EVALUATION OF MARKING TECHNOLOGY FOR RISK MANAGEMENT IN THE BIOPHARMACEUTICAL SUPPLY CHAIN

By

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Bachelor of Science Mechanical Engineering
Boston University, 2004

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
AND
Master of Science in Mechanical Engineering

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ABSTRACT

Amgen is a leader in the biopharmaceutical industry. It manufacturers and provides human therapeutics that drastically improve lives. Amgen's reputation and brand, its goodwill, is an invaluable asset to its ability to succeed in an increasingly competitive landscape. Because of this, risk management, both in manufacturing and in supply chain arenas, are directly linked to continuing long-term sustainable growth. With an increasingly global market and expanding pipelines, biotechnology companies, like Amgen, face a supply chain challenge to manufacture and distribute products using economically feasible methods that ensure patient safety. Preventing product mix-ups plays a key role in ensuring that safety.

Marking nude product that moves intra-Amgen or to contract manufacturers will provide a higher level of confidence that the right product is reaching the patient. Several solutions for marking nude vials and syringes immediately rise to the top of the strata of potential technologies. Despite being promising, each technological solution has key unknowns that must be answered by rigorous lab-scale testing to provide quantitative data to make the best decision on the future of this process within Amgen. Along with the testing, it is clear that the financial landscape of the different solutions varies a great deal. Each potential solution will be analyzed to determine its capital requirements as well as ongoing costs. Lastly, the solution must be realistic to implement into Amgen's current GMP. And thus, each technology will be evaluated as it relates to the overall complexity of implementation into an already tightly controlled process.

From a more macroscopic industry perspective, the FDA, as well as other regulatory agencies, has been discussing this issue for several years. Strategically, biotechnology companies are all hesitant to invest in a particular solution at the moment for fear that the FDA will require a different solution in the near term. In reality, biotechnology companies risk billions in R&D and drug development and are therefore, in a way, naturally risk averse when it comes to their processes and operations. Inventory and manufacturing operations are more driven by risk management than by cost. Of course, the important factor to remember is that risk management is a precursor to drug quality and patient safety. The majority of the risks that are controlled are risks that would either prevent environmental contamination of the drugs or affect the quality of the drugs. Altruistic or not, this has profound long term business strategy implications in an ultra-competitive marketplace where another biotechnology firm would certainly oblige taking market share if Amgen were to suffer a reputation ruining event.

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GLOSSARY

cGMP – current Good Manufacturing Practice

EMEA – European Agency for the Evaluation of Medicinal Products

RFID – Radio Frequency Identification

2D Matrix Barcode – A two-dimensional barcode with the capability of holding many digits of information.

DP&DD – Drug Product and Device Development

AML – Amgen Manufacturing Limited

ABR – Amgen Breda

EU – European Union

EOQ – Economic Order Quantity

Fill-Finish – The process by which bulk drug product is filled into the primary packaged and then labeled and packaged.

WIP – Work in Progress

DOE – Design of Experiments

1 Introduction

1.1 Project Drivers

With an increasingly global market and expanding pipelines, biotechnology companies like Amgen face a supply chain challenge to manufacture and distribute products using economically feasible methods that ensure patient safety. Preventing product mix-ups is a key arena for ensuring that safety. Many precautions and steps are taken to ensure the highest quality product. Both the product and the glass are inspected 100% at specific points throughout the process either by a human inspector or by a specially designed inspection machine. Precise procedures are in place that governs how product is packaged, handled and labeled. Procedures in product handling require physical counts of incoming and outgoing product to match. These actions are taken to minimize and mitigate the risk both in the manufacturing process but also in the supply chain.

Amgen's aspiration to completely mitigate all risk is strongly driven by industry and consumer dynamics. In the biopharmaceutical industry, because of the immense financial risk involved in upstream research and development, Amgen hedges its risk in many other areas. For example, Amgen has qualified contract manufacturers on hand if anything were to interrupt the production of its products. As an illustrative example of the why this is so important, in June 2009, Genzyme "halted production of two drugs for rare genetic disorders after a virus was discovered in production equipment at its Allston [MA] plant. As a result of the plant's shutdown, the Cambridge-based company said, *Cerezyme* patients could go without one or two treatments, while those taking *Fabrazyme* may need to skip up to four doses. Patients usually receive the drugs intravenously every two weeks."[1] Now, uniquely, Genzyme has no competition for these drugs so it will not suffer loss of market share, just lost revenues from the forced missed doses. Yet still, "some industry watchers and patients fault the company for not having enough drug inventory on hand to keep patients from missing doses of the enzyme treatments."[1]

Amgen's supply chain consists of two main arenas: North America and the EU (see Figure 1). While the separating the world between only two main areas might seem grossly lacking, it is important because of how product flows to these two areas from the manufacturing or fill-finish facility. Product destined for North America is filled, finished, labeled and packaged for consumer sale all prior to shipping. In contrast, product destined

for Europe, for example, is filled and finished in Puerto Rico then shipped nude in WIP packaging. Once at the European facility, the product is then labeled and packaged for consumer use. It is this latter scenario where risk is inherent in the process. Because all of Amgen's products look identical and for the most part are packaged in the same primary container (a 3cc vial or a 1mL syringe), there is the potential for product mix-up or mislabeling.

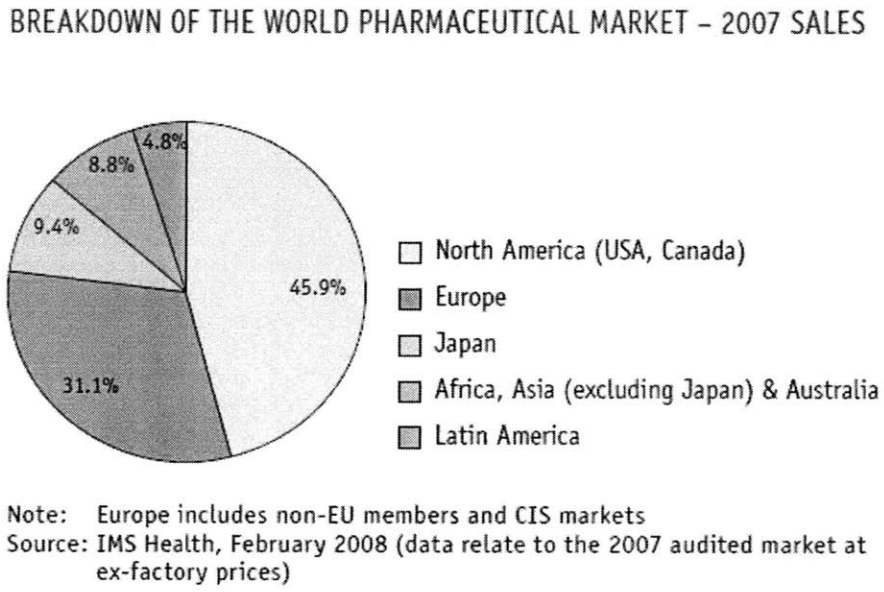


Figure 1: World Pharmaceutical Market by Sales

What drives the need to delay labeling is a function of flexibility. The Puerto Rico facility is set-up to run labeling operations for large batches of product all destined for the largest market in the world, the US. Although Europe is the second largest pharmaceutical market, it is a conglomeration of many different countries which all have different language and labeling requirements. Amgen's European labeling and distribution facility was set up to handle small batches and large numbers of labeling changeovers. Another component of flexibility is the function of customization postponement or delaying country specific packaging until closer to the point of sale. An example from the Sloan Management Review, "a US computer manufacturer makes printers for worldwide distribution. The printers have a few country-specific components, such as the power supply and owner's manual. The U.S. factory produces to meet demand forecasts, but by the time the printers reach regional distribution centers, demand has changed. Because the printers have been prepared for specific countries, the distribution centers have no flexibility to respond to changing demand

patterns. The result is simultaneously high inventory stockpiles and backlogs."[2] On top of these problems, biotechnology companies have to also be concerned about shelf life and expiration dates of their products. While a simple example from different industry, it sheds light on the motivation for biopharmaceutical companies to delay labeling operations.

Indeed, this is an industry-wide risk that exists within Amgen's peer companies as well. Regulatory bodies including state governments, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have all included recommendations for the discontinuation of transport of unmarked product. (See Appendix 1 for the cGMP regulatory framework.) As technologies improve and Amgen's pipeline of drugs in development becomes commercialized, the need for a unit-level distinguishing mark becomes increasingly important to mitigate a potentially large risk. If the entire drug discovery, development and commercialization process is modeled as one long manufacturing process, then the farther along in the process, the costlier the mistake for Amgen. Thus, a mistake or mix-up after or during commercialization is much more expensive than a mistake during discovery.

1.2 Problem Statement

Biotechnology companies currently approach unit-level marking technologies with the belief that, in the very near future, some sort of unit-level identification and tracking will be a regulatory requirement. It is already a regulatory expectation (see Appendix 1). Although there is potential for this requirement plus the potential risk, biotechnology companies have only just begun applying some marking technologies to their processes. The purpose of this business case is to examine the industry of marking technologies and determine if any feasible solutions exist. Amgen will be used as a representation of a large biotechnology company so as to understand the variables required for implementing marking technology in the industry.

1.3 Thesis Overview

Chapter 2

This chapter captures the background of the problem including company information, state-of-the industry of marking technology as well as a benchmark review of the current technologies and peer companies' marking processes.

Chapter 3

This chapter presents the hypothesis of this document.

Chapter 4

This chapter describes the methodology utilized as well as a decision framework for choosing among the different technology options that can be used for other projects within Amgen.

Chapters 5-7

These chapters present the laboratory tests and results of three most promising technology options to mitigate the risk of product mix-up in the supply chain.

Chapter 8

This chapter discusses the various technological advancements that could impact the landscape of marking technologies and options including LaserJet and plastic primary packages.

Chapter 9

This chapter shows the financial and implementation repercussions of the solutions to Amgen's internal operations. Specifically, the implementation focuses on clear label technology.

Chapter 10

This chapter summarizes the results and presents conclusion remarks.

2 Background

2.1 Biopharmaceutical Industry

The biotechnology industry can trace its roots first to the 1953 Watson and Crick discovery of the double-helix structure of DNA and second to the 1973 Cohen and Boyer discovery of recombinant DNA cloning. The discovery of this genetic engineering technology is considered the starting point for the biotech industry, which allowed scientists to produce proteins from any organism in mass quantities. Venture capitalist Robert Swanson partnered with Boyer to found Genentech, the first biotechnology company, whose first product successes were around cloning the gene for human insulin and human growth hormone.[3] See a summary of the biopharmaceutical process below:

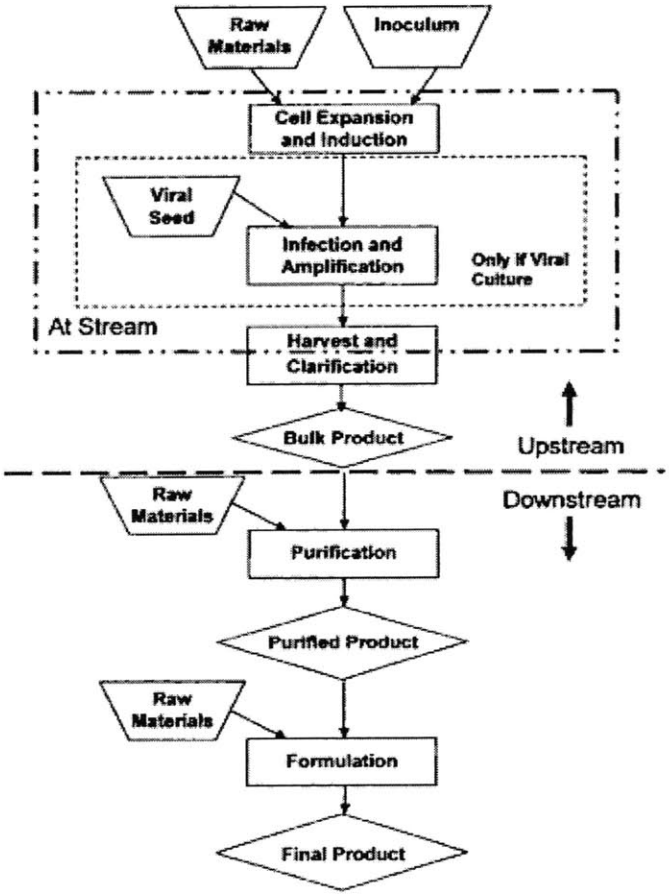


Figure 2[4]: Biopharmaceutical Manufacturing Process

Since this relatively modest almost niche beginning, the biotechnology industry has grown at a furious pace fueled by the 1980 landmark U.S. Supreme Court decision to allow the patent of bioengineered organisms. Now a dominating global industry, the biotechnology industry currently has the following statistics:

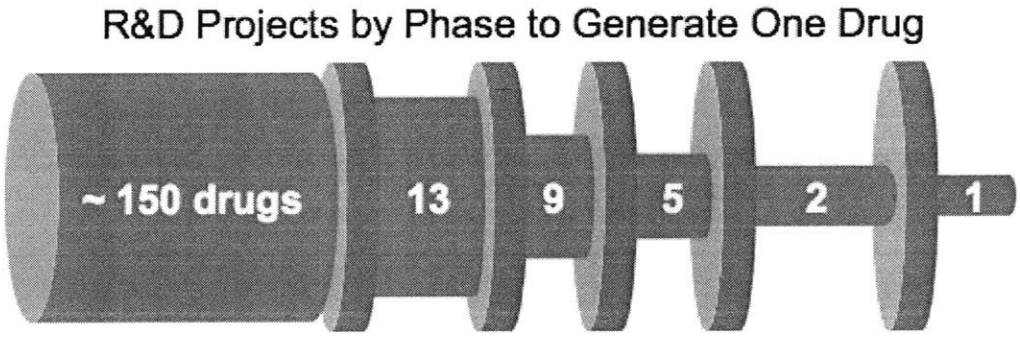
Global biotechnology at a glance in 2008 (US$m)

	Global	US	Europe	Canada	Asia-Pacific
Public company data					
Revenues	89,648	66,127	16,515	2,041	4,965
R&D expense	31,745	25,270	5,171	703	601
Net income (loss)	(1,443)	417	(702)	(1,143)	(14)
Number of employees	200,760	128,200	49,060	7,970	15,530
Number of companies					
Public companies	776	371	178	72	155
Public and private companies	4,717	1,754	1,836	358	769

Source: Ernst & Young
Numbers may appear inconsistent because of rounding
Employment totals are rounded to the nearest hundred in the US and to the nearest ten in other regions

Table 1[5]: Global Biotechnology Industry Statistics of 2008

Consolidation has since changed the face of the industry. Once dominated by a flurry of start-ups throughout the late 1970s, 80s and 90s, the industry is increasingly a function of merger and acquisition as well as alliance. The Merck/Schering-Plough, Pfizer/Wyeth and Roche/Genentech mergers are all good examples of some of the biggest firms merging. It seems that due to ever increasing costs of R&D as well as commercialization have created the scenarios where indeed bigger is better. According to an *Innovation.org* study from 2009, "To bring a new drug to market (from discovery through clinical trials and FDA approval) costs an estimated $1 billion and can take 10 to 15 years or longer. Only one in 10 new drugs that makes it into human testing actually makes it to market. Given this high failure rate and the tremendous cost of bringing a new therapy to market, companies depend on successful drugs to produce enough revenue to compensate for both the R&D costs of the successful therapies and the expense of failed ones."[6] The figure below shows the timeline as well as costs for each phase of the development process:



	Research	Preclinical	Phase 1	Phase 2	Phase 3	Approval
Years	6	1.5	1.5	1.5	2.5	1.5
Costs	$150M	$200M	$80M	$120M	$250M	$130M

Figure 3[7]: Biopharmaceutical R&D Process

Industry experts from the publication *BioQuality* also report that both pharmaceutical and biopharmaceutical companies believe that it is becoming more difficult to achieve product approval due to longer trials, more stringent safety and efficacy requirements and a lengthier review process.[16]

With acquisitions like Pfizer/Wyeth and companies like Merck forming a BioVentures unit in late 2008, the lines between traditional pharmaceutical and biotechnology companies are blurring. Amgen's drug SENSIPAR is considered a small molecule drug traditionally seen at pharmaceutical companies. Amgen's mission to become the best therapeutics company is not indication or drug complexity specific. Increasing costs and longer timelines for approval require that all companies in the biopharmaceutical space become more adept are bringing any drug to market. These blurring lines between pharmaceutical and biotechnology will continue to make waves throughout the industry in the coming years.

2.2 Amgen, Incorporated

Amgen was founded in 1980 during the early days of the biotechnology industry. Amgen's stated missions is to, "serve patients by transforming the promise of science and biotechnology into therapies that have the power to restore health or even save lives."[12] Amgen's success began with the FDA approval of its first drug, an industry blockbuster called EPOGEN in 1989, followed by another blockbuster NEUPOGEN in 1991, and both

anemia drugs. Amgen too is no stranger to acquisition and alliance. In the last ten years, Amgen's growth has been largely a function of acquisition starting with the purchase of Immunex in 2002. This purchase allowed Amgen to bring their next success, a rheumatoid arthritis drug called ENBREL, to market. Since then, Amgen has grown from $3.5billion in sales in 2002 to its 2008 mark of just shy of $15 billion. Today, it is the largest biotechnology company in the world with just over 17,000 employees. It is headquartered in Thousand Oaks, CA.

2.3 Current Challenges and Opportunities

Amgen, as well as the biotech industry as a whole, is facing serious challenges. In 2007, the FDA raised warnings concerning the risks of overuse of anemia drugs, a large part of Amgen business. This led to a reduction in sales for that year as well as subsequent years in that therapeutic area. Today, the global recession has started to affect even what some industry experts say is a recession proof industry. One Amgen employee stated, "Biotech is recession resistant, not recession proof." The massive increase in unemployment has led to the loss of medical insurance coverage. This in turn has led to patients forgoing treatment due to lack of funds. On top of that, healthcare reform is making its way through the legislation process and could affect the reimbursement rates for certain Amgen drugs, reducing its profits. Healthcare reform could also affect the length of patent protection afforded biotechnology companies. With upfront investments in the billions, it is not surprising biotechnology companies are pushing for the longest protection possible to recoup their R&D costs. Facing these challenges, Amgen has renewed its focus on operational excellence with a continued mission of serving patients and as shown in Figure 4 below, Amgen has a history of success in an industry where it is difficult to be operating in the black.

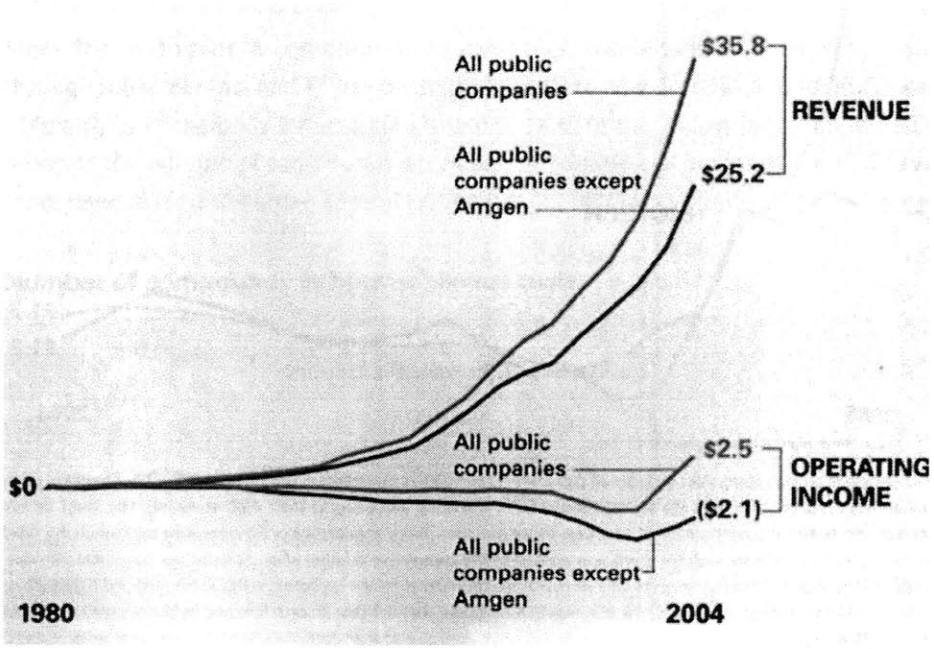


Figure 4[8]: All Public Biotechnology Companies and Amgen

Amgen is in the process of bringing a new, internally developed post-menopausal osteoporosis drug called PROLIA™ to market. It is a drug that could drastically improve the lives of its patients. Thus, it is a great opportunity for Amgen to immerge anew from the challenges it has been facing with a new drug in a growing market. Along with PROLIA™, Amgen has what is considered to be one of the best drug development pipelines in the biotech industry. Capitalizing on that pipeline will be paramount to Amgen's continued success.

2.4 Parenteral Primary Packaging at Amgen

Biotechnology or biologic drugs are mainly administered parenterally or via a needle. Drug product is presented to customers in one of two ways: vial or syringe. Vials generally contain lyophilized or freeze dried product and the patient is provided a syringe filled with a diluent such as WFI (water for injection). The patient then injects the vial with the diluent, allowing the product to mix before pulling the product back into the syringe and finally injecting the product into their body. Conversely and not surprisingly, the preferred primary package is the pre-filled syringe, which is simply a syringe that already contains a single dose in liquid form. Currently, for Amgen and for the biotech industry, both vials and syringes are made of a specialized medical grade glass. Another important distinction between vials and

syringes is the method of purchase of each at Amgen. Vials are bought in bulk; meaning Amgen completes the final sterilization of the vials prior to filling them with product. Syringes are bought pre-sterilized and therefore need no further processing prior to filling.

2.5 Marking Technology

2.5.1 Marking Technology Industry

The technology around marking nude syringes and vials has existed in some form since the beginning of the biotechnology industry. Because biologic drugs all look the same after the many steps of the manufacturing process prior to filling, biotechnology companies have always been concerned with ensuring the ability for differentiation of product in some way to prevent mix-up. For example, after a product is placed on the filling line and dispensed into vials or syringes, the manufacturing personnel have to complete a procedure called line clearance. Although a commonplace practice in manufacturing, in some ways, it is much more important for a company like to Amgen to follow strict line clearance procedures. The procedure even includes clearing the pumping and filling tubes used for that fill run to prevent cross-contamination.

Marking products at the unit level is performed in many other manufacturing industries. Food and beverage companies place lot and expiration dates on bottles and packages. Amgen places that same information on its final, consumer label for every vial or syringe. In the last two decades, the technology around marking at the unit level has been primarily basic 1D barcodes, alpha-number codes and simple color-coding on labels or vial caps. The focus of this research is on marking technologies for nude or product without a commercial label.

2.5.2 Color Coding

The simplest of the marking methods, color-coding, uses color to distinguish between products. Figure 5 and Figure 6 below show examples of how syringes and vials could be color-coded. Another possibility is the color-coding of the plunger or the needle guard. In any form, color-coding presents an extremely simple solution that is used in many applications in the biotechnology industry, especially on consumer labels. Many

biopharmaceutical companies utilize this type of product distinction for vials but has not yet been applied to syringes.

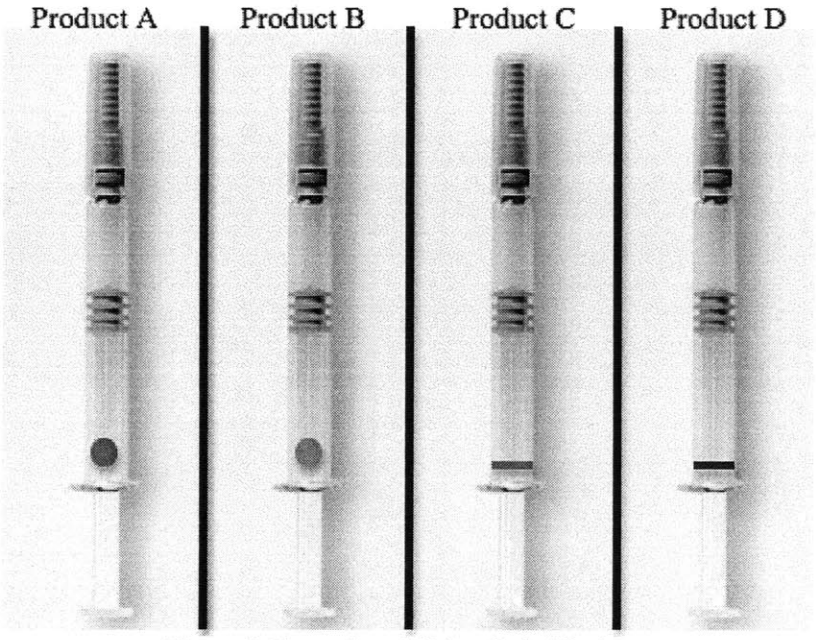


Figure 5: Examples of Color Coded Syringes

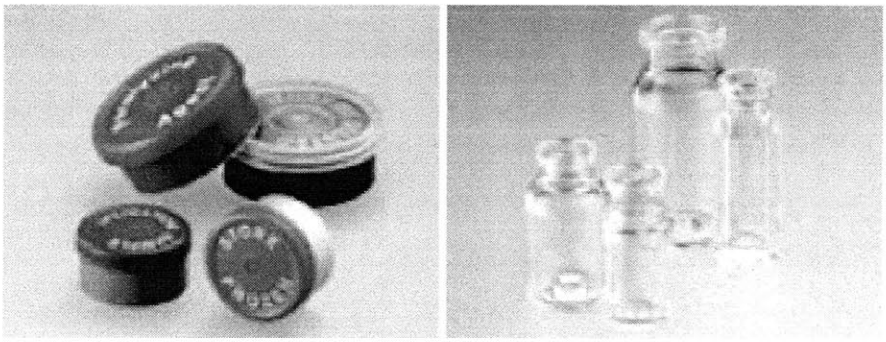


Figure 6[9]: Examples of Color Coded Vial Caps

Despite the simplicity, color-coding has had its bad press in the past. In December 2007, actor Dennis Quaid filed a lawsuit against Baxter, the manufacturer of the Heparin misused on his twins. According the LA Times, "The lawsuit also faults Baxter for using similar background colors on the labels of both the high- and low-concentration vials, despite the possible confusion it would cause."[10] (See Figure 7.) The point is that color-coding still allows for human error. Although human error can never be completely mitigated, color-coding is more susceptible than other technologies to this type of mistake.

