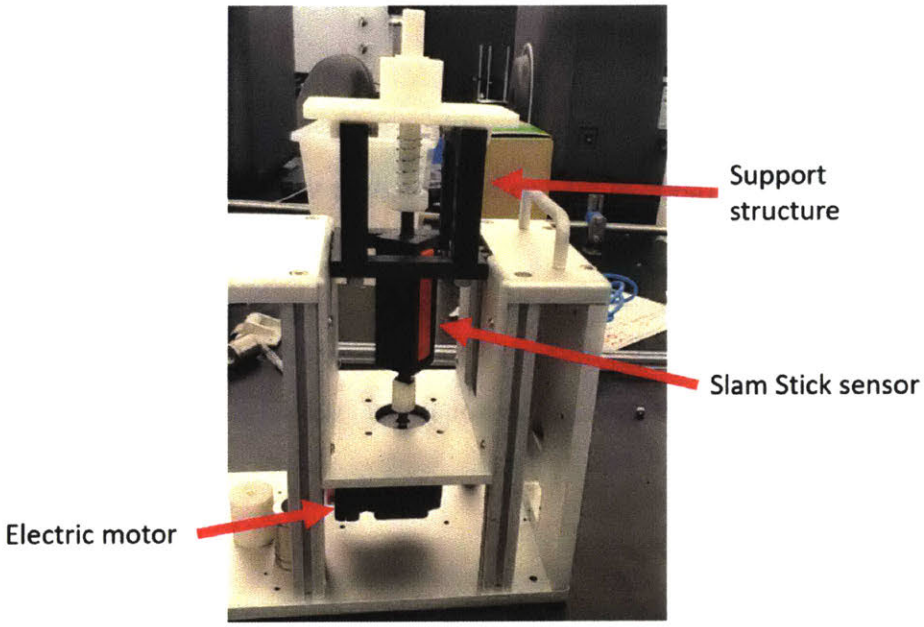

Figure 4.2: Sensor experimental setup

The Slam Stick sensor was rotated at different rotational velocities while the sensor recorded acceleration and rotational information on to its internal memory. Sensor readings were taken at 14 different rotational speeds: 0, 100, 200, 300, 500, 1000, 1300, 1500, 1800, 2000, 2200, 2500, 3000 and 3500 RPM.

4.4.4 Results

The gyroscope only measured rotational speeds up to 333 RPM. The limited range of the gyroscope, however, did allow for a direct comparison between the set rotational speed of the electric motor and the readings from the sensor. The table 4.2 below shows the percentage variation between the set RPM and what was measured by the gyroscope.

Table 4.2: Comparison between set RPM and sensor measurement

Set RPM	Measure RPM - Gyroscope	% Variation*
100	98.8	1.20%
200	197.6	1.20%
300	296.3	1.23%

*% variation is calculated by dividing the difference between set RPM and measured RPM, and then dividing by the set RPM

As can be seen from table 4.2, the differences between set RPM and measured RPM are less than 1.3% of the set rotational speed. Experiments were not conducted to determine why there was a difference, because it was small enough to be accounted for by the accuracy of the gyroscope.

Data collected at 200, 1300, 2000 and 3000 RPM was excluded from the initial model testing and would be used to test the model performance. From equation 4.2, we expect centripetal acceleration to vary linearly with the square of the angular velocity. A linear regression model was applied to the data in order to determine the radius of rotation. The output of the linear regression was expected to be in this format.

$$y = kx + c \tag{4.2}$$

Where x is the independent variable, which in this case is ω^2, and y is the dependent variable, which in this case is the measured centripetal acceleration, k and c are calculated by the regression model and represent the radius of rotation and offset of the accelerometer respectively.

The figure 4.3 below shows the initial results from the line regression model. The dots represent actual data and the linear regression fit line in also shown. Even though the R^2 value of 80% it is clear that the data does not follow a linear pattern, especially for high values of ω^2. On further analysis of the data, it was discovered that experiments at 2,500 RPM and above exceeded the ± 150 ms^{-2} measurement range of the Slam Stick accelerometer.