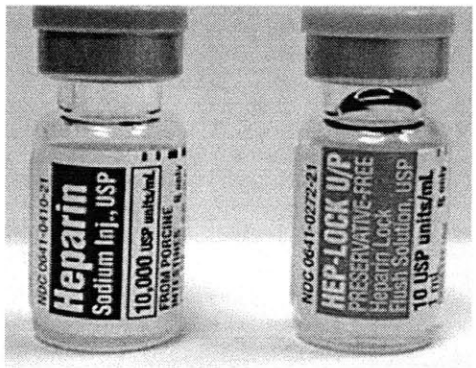


Figure 7[11]: Two Vials of Heparin in the 2007 Quaid Case

Again, looking at nude primary packages, in order to color-code, vial caps will have to be ordered for specific products. Syringes will also have to be ordered for specific products. What this does is create product specific raw material. As mentioned previously, Amgen orders raw material for all products. For example, a 3cc vial or 1mL syringe is ordered for all products that are filled into 3cc vials or 1mL syringes. Changing this order process to begin ordering product specific raw material creates three problems:

Problem 1: Risk Swapping

The reason for marking a nude vial or syringe is to prevent a product mix-up or incorrect label from being placed. Purchasing product specific raw material will only swap another risk for the current risk. The new risk would be that product A is filled into a product B syringe. It is difficult to say if the probability of one risk occurring is higher than the other but the point is, by solving the current problem, another complexity and risk is added.

Problem 2: Raw Material Procurement Management Complexity

Amgen fills product into a variety of primary packages the most common of which are 3cc vials and 1mL syringes. Amgen also fills product into 5, 10 and 20cc vials as well as other primary packages. Already the raw material procurement team has to manage the ordering quantities as well as frequency of order for each product. If Amgen were to begin purchasing product specific raw material, the complexity of the management of the raw material procurement would increase immensely. On top of that, it would provide a new risk of not being able to procure a particular syringe or vial. Amgen is already in the process of qualifying a second source for syringes to mitigate that exact risk (among other benefits of a

second source). Figure 8 below is an ordering quantity model of how the complexity would increase with product specific raw material:

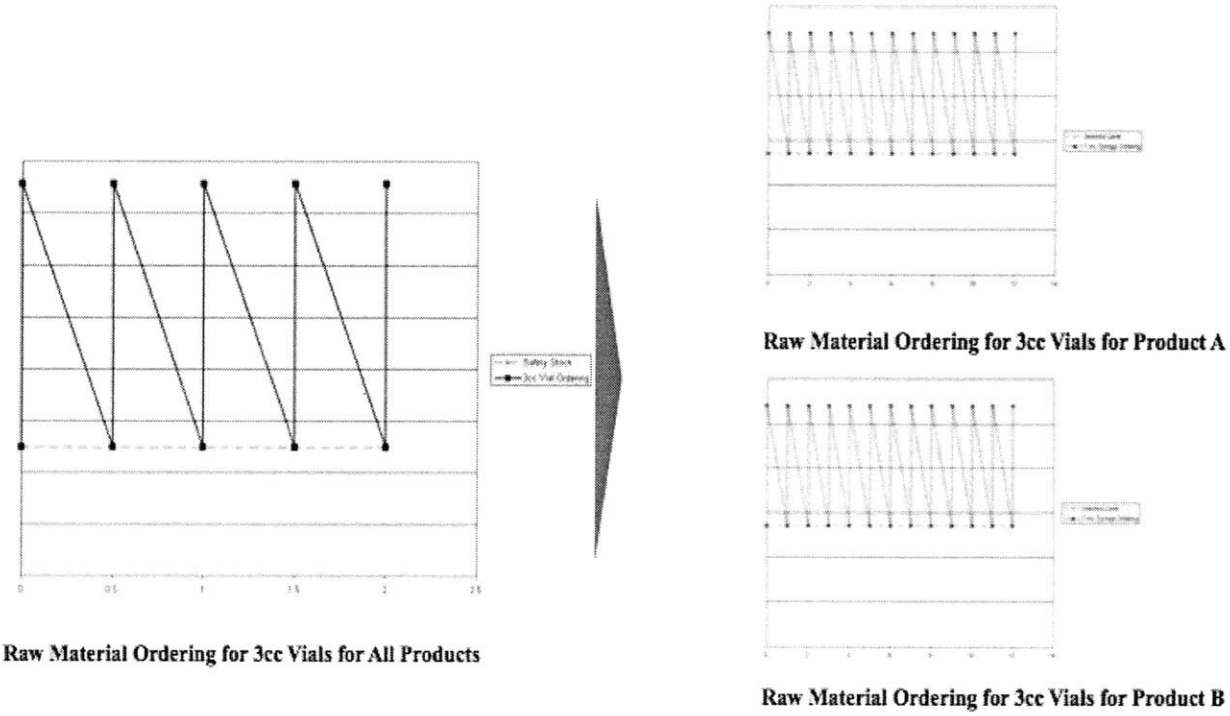


Figure 8: Raw Material Ordering Complexity Model

Problem 3: Increased Safety Stock Required

Increasing the number of different types of raw materials needed for production by marking or color-coding at the vendor would increase the complexity and amount of inventory needed to achieve a given service level.[13] The reason for this increase is due to how the total inventory is calculated. Total inventory is function of operating inventory as well as safety inventory. The amount of inventory held is more a function of risk mitigation than a response to demand volatility in the market. Even if the assumption is that with the increased number of types of raw material the operating inventory will not increase, the safety inventory will. Safety inventory or safety stock is defined as follows:

$$I_{safety}^{all} = z \times \sigma_{LTD}$$ [13]

where z = service level and σ = standard deviation of lead time demand

Because "the total inventory required to provide a specified level of service increases by the square root of the number of locations in which it is held"[13], the assumption here is that the same holds true for the number of raw material types. Therefore, assuming 8 different products, the new formula derives from the above equation and will approach the following:

$$I^{8}_{safety} = z \times \sqrt{8}\sigma_{LTD}$$

The increase in safety inventory for Amgen would be about 280% and is approximated by the graph below:

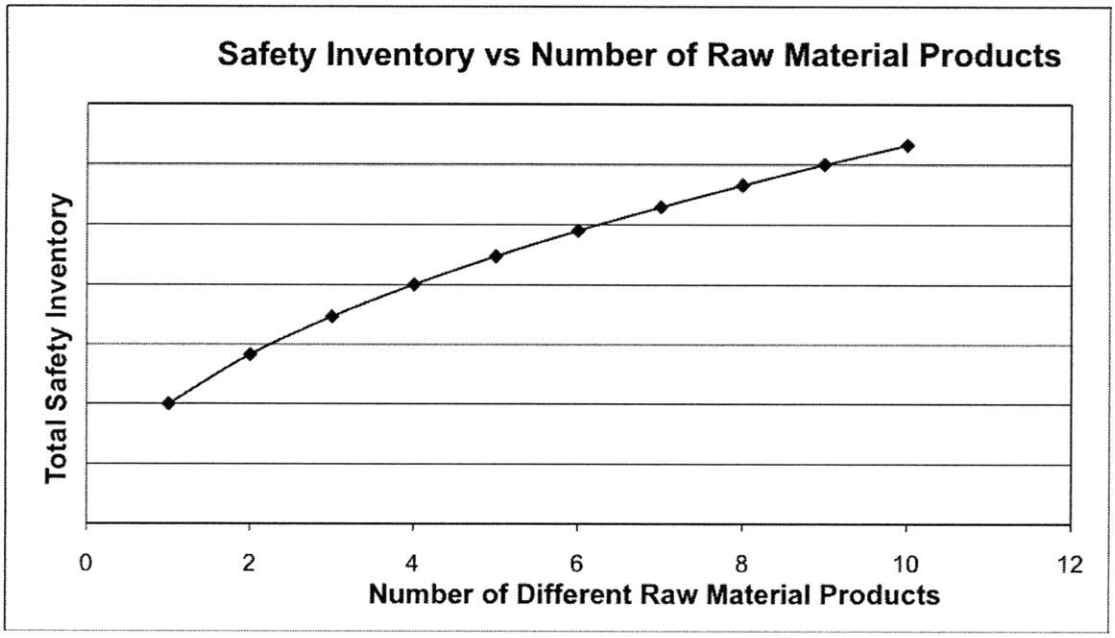


Figure 9: Square Root Law applied to Multi-Raw Material Products

Despite the obvious application and simplicity of color-coding as a solution for marking nude vials and syringes, the problems outlined above outweigh any risk mitigative benefits this solution would provide. Therefore, it was not analyzed any further as a viable option.

2.5.3 Inkjet

Technology developed in the 1950s and applied to printing in the 1970s, inkjetting has been used as a solution to nude vial marking for decades. Typically, ink is jetted onto the side, the top or the bottom of vials in the form of barcodes or alphanumeric codes. Inkjet technology is inexpensive in comparison to other solutions. It is also an industry-tested solution, at least for vials, and therefore, systems are essentially turnkey and ready for

application. Despite their use in the industry for vials, inkjet technology has several drawbacks. The fill and finish process of biologic drugs is performed in Class 10,000 clean rooms and having a solution that is spraying microscopic droplets of ink at the surface of the glass is less than ideal. Also, due to siliconization process variation upstream at the supplier of the glass syringes, silicon oil is sometimes present on the external surface of syringes, making it almost impossible to get the ink to stick consistently. The consistency is important in an industry where six-sigma quality is in some situations not high enough. With tens or hundreds of millions of units being produced each year, a solution must be extremely accurate as well as precise. Currently, many biotechnology manufacturers including Wyeth employ inkjet technology for vial marking. Below is an example of a vial with a standard inkjet 2D matrix barcode:

Figure 10: Inkjet 2D Matrix Barcode

2.5.4 RFID

RFID or Radio Frequency Identification is an automatic ID technology that utilizes a tag to track objects using radio waves. Tags contain an integrated circuit and an antenna so as to be able to store information as well as transmit a signal. RFID is being used in applications from asset tracking to toll collecting to animal tagging. MIT Mechanical Engineering Professor Sanjay Sarma comments "RFID systems are different from other means of identification because RF communication is non-contact and non-line-of-sight, whereas other means of identification are either contact-based or require line-of-sight."[14] See Appendix 9 for a summary of RFID versus barcodes. Factors that limited its use such as size

and cost are quickly becoming problems of the past.

In 2004, Accenture completed a study of RFID application to the biopharmaceutical industry: "Findings, based on shipping, tracking and tracing nearly 13,500 packages of pharmaceuticals over an eight week period, show that EPC/RFID can help satisfy regulatory and retailer requirements, increase product security and consumer safety, enhance order accuracy and labor productivity and increase the efficiency and speed of recalls and returns."[15] Investments in RFID have increased and, in a large way, have come in the form of mandates in the last five years. In 2005, Wal-Mart required its top 100 suppliers to place an RFID embedded label on all shipments to Wal-Mart. The Department of Defense has also mandated the use of RFID for asset tracking on packages. This massive investment, although not the silver bullet for supply chain management as previously thought, has driven increased innovation and reduced tag costs. For example, the costs have decreased at a similar pace to PCs as seen in this adaptation of Richard Moscatiello's price prediction model for RFID. The model is simply that, a model; but the model reflects the reality that RFID tag costs are coming down.

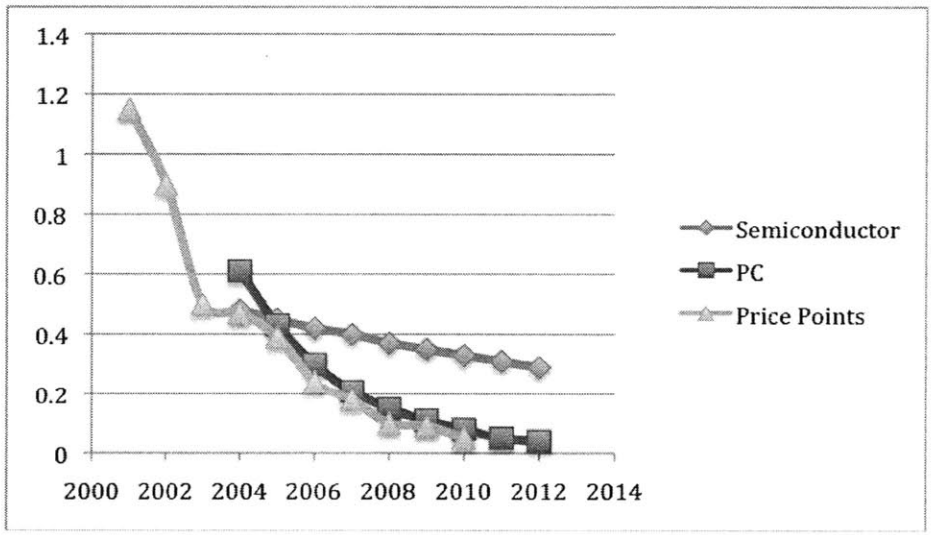


Figure 11[17]: Adapted RFID Price Point Prediction Model

Even with size and cost becoming less problematic, there are still prevalent conerns about privacy, especially when applied to prescription medication. Despite this, Purdue Pharma, manfacturer of the pain killer *Oxycontin*, currently uses RFID to track its bottles, specifically to reduce counterfeiting and shrinkage. "In a recent development, West Pharmaceuticals and Tagsys USA have incorporated an RFID device into the Flip Off seal

of an aluminum cap for parenteral products."[18] It hasn't yet been applied by biotechnology manufacturers but remains an attractive option for marking nude product with the added benefits of track and trace as well as anti-counterfeiting. Finally, for biotechnology manufacturers, there is concern that the sensitive proteins in the biologic drugs will experience a "potential product temperature increase when the RFID tag is exposed to the electromagnetic energy of the UHF RFID reader for extended periods of time."[18]

2.5.5 Laser Marking

Laser marking is a technology in which a laser is used to burn a mark into a substrate, which, in this case, is glass. Laser marking is an attractive solution compared to inkjet because it is much cleaner, potentially faster and more permanent. Laser marking on glass generally comes in two forms: (1) marking on the outside surface on the glass and (2) marking on the inside of the glass. Several types of lasers are used for glass laser marking from CO_2 to YAG to ArF. Each has its specific uses for particular applications or glass types.