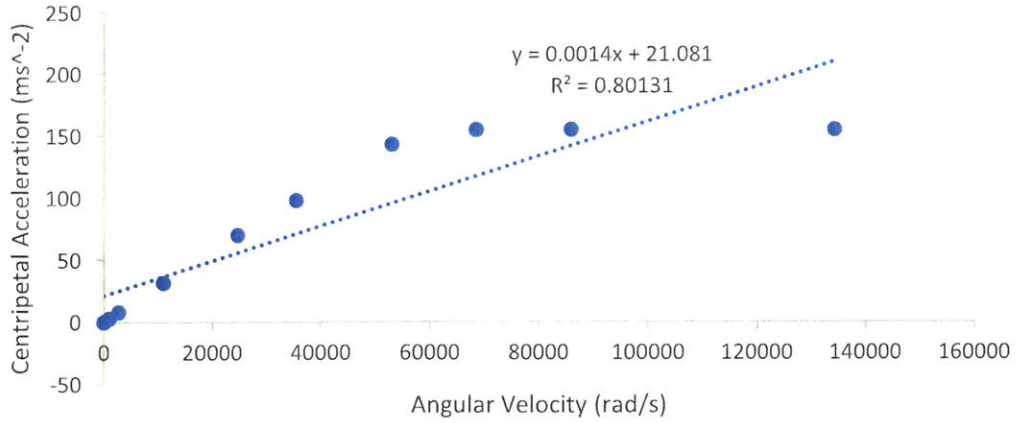

Figure 4.3: Experimental results with linear regression fit

After removal of data involving rotational speeds at or above 2,500 RPM a linear regression model was applied to the remaining data. Figure 4.4 below shows the results from that analysis:

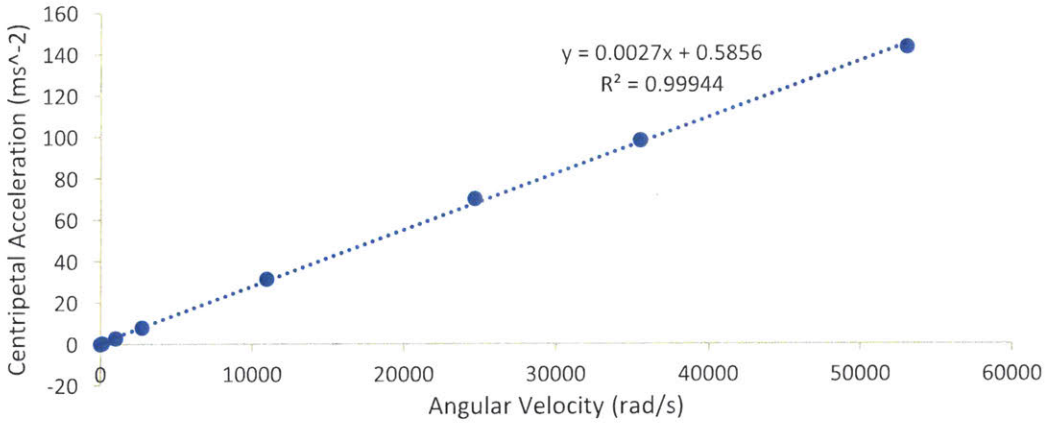

Figure 4.4: Experimental results excluding speeds above 2,500 RPM with linear regression fit

The new linear regression model does a better job than the first model at fitting the data points. The high R^2 of 99.94% shows just how good the model is at fitting the data. From the model, it can be deduced that the accelerometer was 2.7 mm away from the center of rotation. The radius of rotation value seems reasonable, as it lies within the dimensions of the sensor (plane perpendicular to the axis of rotation 29.8 mm x 15.0 mm).

In order to validate the performance of the model, it was tested on the three data points that were omitted from the model development. As mentioned earlier, data from 200, 1300, 2000 and 3000 RPM was separated from the rest of the data that was used in the model development for this very purpose. Unfortunately, at 3000 RPM, the centripetal acceleration exceeds the measurement range of the Slam Stick sensor that was used in the experiments. The table 4.3 below shows a summary of the results comparing electric motor set rotation velocities with those calculated by the model using accelerometer measurements.