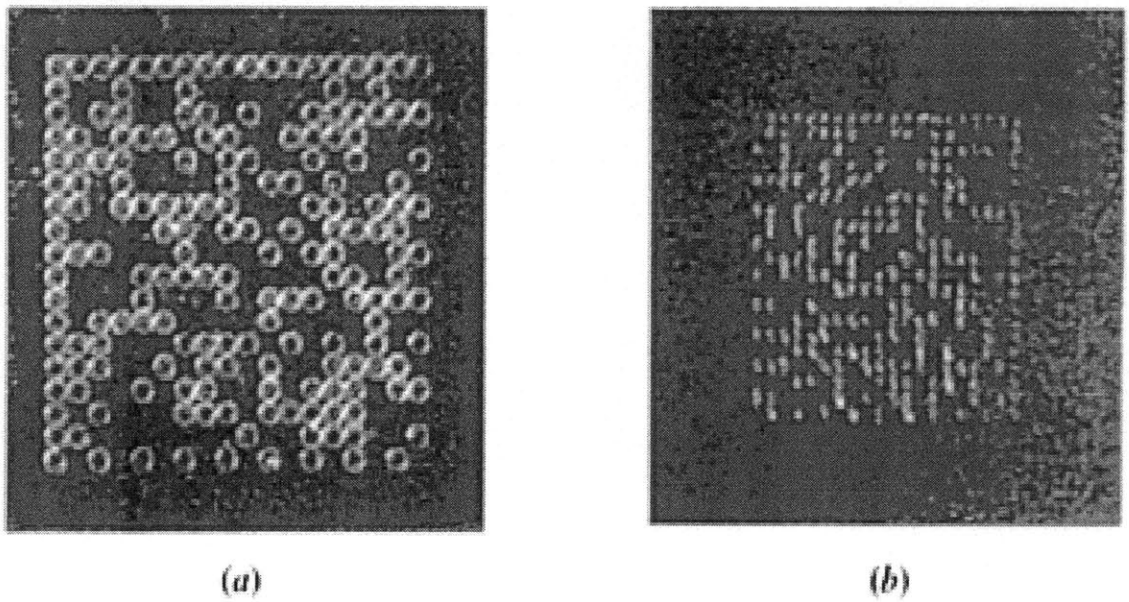


Figure 12[19]: Examples of Laser Marking on Glass

Laser marking has been considered as a marking option for a long time. Lasers are used to etch lot number and expiration date onto commercial labels but have not yet been applied to

any biotechnology manufacturer's fill and finish operation for marking glass. Despite lower maintenance and higher reliability numbers over inkjet technology, the concerns of increased glass breakage along with worry of deleterious affect on protein stability have precluded any real industry adoption.

2.5.6 Clear Label

Labels are placed onto every syringe and vial headed for consumer use. Another technological solution to marking nude product that is shipped to internal sites or external companies is to apply a clear label with some sort of distinguishing mark, which at a minimum would denote one product from another. A leading biopharmaceutical company is using this technology for their brand name vaccine. Not only has it proved successful at marking each syringe, it yielded a secondary benefit of reducing syringe glass breakage. There are several incentives for the application of clear label technology versus other technology solutions. First, labeling is a core competency of biotechnology companies as it is an action performed millions of times per year within the firm. Second, it allows use of capital equipment already owned by the company. Lastly, at least in the short term, it is significantly lower cost even on per unit basis. Although only one biotechnology firm in the industry uses clear label technology, it has immense potential as a solution to marking nude product.

2.5.7 Technology Advancements

2.5.7.1 "LaserJet" Ink Ribbon Technology

LaserJet ink ribbon technology is a modern innovation on applying ink to glass substrates. A consumable ribbon of ink is passed in front of laser, which is fired on the ribbon in the correct pattern to deposit the mark on the glass. Developed by Panasonic in conjunction with Tesa, the technology claims near indelibility of the mark on the glass along with no mess. As a marking solution, the laserjet mark could yield the benefit of the indelibility of a laser mark without the potential for microscopic glass damage. A potential issue of this technology is whether the ink will adhere to the glass in a robust and repeatable manner.

2.5.7.2 Plastic Resin Syringes and Vials

Although currently used in the Japanese biotechnology industry, plastic (cyclic olefin polymer) syringes and vials are not currently used as primary packages in the US. Long-held concerns of leachable materials in the plastic compounds have kept the application of the technology from the industry. With an already complex regulatory process for FDA approval, companies also have a lower incentive to try for approval of an entirely new primary package for their drugs (which would require years of protein stability studies and millions of dollars). But, increased pressure from the FDA and EMEA to reduce preventable glass breakage to zero along with new innovations in plastic compounds is making the idea of plastic syringes for biologic drugs much more attractive to a manufacturers. The presence of plastic syringes and vials would not only reduce waste from preventable breakage but it would also reduce the need for complex packaging during transport. Along with those benefits, it would also make marking syringes and vials simplistic. Most, if not all, of the issues with inkjet and laser marking technology would disappear because of the physical nature of plastic. In short, the use of plastic syringes and vials by a biotechnology manufacturer would allow for their choice of technologies with many fewer concerns.

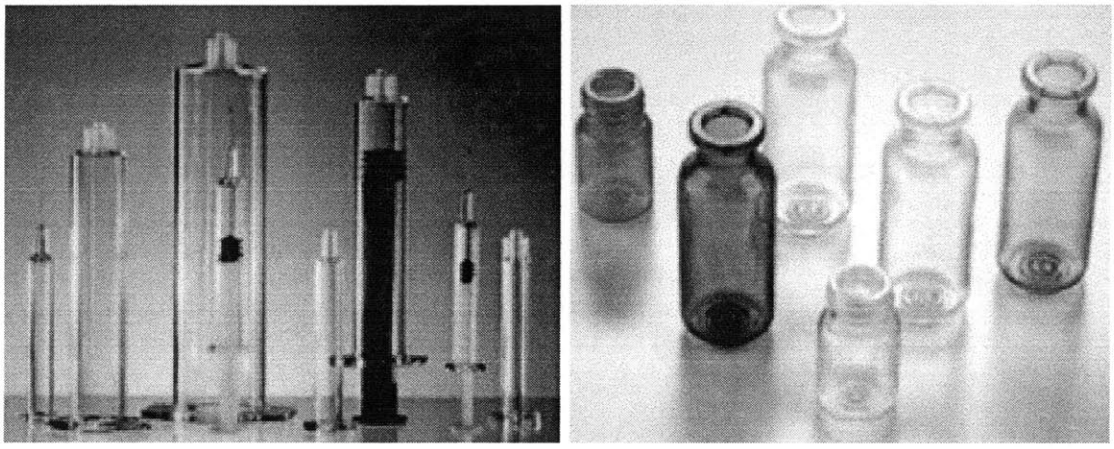


Figure 13[20]: Topas™ Cyclic Olefin Copolymer Syringes and Syringes

3 Hypothesis

Applying marking technology to internal operations can both mitigate the potential risk as well as alleviate future regulatory pressure, domestically and internationally. Marking technology, although requiring capital investment, is a key component in a sustainable, competitive business operation for a biopharmaceutical company like Amgen. Specifically, in evaluation of current marking technologies, applying a specially designed clear label directly after fill presents a low-cost, near-term solution that will:

- Reduce risk of product mix-up
- Increase brand protection
- Increase flexibility to use external final labeling contractors

4 Methodology

4.1 Data Collection and Analysis

Lab scale testing, data collection and analysis were performed at Amgen's corporate headquarters in Thousand Oaks, CA. Three labs were primarily utilized: the Device Lab, the Technology Transfer Lab and the Transportation Simulation Lab. However, some of the testing was performed at various supplier sites and the data will denote that fact.

Because of the broad business implications marking technology could have across several corporate functions, interviews were conducted across Amgen to understand all facets of the problem and its likely affect. From supply chain and manufacturing to raw material procurement and finance, a broad swath of views were studied about marking technology for risk management in the supply chain.

For practical purposes, testing was completed on a lab scale. Even on a lab scale, some of the equipment necessary was expensive. Where appropriate, the supplier performed testing and data was shared to highlight the different issues with different technologies. Specifically, three technologies were chosen after working closely with the process development and DP&DD teams. Each of those technologies is presented in later chapters with thorough analyses about their feasibility to be incorporated into Amgen's current operations.

4.2 Project Methodology

The project methodology roughly followed the DMADV model.

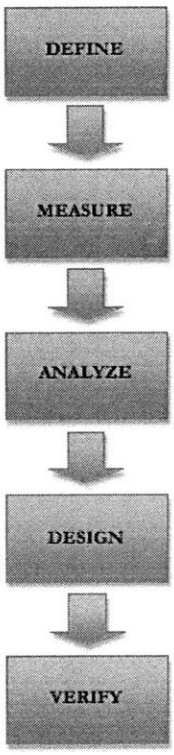


Figure 14[21]: DMADV Model

Define – Understanding the problem and the processes involved in marking a syringe or vial in Amgen's current operations. Figure 15 is a basic value stream map of the entire process, beginning immediately after the fill-finish process. The red boxes denote the defined areas of this project.

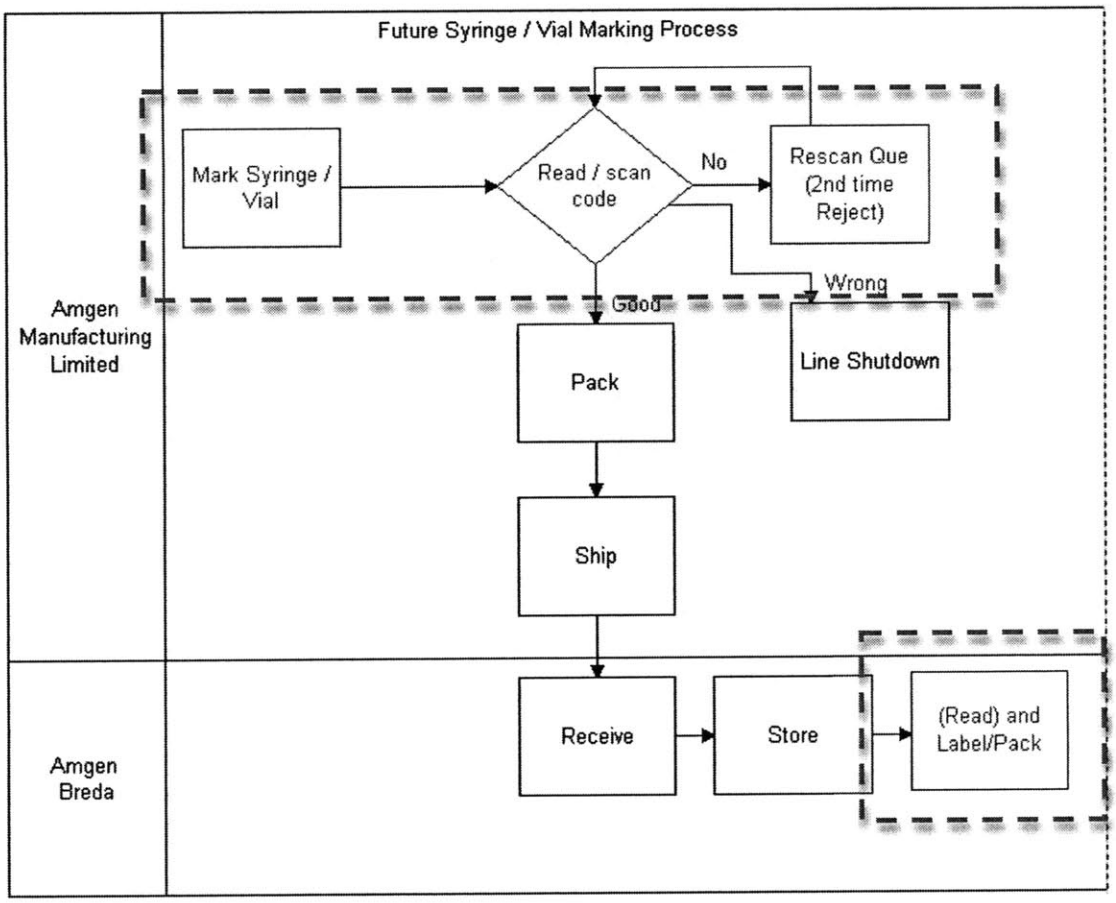


Figure 15: Value Stream Process Map

Measure – Having researched the many options available for marking syringes and vials, customer needs and specifications are measured against options to determine best fit.