Table 4.3: Performance of linear regression model

Target RPM	Calculated RPM	Difference RPM	% Error*
200	158.7	-41.3	-20.6%
1300	1267.9	-32.1	-2.5%
2000	1988.0	-12.0	-0.6%

* Error is calculated by deducting the target rotational velocity from the rotational velocity calculated using the linear regression model.

The results in the table show that the model does not perform well at lower rotational velocities when the percentage error is 20.6%. However, at higher rotational velocities, where the chance of causing damage to the product is higher, the model is very accurate with a percentage error of only 0.6%. The high error level at lower rotational speeds most likely stems from the noise in the experiment system. Even though measures were taken to reduce vibration, the test apparatus still had some vibration.

4.4.5 Discussion

Experiments were conducted to test the feasibility of using accelerometers in embedded sensors to measure rotational velocity. A Slam Stick sensor used in the experiments showed promise. It provided an accurate rotational velocity at high speeds. However, it did not perform well at lower rotational speeds, with errors of 20.6% at 200 RPM. The error at lower rotational velocity can be compensated by using gyroscopes that are already present in the embedded sensor. The experiments were limited by the range of accelerometers. The Slam Stick sensor is already

configurable, with higher range accelerometers up to ±5000 ms^{-2} which would be able to measure up to 12,000 RPM. 12,000 RPM is higher than the maximum expected upper range of 4,000 RPM in automated visual inspection machines.

Separate from measuring rotational velocity, accelerometers also need to measure the lateral accelerations that the product incurs. Measuring both lateral and centripetal acceleration at the same time would be challenging as it is difficult to distinguish between them. This is because the accelerometers would record a mixture of both accelerations. Multiple runs through the machine would be needed to have an accurate measure of the accelerations. The first run could be a baseline run that has the spin velocities set to zero. This would mostly measure the translational motions. After that, another run could be done, but this time using target spin speed for each inspection station. By subtracting the translation acceleration data in the first run from the results in the second, an estimate of the centripetal accelerations can be obtained.

Once the mechanical history of the product through the machine has been mapped, it can be translated to robot code to conduct product impact testing without disrupting the productivity of the automated visual inspection machine. This project only went as far as testing the feasibility of using accelerometers as a way of expanding the upper limit for measuring rotational velocity using embedded sensors. Future work would be needed to achieve the goal of having an offline product impact testing system for automated visual inspection machines.

5 Automated Visual Inspection Cost Analysis

One of the challenges associated with the implementation of automated visual inspection machines is understanding its costs and benefits compared to manual visual inspection. There are situations for which manual inspection would be the most ideal solution, but it is not well understood to what extent different parameters influence this decision. This chapter will explore the use of cost-benefit analysis applied to manual inspection and automated visual inspection machines to discern the parameter sensitivity of the visual inspection method decision. Knowing the influence of different factors could help inform investment decisions on potential improvements in automated inspection machines to make them more applicable to the Amgen manufacturing network.

5.1 Cost Model Considerations

Automated visual inspection machines and manual visual inspection machines have different characteristics that should be considered in the building of the cost model. The selection of an inspection method has financial implications as companies have to invest resources like capital and time. The financial consequence of this selection is one of the most important considerations. Also, since the final product inspection is an important step in the manufacturing process, the cost-benefit model considers the operational aspects of the different inspection solutions. These considerations will be further explored below.

5.1.1 Financial considerations

The cost-benefit analysis model used in this project considered the major costs that are associated with the inspection method. Financial costs can be divided into three main buckets: pre-operational costs, operational costs and decommissioning costs.

5.1.1.1 Pre-operational Costs

Pre-operational costs are all the costs that are associated with getting the inspection system set up for production. Both automated visual inspection machines and manual inspection have similar cost breakdowns. Automated inspection machines cost more in all the cost categories, but can make up for it in terms of increased production rates. Pre-operational inspection costs include capital investment for the design, build, factory acceptance testing, installation and qualification of the equipment and training of operators. For simplicity, only the equipment procurement, installation and qualification costs will be considered in the model as they represent the largest cost categories for pre-operational costs for both manual and automated visual inspection.

5.1.1.2 Operational Costs

Once the equipment is qualified for production and operators are trained, the equipment goes into production. Operational costs are the expenses associated with the running and maintenance of the equipment. Operational costs include rent, overhead, operator salaries and operator retraining. Some of these expenses depend on the number of inspected products, while others are fixed regardless of whether visual inspection is occurring. Operator salaries represent a significant portion of operational cost for manual visual inspection. The cost model will only look at operator salary differences between manual visual inspection and automated visual inspection.

5.1.1.3 Decommissioning Costs

Decommissioning costs are the costs associated with decommissioning at the end of the equipment's lifecycle. Decommissioning costs include the cost associated with obsoleting relevant documentation and uninstalling equipment. There is scarce information available on end of life costs for these types of equipment in the pharmaceutical industry. Therefore, for simplicity, the model assumes that there is a zero salvage cost of equipment used in automated visual inspection and manual visual inspection.

5.1.2 Operational Considerations

Delivery of drugs to patients in a timely manner is very important for patients' well-being. Operational excellence is also a competitive advantage that Amgen strives to maintain. Operational considerations have to be factored into the decision of which inspection system to utilize. Since Amgen wants to maintain the "every patient, every time" mission, it has implemented a production capacity planning strategy where manufacturing capacity is flexible to ensure demand can be met. Speed of deployment of the inspection methods allows Amgen to deal with unexpected changes in demand. Manual inspection has a faster deployment compared to automated visual inspection, which could take multiple years to qualify. Percentage utilization of equipment is also important to consider in the selection of inspection type. Equipment with high utilization would have a lower per unit cost, but would present difficulties when dealing with variability in demand. A balance between percentage utilization and per unit cost has to be struck.

5.1.3 Risk Considerations

As discussed briefly in section 5.1.2, there is uncertainty in the demand. Amgen aims to provide a high service level to its patients and supply of their medicines to their patients. In order to ensure this, Amgen keeps a certain threshold of inventory to mitigate variability in demand and potential issues with production rate. At the end of 2018, Amgen had USD 1.023 billion in finished product inventories[30]. Inventories required to maintain the same service level can be reduced if the lag between demand and production capacity ramp up is minimized. Reducing the level of inventories cuts the costs that are associated with it. Manual visual inspection can be deployed faster than automated visual inspection, which could potentially reduce the need for inventory. The benefit of having a faster response to demand changes is hard to measure without access to detailed demand information and knowledge of all the constraints in the production system. Consequently, this will not be included in the cost model.

Inventories only cover risks associated with demand outpacing production. However, it is possible for overestimation of demand to lead to wasted capital investment, as equipment lies underutilized. The manual inspection booths are smaller and cost significantly less than automated inspection machines and the incremental risk of underutilizing the inspection booth is smaller. However, since

manual inspection is more labor intensive than automated inspection, salaries and benefits of inspectors in manual inspection may remain a fixed major cost even when inspectors are underutilized. Automated visual inspection labor is not a major expense as few operators are needed and it would be easier to reallocate the operators to other operations within the factory while demand is low.

There is also risk associated with the performance of the inspection procedure. Presence of particulate matter or other defects in products lead to recalls, as the drugs can cause negative patient outcomes. Automated visual inspection has an advantage that is more consistent compared to human inspectors, and so would be expected to present a lower risk of recalls if set up right. Measuring the value of this benefit is difficult and will not be included in cost-benefit analysis, but is something to consider in making the decision on inspection method.

5.2 Cost-Benefit Model

The cost benefit model presented in this project is a first pass at understanding the sensitivities of parameters associated with deciding which inspection system to use. The model compares the higher capital cost of automated visual inspection to the higher labor cost in manual visual inspection. It was assumed that both manual visual inspection booths and automated visual inspection machines were used in production for ten years before being decommissioned and scrapped. The sections below outline the calculations in the model.