Analyze – Each of the three selected options is lab scale tested to answer key unknowns about the technologies in relation to their application to the process.

Design – The final technology is theoretically applied to the process, using implementation analysis to determine fit and potential problem areas.

Verify – The performance of the final solution is checked and relevant stakeholders verify the solution.

4.3 Decision Framework

The list of technological solution options presented in the Chapter 2, although not exhaustive, is representative of the state of the industry. A framework was created to help analyze the multiple variables against the multiple options. Using multi-attribute utility theory (MAUT), a decision model was created to better understand the whole picture. "Multiple attribute utility theory provides a set of techniques for accomplishing two tasks: (1) quantifying the utility derived from individual attributes and (2) combining the utility from each attribute to arrive at an overall measure of utility."[22] It is a simple, elegant way to quantify qualitative attributes and decide between multiple solution options in any situation.

TABLE 8.1 The Utility of Strategies to Improve Typing Ability

	Attribute			*Overall*
Alternative	*Speed*	*Accuracy*	*Applications*	*Utility*
Large group television presentation	24	49	21	31.7
Large group lecture	39	65	34	46.6
Teacher-based tutorial	95	69	80	83.6
Computer-based tutorial	87	83	41	76.9
Importance weight	0.48	0.33	0.19	

SOURCE: Adapted from Lewis (1989).

Figure 16[22]: Example of Multi-Attribute Utility Theory

As shown in Figure 16, each attribute receives a weighting score depending on that attributes relative importance to the overall utility. Developed in conjunction with subject matter experts at Amgen, the attributes shown in Table 2 below are representative of the most important areas of consideration for evaluation of marking technologies. It is important to note the limitations of multi-attribute utility theory. If a given decision has too many attributes (i.e. more than 10), it will be difficult to weight each attribute significantly to see differences between different options. Therefore, the list of attributes for marking technologies is not exhaustive. Rather, it is a summation of the few most important attributes that may contribute to an options' long-term success.

Attributes	Description
Marking Efficiency	Cycle time and simplicity of marking
Capital Cost	Total fixed cost to procure equipment
Ongoing Cost	Consumable and maintenance costs
Supply Chain Effect	Solution impact on current supply chain
Ease of Implementation	Implementation simplicity
Scalability	Ability of technology to be scaled to larger volumes
Risk	Risk inherent in the technology applied to the process

Table 2: Multi-Attribute Utility Theory Attributes

Attributes can be divided into two categories for this type of decision analysis: qualitative and quantitative. Capital cost, ongoing cost and scalability are the only attributes that are quantitative. Scalability is a quantitative measure of cycle time and overall complexity of reading the mark. The results of the multi-attribute utility theory model are presented in Appendix 10.

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5 Laser Glass Marking: A Technical Evaluation

This chapter presents the strategy and tests performed during the evaluation of glass laser marking as a potential solution to mark syringes and vials. The tests were completed at both Amgen's laboratory as well as at the vendor's site.

5.1 Laser Marking Lab Scale Evaluation Strategy

The objective of the lab scale testing is to determine if laser marking is a feasible solution given the current fill-finish processing techniques used in the industry. Feasibility for this and all other technologies relies on the following factors:

1. Cycle time of laser marking process is not prohibitively low so as to create a bottleneck in the current fill and finish process
2. No affect on primary package structural integrity and container closure integrity (CCI) as compared to a control sample of unmarked syringes
3. No affect on protein stability for any of Amgen's drugs

Amongst glass and biotechnology-manufacturing experts, the key unknown of this technology is whether laser marking will create micro-cracks in the glass due to the immensely localized heating and cooling at the location of the mark. Amgen's tolerance for glass breakage rates is extremely low. Rates at even a few parts per million are enough to create problems for a manufacturer with the FDA. Therefore, if laser marking were to increase glass breakage during processing, it would be an unsatisfactory solution.

In Loch and Krause's *Mathematical Simulation In Glass Technology*, the theoretical view of micro-cracks as a result of laser marking in borosilicate glass, the type of glass used to manufacture biopharmaceutical vials and syringes, looks like the figure below:

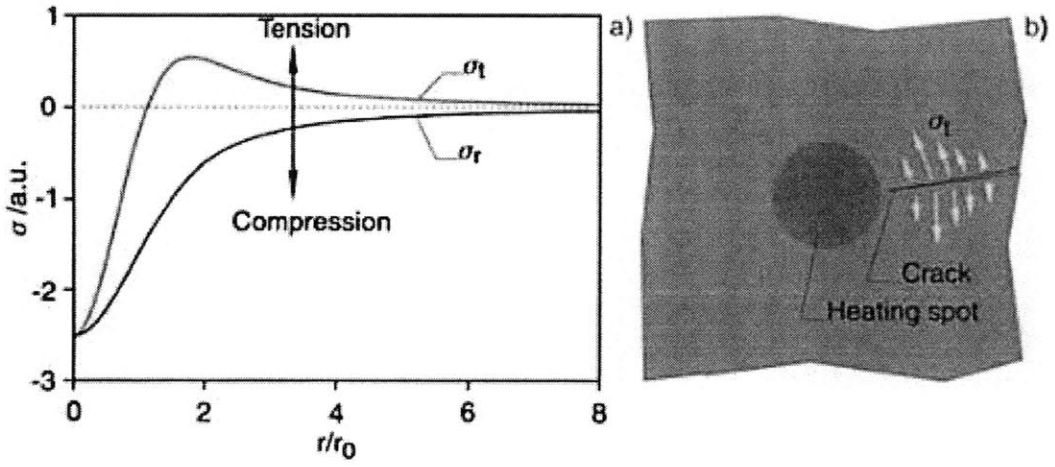

Figure 17[23]: Estimate of Localized Laser Heating and Forces Created

Theoretically, laser-marking glass will cause micro-cracks if only at a microscopic level. A battery of tests was performed to yield significant data to prove the viability of laser marking as a solution. The tests combined testing done at Amgen as well as tests performed at vendor and peer firm sites.

Laser marking onto a glass substrate is a difficult task to achieve in a reliable, non-destructive fashion. Mechanical Engineering Professor David Parks of MIT remarks, "[there are] at least two issues which need to be addressed: one is the possibility that the laser marking inducing micro-cracks. A second possibility is that the rapid thermal transients of the marking manages to impart local residual stress that, if significantly tensile, could also become problematic." The "problematic" aspect of residual stress for this industry is that it could cause latent failures in the field where they are the most damaging. Even a tremendously small field failure rate can be cause enough to spark an FDA recall. To illustrate the complexity of laser marking, for example, one vision and laser supplier had immense difficulty with exactly the problems Professor Parks outlined. Below is a picture from a vial barrel after a laser mark was performed at the supplier's facility:

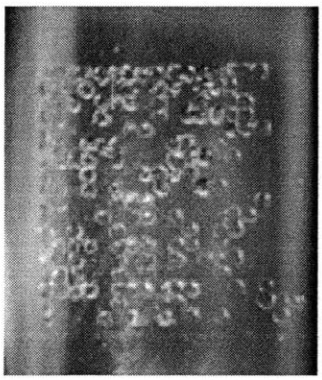

Figure 18: Vial Barrel Surface Cracking induced by Laser Marking

Particular notice should be paid to the blistering along with the cracking at the surface of the vial. Furthermore, this test was done to a static vial in a clamp in a controlled laboratory test. The reality is that laser marking not only has be successful in a laboratory but also in a fully functioning commercial-scale biotechnology manufacturing facility with vial and syringe processing speeds up to 400 or 600 units per minute. The technology to be applied in this situation is a tool and should not hamper the firm's ability to conduct business nor should it increase the product risk. Laser marking is in some ways as much an art as it is a science. With subtle and minute differences between glass formulations, devising a laser solution is indeed a monumental task; too much power and the glass will blister and crack as in Figure 18 above. Also, too long or too short a wavelength will lead to too much absorption or too much transmission of the laser light, which then could damage the protein inside.

5.2 Lab Scale Tests

Given the discussion and results above from some suppliers, a main supplier was used for all laser marked material in the following lab tests. The tests were devised to answer unknowns about the technology as well as address areas of testing that had not already been completed by the supplier. The main supplier is Frewitt Printing SA, a Swiss company that designs and manufactures "security marking systems designed to prevent counterfeiting (track and trace system) and to guarantee a 100% traceability of products."[24] Specifically, "Frewitt has developed a laser marking system using a low energy laser to engrave a [2D] Data Matrix code directly on the glass syringe barrel. Seidenader provides the high-speed vision system and illumination technique to verify this type of code reliably."[24] Frewitt is the only supplier in the industry that has shown reliable and repeatable results in marking

biopharmaceutical glass at production speeds. Data and graphs from Frewitt's testing in conjunction with other firms in the biopharmaceutical industry can be found in Appendix 4.

The following sections are the results and discussion of both qualitative and quantitative testing of Frewitt laser marked syringes in various laboratories at Amgen Inc. Tests were designed with help from Amgen glass experts, Frewitt employees and other industry professionals.

5.2.1 Qualitative Microscopy

In order to understand possible gross effects of the laser marking, microscopy was performed on a large number of marked syringes as well as vials. From a qualitative perspective, "When stress is applied to a material internal strain results. With transparent materials [such as glass], strain often results in regions of optical activity. Essentially, waves of light passing through these regions are more or less twisted (i.e., go through a sort of change in their orientation) by the optical activity."[25] Thus, the purpose of microscopy is to determine location and possible level of 'optical activity'. Although the presence of strain regions is not conclusive in the absolute sense, it does yield a significant amount of qualitative understanding of the nature and location of the strain in the glass.

The testing setup consisted of a 500x microscope combined with lights, a camera and a polarizer. A polarizer takes mixed polarization light and converts into a uniform polarization, allowing the ability to see the changed direction of light passing through transparent materials. Each of the 200 standard *Becton Dickinson* (BD) syringes is analyzed using both standard and polarized light. In looking for the regions of optical activity, an Amgen glass expert recommended looking for specific 'bright' spots, as these spots were indications of increased stress in that location. Under standard light, the laser mark across all samples appeared as it does in Figure 19 below:

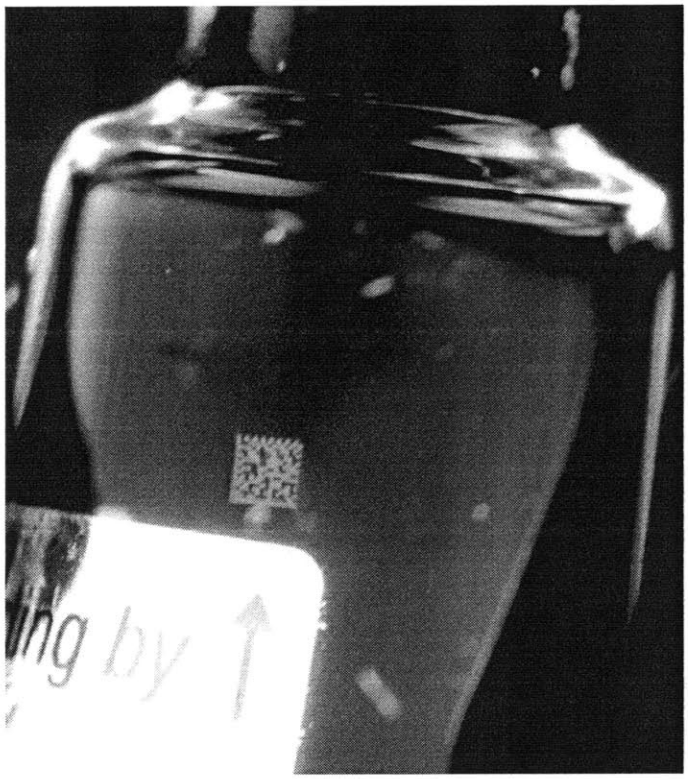

Figure 19: Microscopy of Laser Mark under Standard Light

It is important to note the location of the laser mark from the Frewitt system. The previous supplier with the blistered glass mark in Figure 18 applied the laser mark to the surface of the syringe. Frewitt actually embeds the mark inside the wall of the syringe or vial using unique combination of wavelength and power. As a point of clarification, refer to the not-to-scale Figure 20 below of a wall of a syringe or vial:

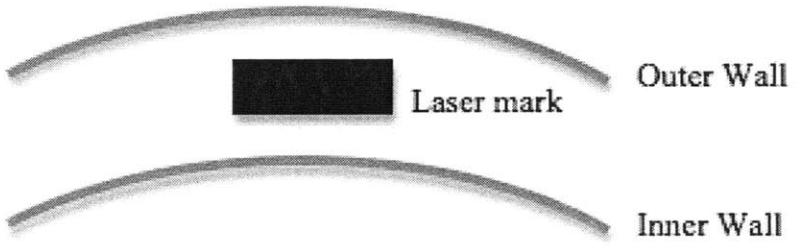

Figure 20: Location of Laser Mark in Glass Wall

The location of the Frewitt laser mark has benefits and drawbacks. Given the nature of the process the Frewitt system would be placed into (i.e. biopharmaceutical processing), marking inside the wall of the glass produces less byproduct than marking on the surface. According to Frewitt, 0.5mg of glass particles are produced per 1 million codes. The drawback is the potential for increased internal stresses that could lead to crack propagation during handling or transportation. Sections 5.2.2 through 5.2.4 are lab scale tests that attempt to answer of there is any increased risk of breakage during handling and transportation.