5.2.1 Capital Expenditure (Capex)

Capital expenditure is the money spent to buy the inspection booths and automated inspection machines. For simplicity, it will be assumed that all capital expenditure will be made at year zero and production is going to start the following year. Typically, automated visual inspection machines are made to order, so they take longer than inspection booths to be operational. The yearly cost of making an investment in capital can be calculated using the cost of capital. A company's cost of capital is the minimum rate of return that investors expect for providing capital. The yearly cost of capital for the inspection method is calculated by the following equation:

$$Yearly\ Cost\ Capital = Capital\ Expediture \times Cost\ of\ Capital \quad (5.1)$$

5.2.2 Depreciation

Depreciation is the decrease in value of a tangible fixed asset. The loss in value of the asset is charged to the income statement as a way of distributing the capital expenditure used to buy it over the useful lifetime of the asset. The manual inspection booth and automated inspection machines will be depreciated completely to a zero salvage value over their ten-year operational lifetimes. The straight-line method was used to calculate the yearly depreciation cost. The value of the equipment was divided by the number of useful years, which in this case is ten, to determine the yearly depreciation charge as shown in equation 5.2 below:

$$Depriciation = \frac{Capital\ Expenditure}{Asset's\ Useful\ Years} \quad (5.2)$$

5.2.3 Operator and Inspector Salaries

The number of operators and inspectors depends on the number of units that need to be inspected. For manual visual inspection, the number of inspectors is given by the units to be inspected divided by the inspection rate per operator as given by equation 5.3 below:

$$Number\ of\ Operators = \frac{Daily\ Units\ to\ be\ Inspected}{Units\ Inspected\ per\ Operator\ per\ Day} \quad (5.3)$$

Automated visual inspection also utilizes manual visual inspectors to inspect products flagged by the automated visual inspection machine as potentially containing particles. As discussed in section 1.5.3, automated visual inspection machines have a high false eject rate, so manual inspectors are necessary to prevent wastage of good products. A product flagged by the automated visual inspection machine for presence of particles needs to be manually inspected twice in order to be accepted. The number of manual inspectors needed is given by equation 5.4 below:

$$Number\ of\ Operators = \frac{Daily\ Units\ to\ be\ Inspected \times False\ Eject\ Rate \times 2}{Units\ Inspected\ per\ Operator\ per\ Day} \quad (5.4)$$

Automated visual inspection also has machine operators. About three people are needed to operate the machine. The cost of labor is calculated by multiplying the number of operators and/or inspectors by their yearly salary as shown in equation 5.5:

$$Cost\ or\ Labor = Number\ of\ Inspectors\ or\ Operators \times Salary \quad (5.5)$$

5.2.4 Model Data and Assumptions

The data used in the model to generate the information in the results section of this chapter are all estimates. Several of the values are estimates obtained from conversations with subject matter experts. Other data values were obtained by visiting automated visual inspection machine websites.

The number of units inspected per year was assumed to be equal to the number of units inspected by an automated visual inspection machine operating for six hours a day at 95% utilization. The six hours of operation takes into account time for validation of equipment at the beginning and at the end of a typical eight-hour workday. Six hours of inspecting units per workday was assumed for manual visual inspection as well, taking into account eye breaks that inspectors are allowed to take. 95% utilization of the automated visual inspection machine takes into account disruptions in the operation of the machine during repair and maintenance. The automated visual inspection machine inspection rate was assumed to be 24,000 units per hour [10]. Inspection rate for manual visual inspection was assumed to be 180 units per hour. The false reject rate was assumed to be 15%.

A $3 million capital expenditure cost was assumed for an automated visual inspection machine, including installation and validation. Whereas manual visual inspection machines were assumed to be $7,000. A cost of capital of 30% was assumed.

5.3 Results

The model developed in section 5.2 analyzes a high labor operation and a high capital operation. The results from the model will compare capital investment costs to labor costs. Capital costs are given by equation 5.6:

$$Capital\ Cost = Cost\ of\ Capital_{Automated} + Depreciation_{Automated} - Cost\ of\ Capital_{Manual} - Depreciation_{Manual} \quad (5.6)$$

Whereas labor cost is given by equation 5.7:

$$Labor\ Cost = Cost\ of\ Labor_{Manual} - Cost\ of\ Labor_{Automat} \quad (5.7)$$

By using this notation, if capital cost is greater than labor cost, manual visual inspection is the cheaper method of inspection. However, if capital cost is less than labor cost, then automated visual inspection is the cheaper method of inspection.

5.3.1 Base Case

Using the assumption outlined in section 5.2.4, the cost of capital is $950,800 compared to a cost of labor of $8.54 million. Automated visual inspection has a clear cost advantage over manual visual inspection by a factor of almost nine. The next sections will test how this result is sensitive to some of the assumptions in the model.

5.3.2 False Eject Rates

As mentioned in Chapter 1, automated visual inspection machines suffer from higher false eject rates that manual visual inspection machines. The ejects from automated visual inspection are typically inspected by a human operator twice before they are either rejected or accepted. A test was run to see the effects of changing the false eject rate on the cost of manual or automated visual

inspection. Everything else in the base case is kept constant while false eject rate is varied. The results are shown in the figure 5.1 below. As expected, an increase in the false eject rate reduced the labor cost advantage of automated visual inspection machines. It takes eject rates of over 45% for manual visual inspection to be favored over automated visual inspection.

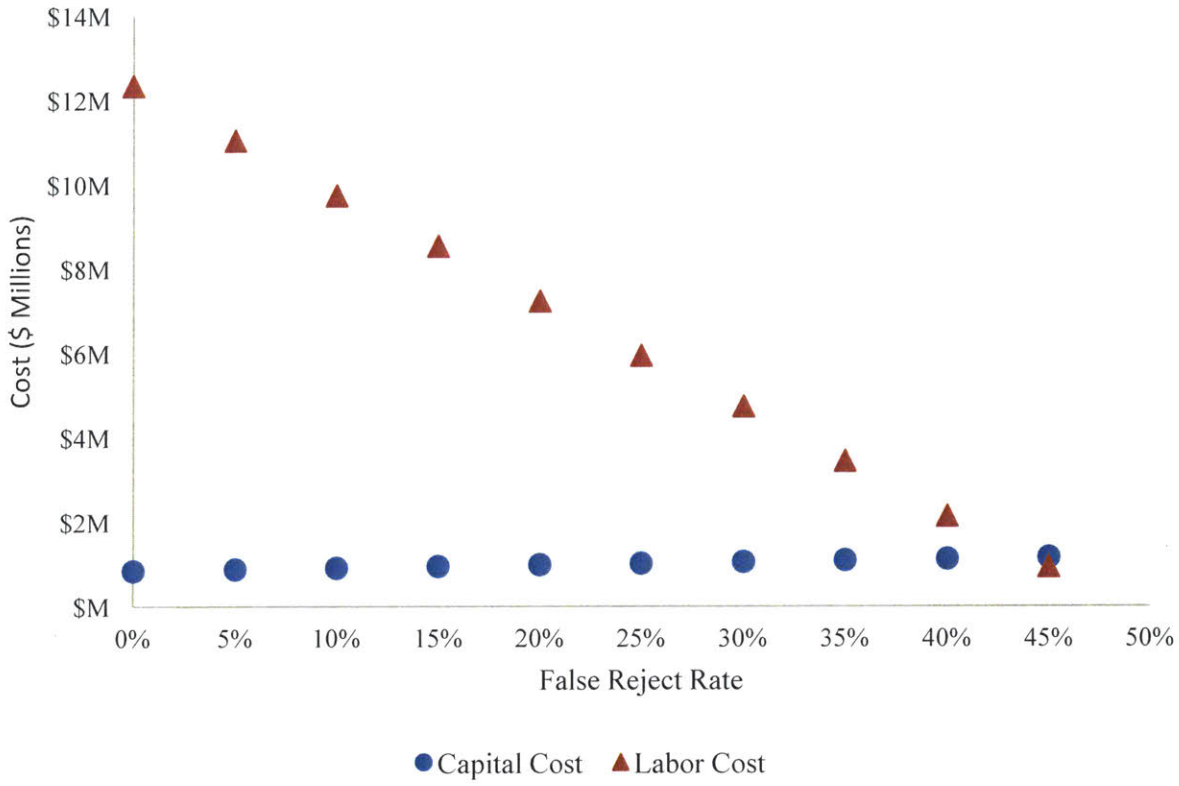

Figure 5.1: Financial model results. Impact of false eject rate on Capital Cost and Labor Cost

5.3.3 Cost of Capital

The sensitivity of the model to the cost of capital was also tested and the results are shown in figure 5.2. As expected, as the cost of capital increased, the capital cost also went up. However, even at 100% cost of capital, capital costs were still lower than labor cost. Therefore, the decision to use automated visual inspection or manual visual inspection is not significantly influenced by the cost of capital assumption.