An example of the laser mark seen under polarized light can be seen in Figure 21 below. Notice the red arrows pointing to areas of increased optical activity, which manifests itself as almost blurry areas surrounding some of the dots of the 2D matrix.

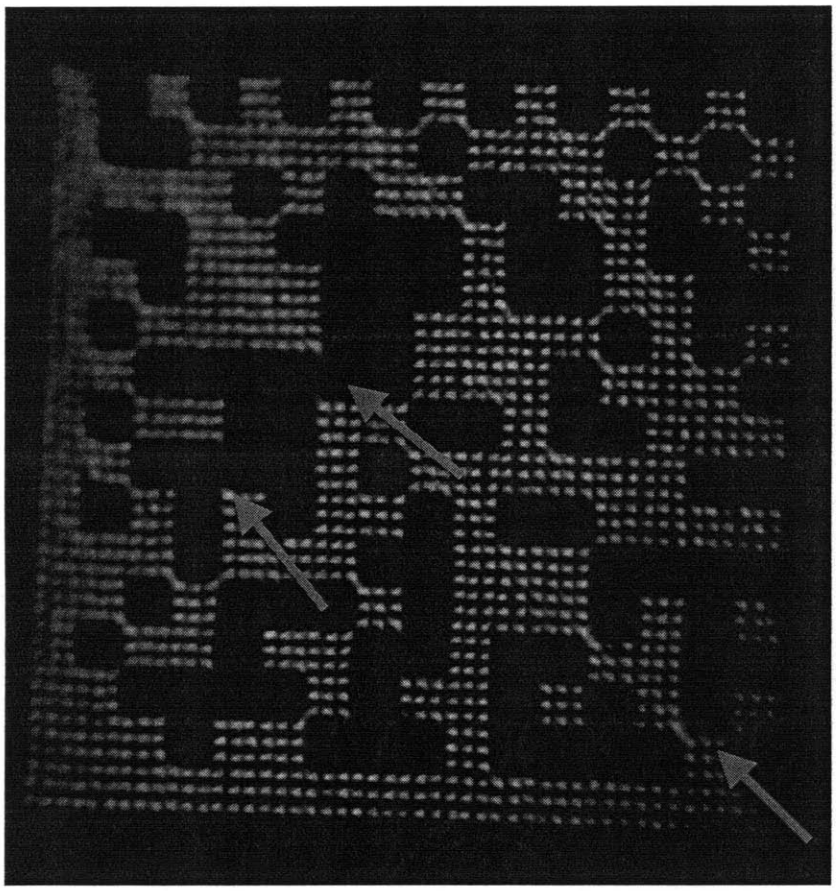

Figure 21: Polarized Image of Laser Mark

Throughout the microscopy analysis of each marked syringe, it was clear that these areas of increased optical activity were signs of enclosed stress. In the words of an Amgen glass expert, "With the polarizer, you can certainly see the areas of enclosed stress in the laser

marked syringe, but that doesn't say anything as to the amount or whether it would actually increase breakage on the manufacturing line".

During the analysis of each syringe, surface pitting was found on about 1% of syringes. The pitting appeared to only be present above marked areas as in the picture below on the left below. The picture on the right is a picture of the same syringe this time with the metal tip of a needle pushed into the one of the pits in the surface. The area clearly lights up showcasing the increased stress from the surface pitting.

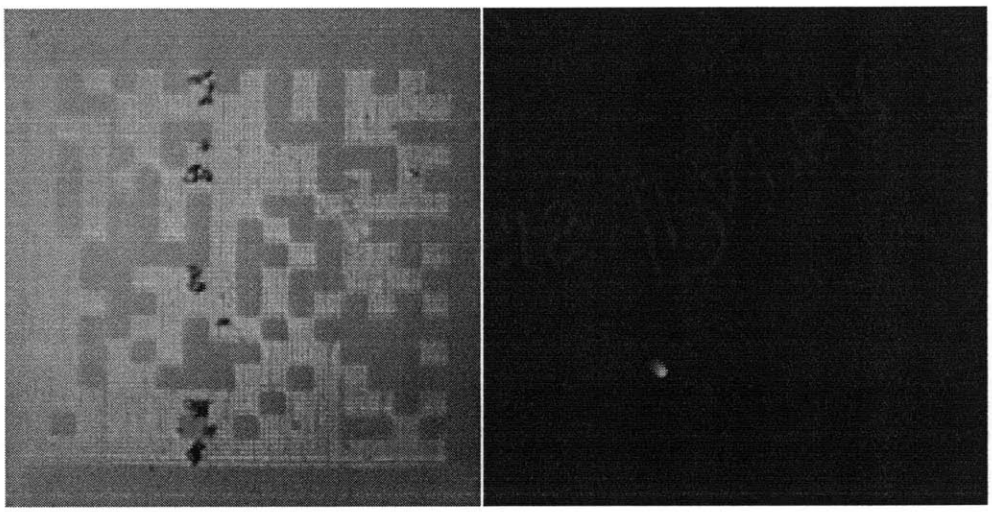

Figure 22: Surface Pitting on Laser Marked Syringes

The results of the microscopy study are a confirmation of areas of increased localized internal stress due to the laser mark. Although not conclusive in terms of the amount of stress, the study validates assumptions of the internal stress and necessitates the further testing to determine the effect, if any, the mark has on the structural integrity of the syringe or vial. Despite a small percentage, the surface pitting seen in 1% of the syringes is also of concern.

5.2.2 Fracture Force Testing

The purpose of this lab scale test was to determine if the enclosed stress of the laser mark would increase breakage during processing. Of particular importance is a processing step in which a mechanical arm picks up each syringe using mechanical fingers placed inside the top of the syringe. Both Wyeth and Frewitt performed a number of tests including shock, compression, handling and thermal cycling. The results of these tests are presented in Appendix 4-6. What those tests did not include was a study of the effects of internal

compression on marked and unmarked syringes to determine if there was a statistical difference, which the tests below did address.

The test set-up consists of a precision force inducing and recording device, in this case an *Instron*™ machine. The syringe was loaded onto a cylindrical gauge above the circular table of the machine. The end of the gauge corresponded to the location of the mark. A total of 100 marked and 100 unmarked syringes were broken in this test to obtain a statistically relevant amount of data. The test set-up can be seen in Figure 23 below:

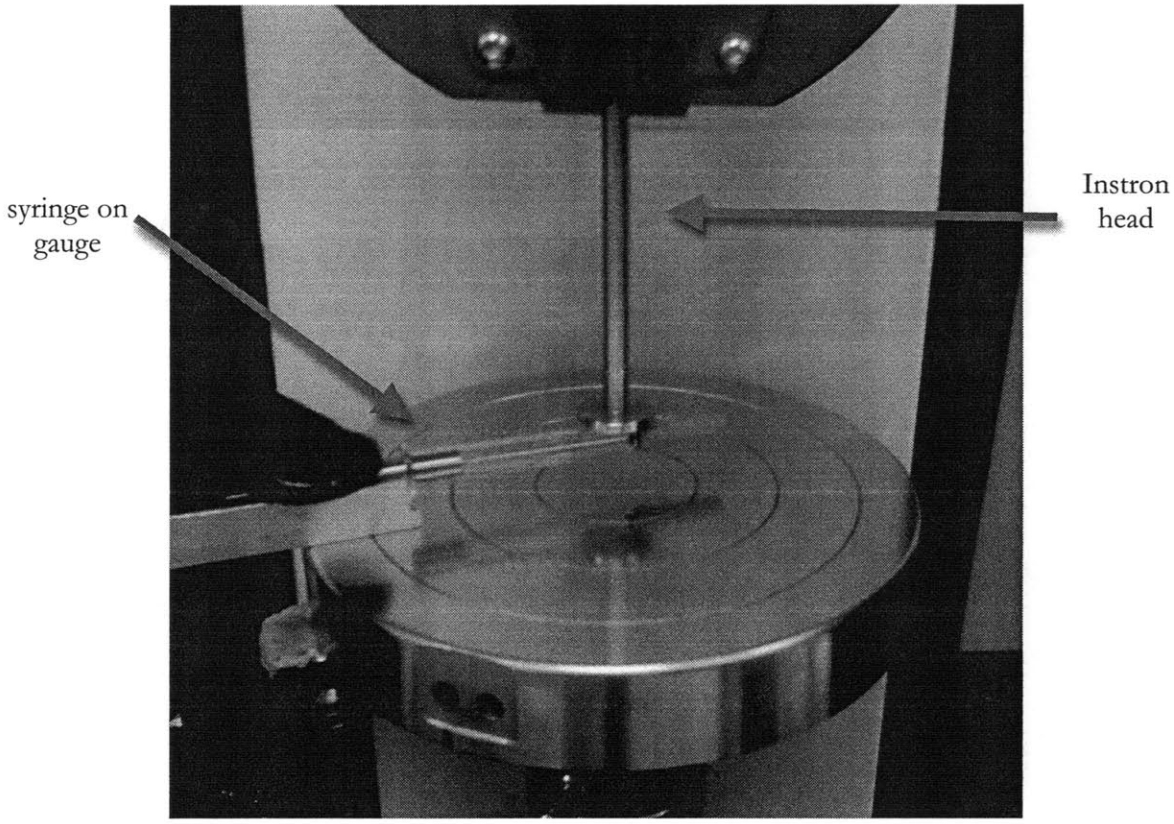

Figure 23: Fracture Force Test Set-Up

The results of the tests are broken into two parts. First, individual breakage results were examined qualitatively. The graph in Figure 24 shows an individual breakage curve. What can be seen is a section of elastic deformation or bending followed by catastrophic failure of the glass syringe. The syringe absorbs the energy during the initial push of the machine to its maximal point before the energy is released in breaking. Second, the total results were tabulated and analyzed for standard deviation. The data from all 200-syringe breakage tests were tested to determine if a statistical difference could be found between the marked and unmarked syringes.

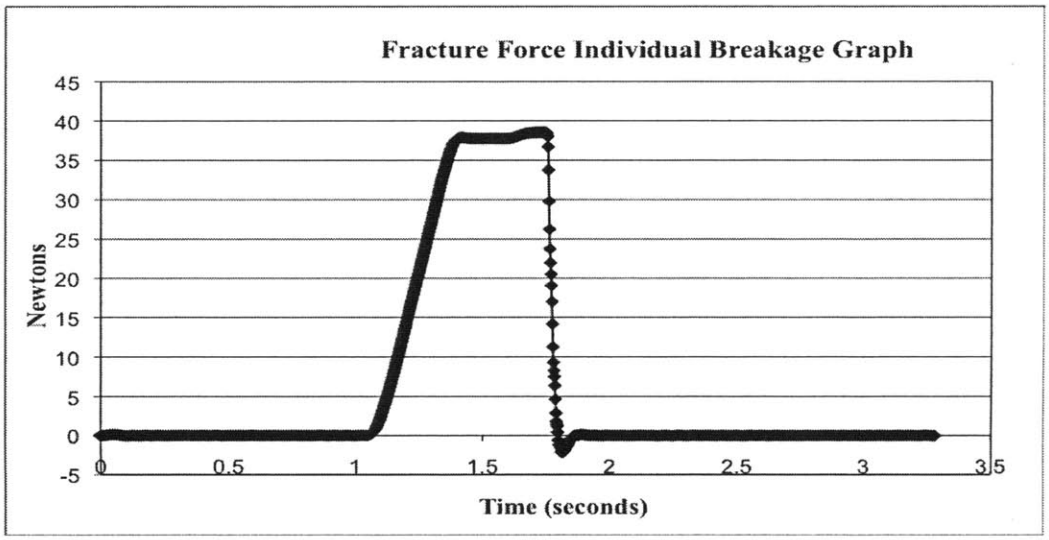

Figure 24: Individual Breakage Graph

The picture below shows the result of the breakage during testing. As can be seen, the breakage happened in a catastrophic fashion with pieces of glass flying out in all directions from the test area. Appropriate precautions were made to ensure the safety of the tester as well as all lab personnel.