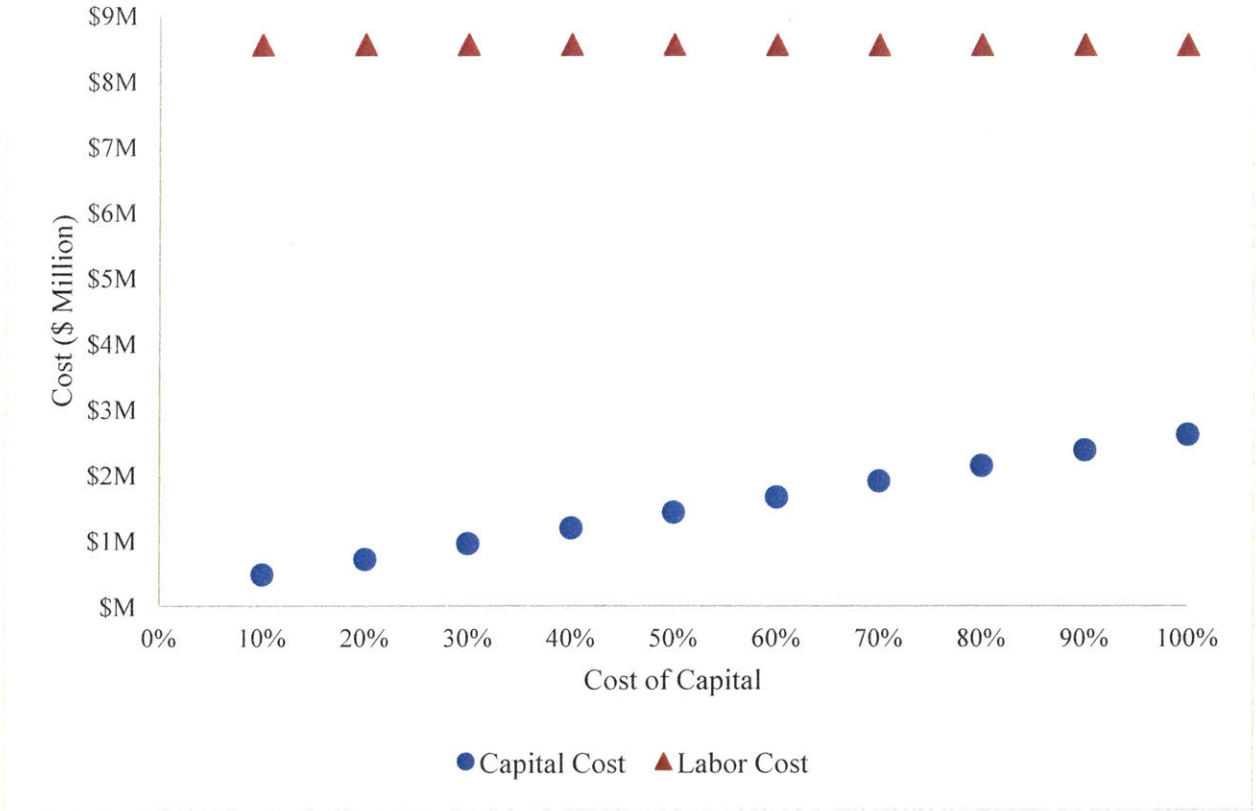

Figure 5.2: Financial model results. Impact of false eject rate on manual visual inspection (MVI) and automated visual inspection (AVI)

5.4 Discussion

The cost analysis model showed expected trends regarding the decision to pick automated visual inspection or manual visual inspection. The model showed very low sensitivities to both false eject rates and cost of capital. Very conservative estimates of 60% and 40% for cost of capital and false eject rates, respectively, result in a capital cost of $1.98 million versus a labor cost of $2.14 million, still favoring automated visual inspection over manual visual inspection. This suggests that automated visuals inspection is better than manual visual inspection even with very conservative estimates of false eject rates and cost of capital. The model is still a first iteration and will need to be developed more to include more granular cost breakdowns to improve its accuracy. The model can be used to make very conscious investment decisions regarding inspection equipment, and shape Amgen's inspection strategy more effectively.