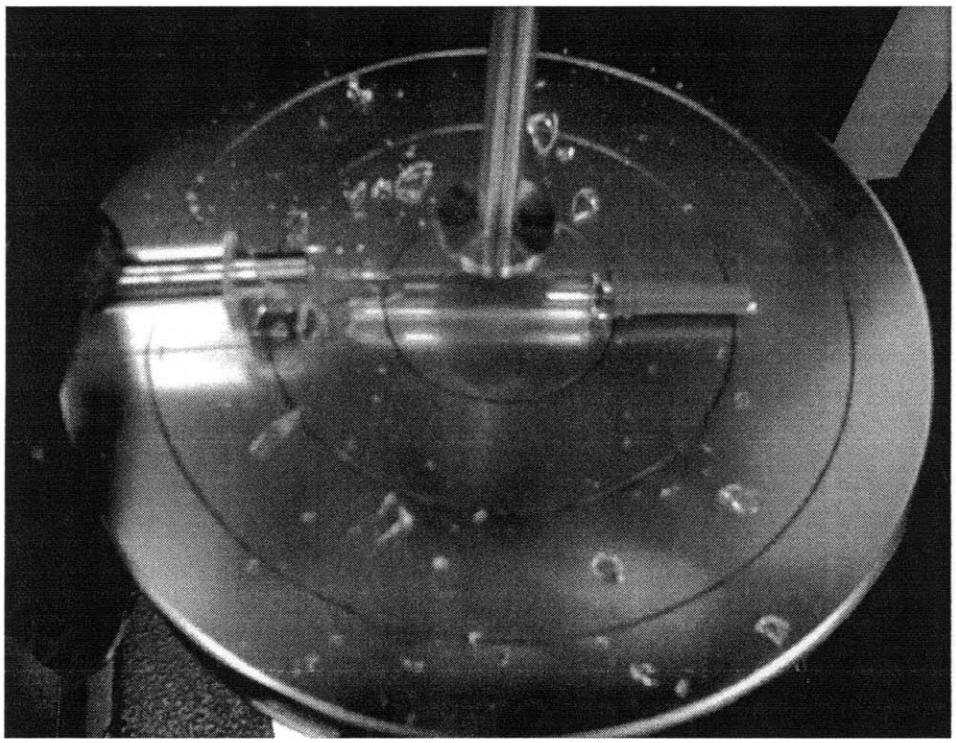

Figure 25: Catastrophic Glass Breakage during testing

The results of the entire study can be found in Table 3 below:

Fracture Force Test Results		
	Unmarked	Marked
Mean	37.7595	37.7357
Standard Deviation	0.1510	0.1271

Table 3: Testing Results

Using a basic t-test to determine if the difference in the two means in statistically significant:

$$t = \frac{\mu_{UM} - \mu_M}{s}$$

where

$$s = \sqrt{\frac{(\sigma_{UM})^2 + (\sigma_M)^2}{N}}$$

Calculating the appropriate values yields a t-value of 0.853, which means that the difference between the two means is not statistically significant. Thus, according to this test, there is no statistical difference between a syringe that has been laser marked and one that has not been marked. It is important to note a few key factors that relate to the sensitivity of this analysis. Given the high volume nature of the biopharmaceutical industry, a sample size of 100 is relatively small. What this means is that given a larger sample size, the effective difference between the two means could be more significant. Also, the data shows that there is a small, albeit statistically insignificant difference between the two means, it would seem natural to assume that the difference is 100% correlated with the laser marking. Although it is likely that it is true, given again the relatively small (>100) sample size, it is possible that glass-manufacturing variation accounts for the difference. Because this is not an industry standard test, there is not data available to test this secondary hypothesis.

5.2.3 Transportation Simulation Testing

The purpose of this lab scale test is to determine if the laser mark creates increases susceptibility to breakage in transportation. The standards organization for transportation simulation and testing is the ISTA. "The International Safe Transit Association is an organization focused on the specific concerns of transport packaging, and ISTA test procedures define how packages should perform to ensure protection of their contents. Use of ISTA test procedures reduces risks in the transport environment and increases confidence

in the safe delivery of a tested packaged-product."[26] More specifically, the lab scale tests performed were in accordance with:

> *ISTA 3 Series*: General Simulation Performance Tests. Designed to provide a laboratory simulation of the damage-producing motions, forces, conditions, and sequences of transport environments. Applicable across broad sets of circumstances, such as a variety of vehicle types and routes. Characteristics will include simple shaped random vibration, different drop heights applied to the sample package, and/or atmospheric conditioning such as tropical wet or winter/frozen.
>
> *Procedure 3A:* Packaged-Products for Parcel Delivery System Shipments 70kg (150 lb) or less (standard, small, flat or elongated) Test Procedure 3A is a general simulation test for individual packaged-products shipped through a parcel delivery system. The test is appropriate for different package types commonly distributed as individual packages, either by air or ground.[26]

The tests were conducted at Amgen's Transportation Simulation laboratory.

5.2.3.1 Vibration Simulation Testing

The vibration simulation is a test model to simulate the vibration forces experienced by the packaging and product in trucks or planes. The methodology behind the test was to package both marked and unmarked syringes in standard packaging and place it on the vibratory table for the prescribed amount of time to determine if there were any instances of glass breakage.

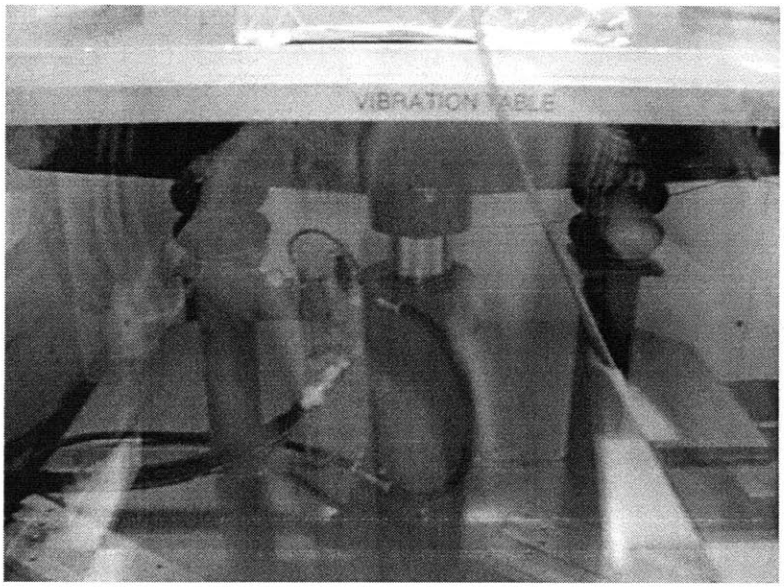

Figure 26: Vibration Table

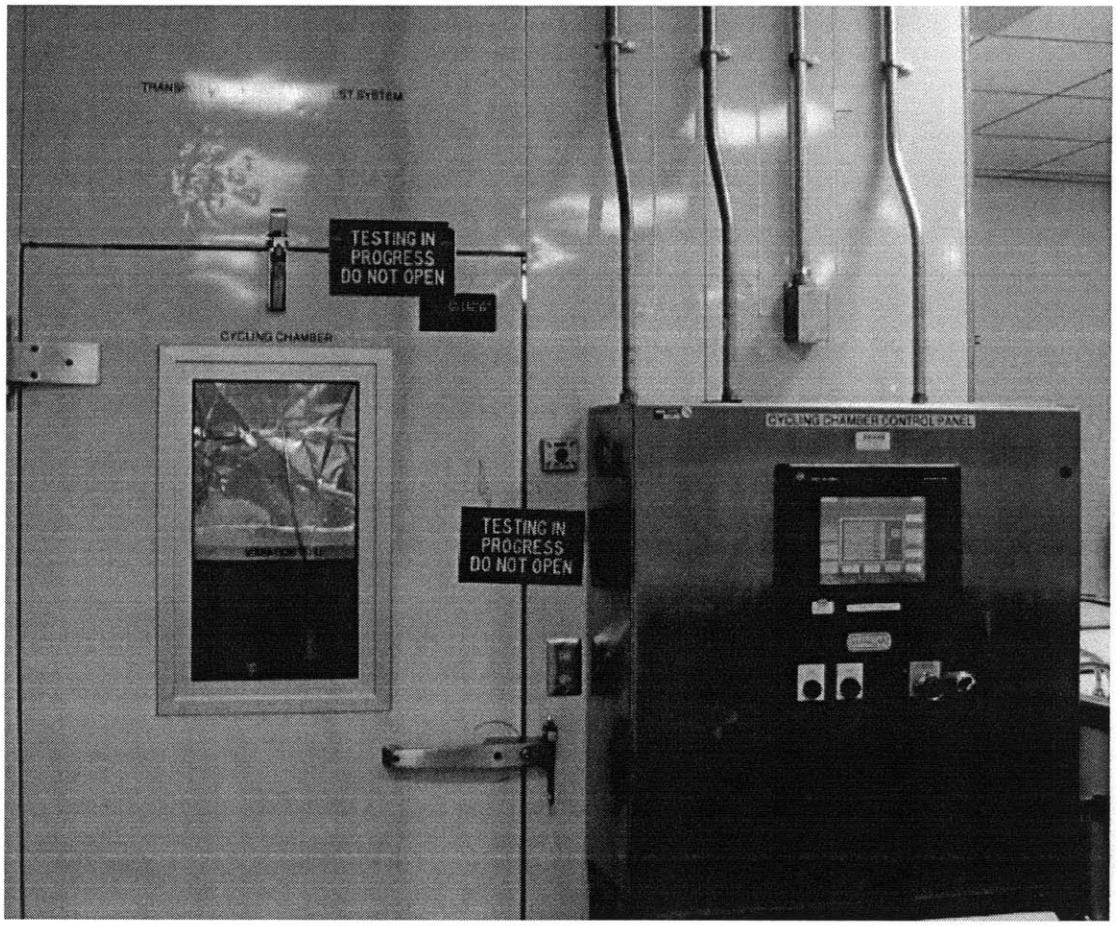

Figure 27: Vibration Table Cycling Chamber

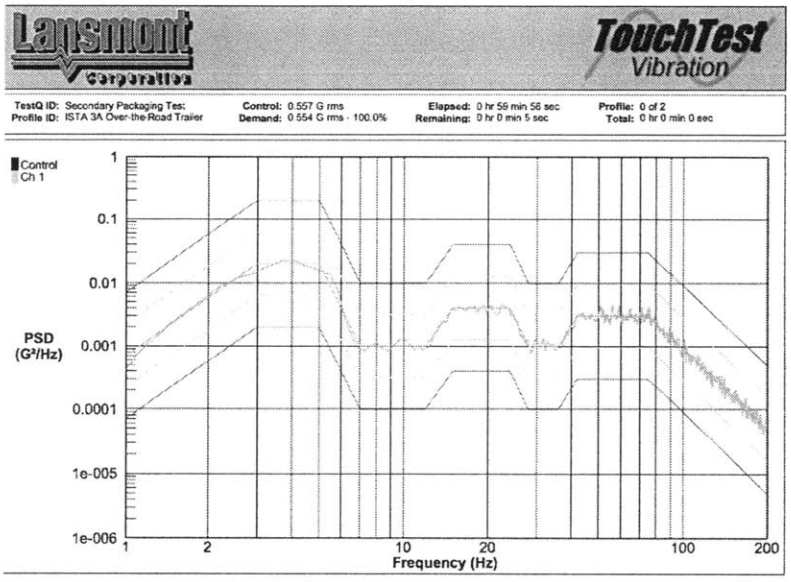

Figure 28: Vibration Simulation Model Screen Shot

The test results are as follows: 50 marked and 50 unmarked syringes identically packaged and tested according to ISTA 3A transportation standards yielded zero broken syringes. See Appendix 7 and 8 for more detailed views of the graphical outputs of the vibration transportation simulation.