6 Recommendations and Conclusion

The objective of this project was to improve the implementation of automated visual inspection machines across Amgen's manufacturing network. After meetings with key stakeholders, three main work streams were made the focus of this thesis. The work streams were namely:

1. Improvement of dense particle detection
2. Elimination of the use of automated visual inspection machines for product impact testing
3. Development of a cost model for making decisions between automated visual inspection machines and manual visual inspection machines

These work streams were discussed extensively in their independent chapters. This chapter will provide a summary of the findings and recommendations for future work.

6.1 Dense Particle Detection

It was hypothesized that modifying the surface of plungers could improve the agitation of particles into solution. Experiments were designed to test the hypothesis. Twenty different plunger surface features were tested for their ability to get dense particles, specifically 400μm diameter glass spheres, into solution resulting in improved detection. The best plunger feature tested consisted of five half cylinder features radiating out from the middle of the center of the plunger. The modified plunger was successful at agitating the glass sphere into solution 97% of the time and the particle achieved an average maximum height of 867μm above the height of the feature. This is a significant improvement from the 11% success rate and average maximum height of 79.1μm of the original plunger design.

The modified plunger surface as a way to improve particle detection is promising and should be pursued. However, before the modified surface plunger design can become a reality, additional work is required. More technical work is required to optimize the surface feature design to agitate a wide variety of particles. Operational challenges, like sourcing and manufacturing of the new plunger design, also need to be solved. In addition, product impact analysis has to be done to determine if the new design impacts the product at any point in the product's life, from

manufacturing to final administration in patients. Lastly, developing a business and regulatory strategy to take advantage of the benefits of the new plunger surface will be important to the successful implementation of the new plunger design.

6.2 Offline Product Impact Testing

Product impact testing for automated visual inspection machines is currently performed on automated visual inspection machines on the production lines. This takes away from their productivity. To remedy this, it was proposed that an offline product impact testing robotic system could be built. In order to accurately replicate the mechanical stresses caused by automated visual inspection machines, the mechanical stress history of the product needed to be measured. Three measuring methods were evaluated and embedded sensors were selected.

However, gyroscopes in embedded sensors suffer from limited measurement range of rotational velocity. It was hypothesized that accelerometers in the embedded sensors could be used to deduce the rotational velocity of the product by measuring the centripetal acceleration caused by the rotating motion. Experiments were designed to test this. The results showed the accelerometers did measure centripetal acceleration caused by spinning the product. A linear regression model based on the results determined the rotational velocity to within 50 RPM of the set value.

These results showed that embedded sensors could be used to map out the mechanical stress history of automated visual inspection machines. Next steps would include running experiments using product-shaped embedded sensors through the automated visual inspection machine to record the mechanical stress, and then developing a robotic system that replicates the mechanical stresses offline. This would allow for the uninterrupted use of automated inspection machines.

6.3 Inspection Method Cost Analysis

A cost-benefit model was developed to understand the sensitivities of the financial aspect of selecting an inspection method. The model compared the additional capital cost required for automated visual inspection and the additional labor cost of manual visual inspection. The useful

lifetime of inspection booths used in manual inspection and automated visual inspection machines were both set to ten years. The results from the model showed expected trends. For example, decrease in cost of capital and false eject rates favored automated visual inspection.

The model developed was only a first pass at cost analysis. The model needs to be updated with more detailed information measured at manufacturing sites and in collaboration with equipment vendors. The model also offers insights into the return on investments for efficiency improvements. For example, an improvement in false eject rates can be given a monetary value.

6.4 Conclusion

Automated visual inspection will be important to Amgen as the company grows its manufacturing capabilities to keep up with growing demand. This thesis explored solutions to three challenges currently faced by the implementation of automated visual inspection machines. All three solutions show promise. It has been recommended to Amgen that they continue with these work streams. This project will be handed off to the responsible teams to continue with the future steps.

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