5.2.3.2 Drop Testing

The purpose of drop testing is to simulate shock events created by transportation and imperfect handling. A free-fall drop tester is used for these tests, like the one below at Amgen:

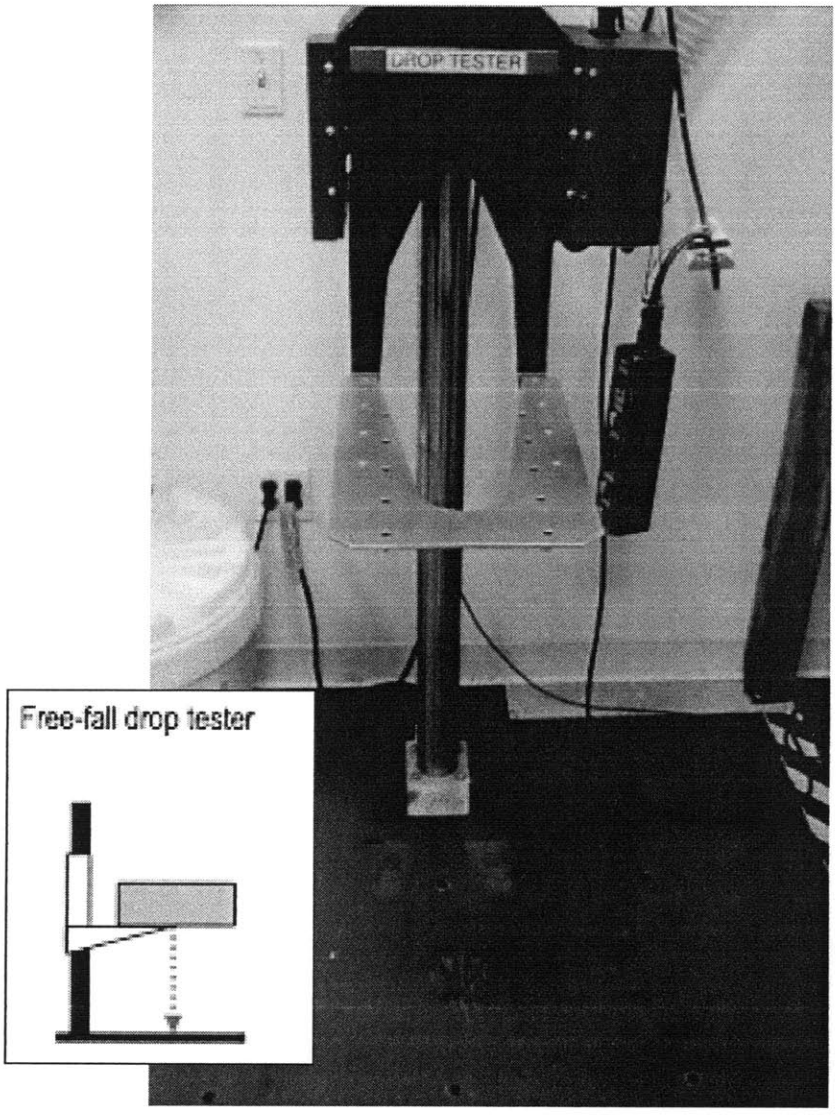

Figure 29: Amgen's Free Fall Drop Tester

As previously mentioned, the testing was completed in accordance with ISTA 3A procedures. For free-fall drop tests, testing follows the table below:

ISTA 3A Drop Test Procedure (Resource Book 2007)			
Drop Number	Drop Height <70 lb	Drop Height 70-150 lb	Drop Orientation
1	18in	12in	Edge 3-4
2	18in	12in	Edge 3-6
3	18in	12in	Edge 4-6
4	18in	12in	Corner 3-4-6
5	18in	12in	Corner 2-3-5
6	18in	12in	Edge 2-3
7	18in	12in	Edge 1-2
8	36in	24in	Face 3
9	18in	12in	Face 3
10	18in	12in	Edge 3-4
11	18in	12in	Edge 3-6
12	18in	12in	Edge 1-5
13	18in	12in	Corner 3-4-6
14	18in	12in	Corner 1-2-6
15	18in	12in	Corner 1-4-5
16	36in	24in	Face 3
17	18in	12in	Face 3

Figure 30[26]: ISTA 3A Drop Test Procedures

The drop test yields a binary response of either unbroken (0) or broken (1) and does not yield any finer granulation of data related to the exact amount of stress placed on the glass syringe from the shock pulse. The results from the three replicates of the test are that zero syringes (marked or unmarked) broke or cracked.

5.3 Technical Summary of Laser Marking

This chapter focused on a methodology of mechanically testing a biopharmaceutical primary package to determine the potential affects of laser marking technology on the structural integrity of the glass syringe. From a technical standpoint, laser marking is an ideal solution as it can mark every syringe at processing speeds and additionally create a source of anti-counterfeiting at a very low cost per unit. Although processing speeds and read rate accuracy are in the range necessary for application to biopharmaceutical fill-finish processes, the structural testing as to the structural impacts on the syringe remain inconclusive. Given the focus on risk mitigation in this business and industry, large-scale studies would need to be executed to ensure that this technology did not introduce unintended breakage.

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6 RFID: A Technical Evaluation

This chapter presents the strategy and tests performed during the evaluation of RFID as a potential solution to identify syringes and vials at the unit level. The tests were completed at Amgen's Technology Transfer laboratory.

6.1 RFID Lab Scale Evaluation Strategy

The objective of this chapter is to determine the feasibility of RFID as a solution for marking syringes and vials at the unit level. The factors for success listed in Chapter 5.1 are also relevant here yet with a different focus. For laser marking, the most important factor was the potential impact on the glass structural integrity. With RFID, the focus of the lab scale testing is primarily the first factor but specifically on read rate and read accuracy. An analysis conducted several years ago had a read accuracy quoted at approximately 80%. In an extremely high volume environment, 80% is completely unacceptable where the idea to is simplify the marking and reading process. Therefore, the strategy of this technology evaluation is to test the hypothesis and assumption that RFID technology cannot sustain the read accuracy necessary for biopharmaceutical processing. Certain aspects of biologic drugs are concerning for the application of RFID. Typically, the presence of water and/or metal can hamper read accuracy. The testing will be set up as a design of experiments to determine if there is any interaction of these factors on the response of read accuracy.

With RFID as a technology solution, there are two other important factors to consider. The first (Factor #3 in Chapter 5.1) is the concern about possible deleterious affects the electromagnetic field can have on the stability of the sensitive biologic products like Amgen manufactures. A plethora of research both in industry and at Amgen has been performed in relation to this concern. See section 6.3 of this chapter. The second is potential for supply chain benefits in the application of RFID. See section 6.4 of this chapter.

6.2 Lab Scale Testing

The laboratory testing utilized a main supplier for the RFID equipment and a separate supplier for the RFID tags. The RFID equipment was purchased through ThingMagic, Inc. from Cambridge, MA. The test equipment was setup as shown below:

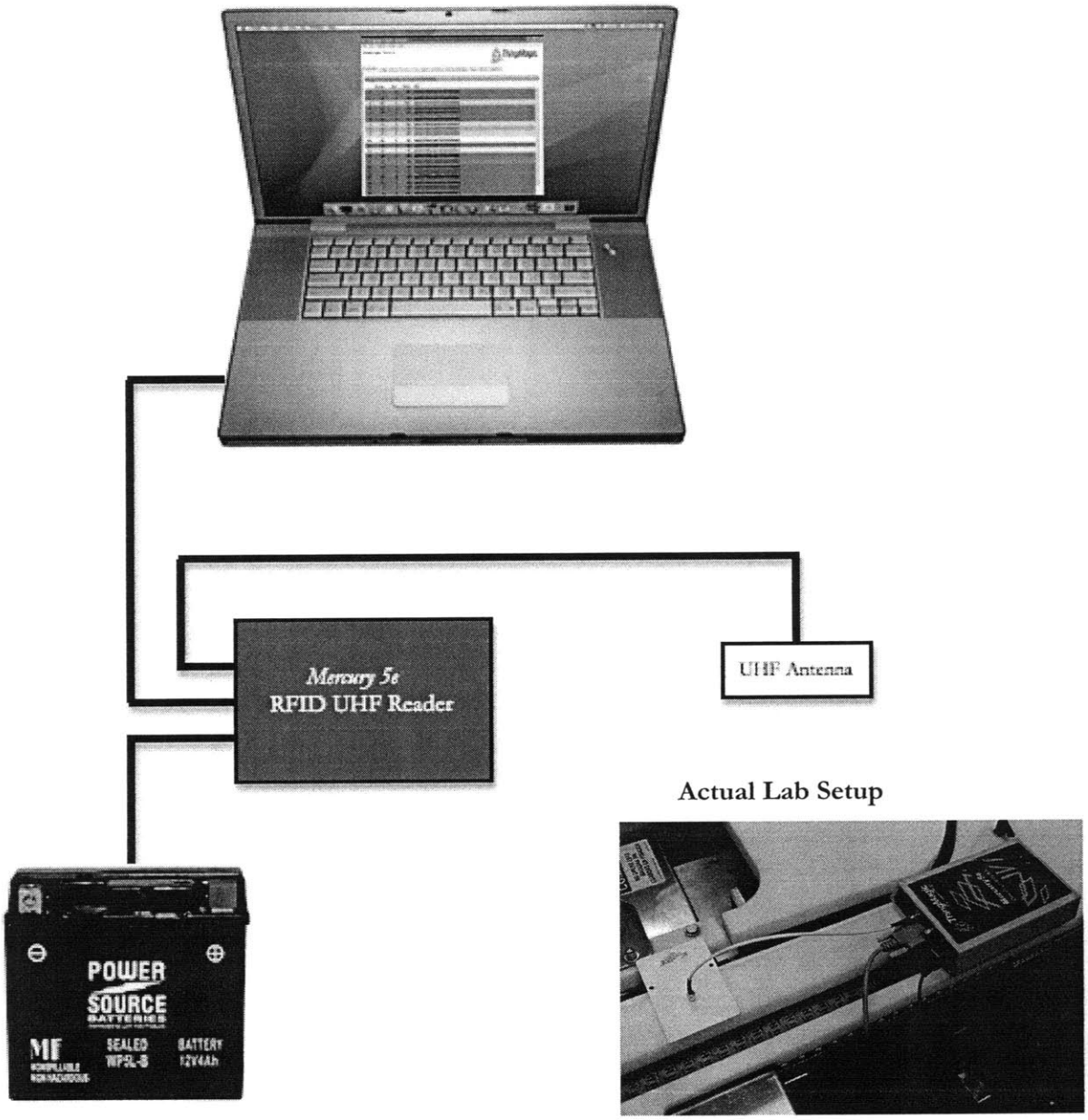

Figure 31: RFID Test Data Capture Setup

ThingMagic also provided the software called *Reader Assistant* that was used to record the testing. See Appendix 3 for an example of the software output.

The RFID tags were purchased through Avery Dennison (AD) RFID Division. The tags are wet-inlay (adhesive) 16x16mm and 10x20mm tags. In the past, companies have had issues with antenna breakage due to the small diameter of the syringe. Although antenna breakage was not seen in testing, adhesion to the syringe and vial barrels was difficult. Even if the labels had adhered perfectly, it is unlikely any biopharmaceutical company would want their vial looking like the test setup vial:

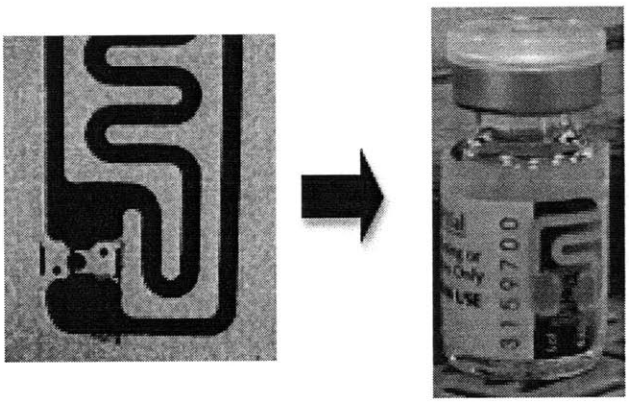

Figure 32: AD RFID Tag and Vial Test Setup

The testing was performed to determine the affect of three factors on read accuracy. The three factors are belt speed, water presence in the form of WFI and metal presence in the form of the metal vial crimp seal. It was assumed that the dielectric properties of the typical biologic drug are the same as the dielectric properties of water. Therefore, a design of experiments (DOE) was set up for the test. Because there are three factors and two levels for each factor, the number of runs is equal to 2^3 or eight runs to test all combinations and run a full-factorial design with two replicates.

	Factors		
Run	**Belt Speed**	**WFI**	**Metal Cap**
1	50%	Yes	Yes
2	50%	No	Yes
3	50%	Yes	No
4	50%	No	No
5	100%	Yes	Yes
6	100%	No	Yes
7	100%	Yes	No
8	100%	No	No

Table 4: DOE Run Setup

The belt speed percentage was on the dial of the machine. In order to understand what that percentage corresponded to, a vial was moved along the conveyor with a ruler to determine the distance traveled in a given amount of time. The 50% speed corresponded to the vial moving 48 inches in 9.56 seconds or about 25 ft/min (25 ft/min ≈ 200 vials/min). The vial spacing of 1.5 inches (center-to-center) corresponded to the spacing on the commercial manufacturing line.

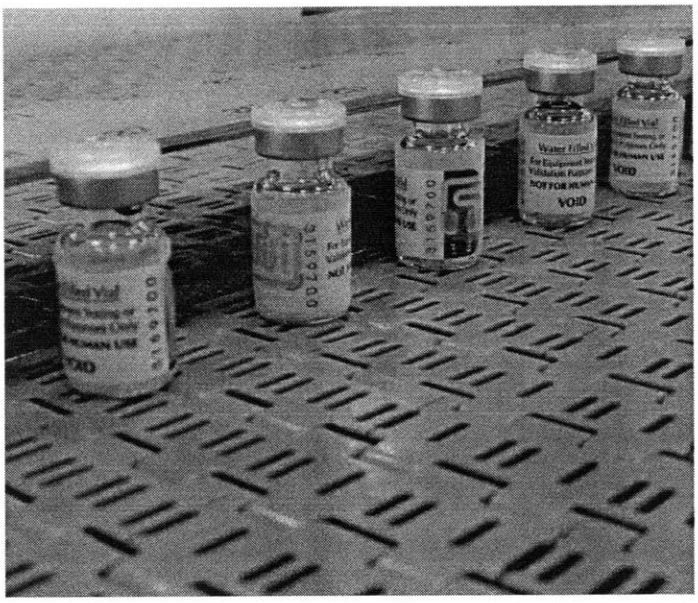

Figure 33: Vials on Conveyor with Spacing

The antenna used for the test was a Laird Technologies Omni-directional 880-960MHz Antenna (3dBi). The antenna connected directly into the reader.

The test setup in the Technology Transfer Lab is shown in the picture below:

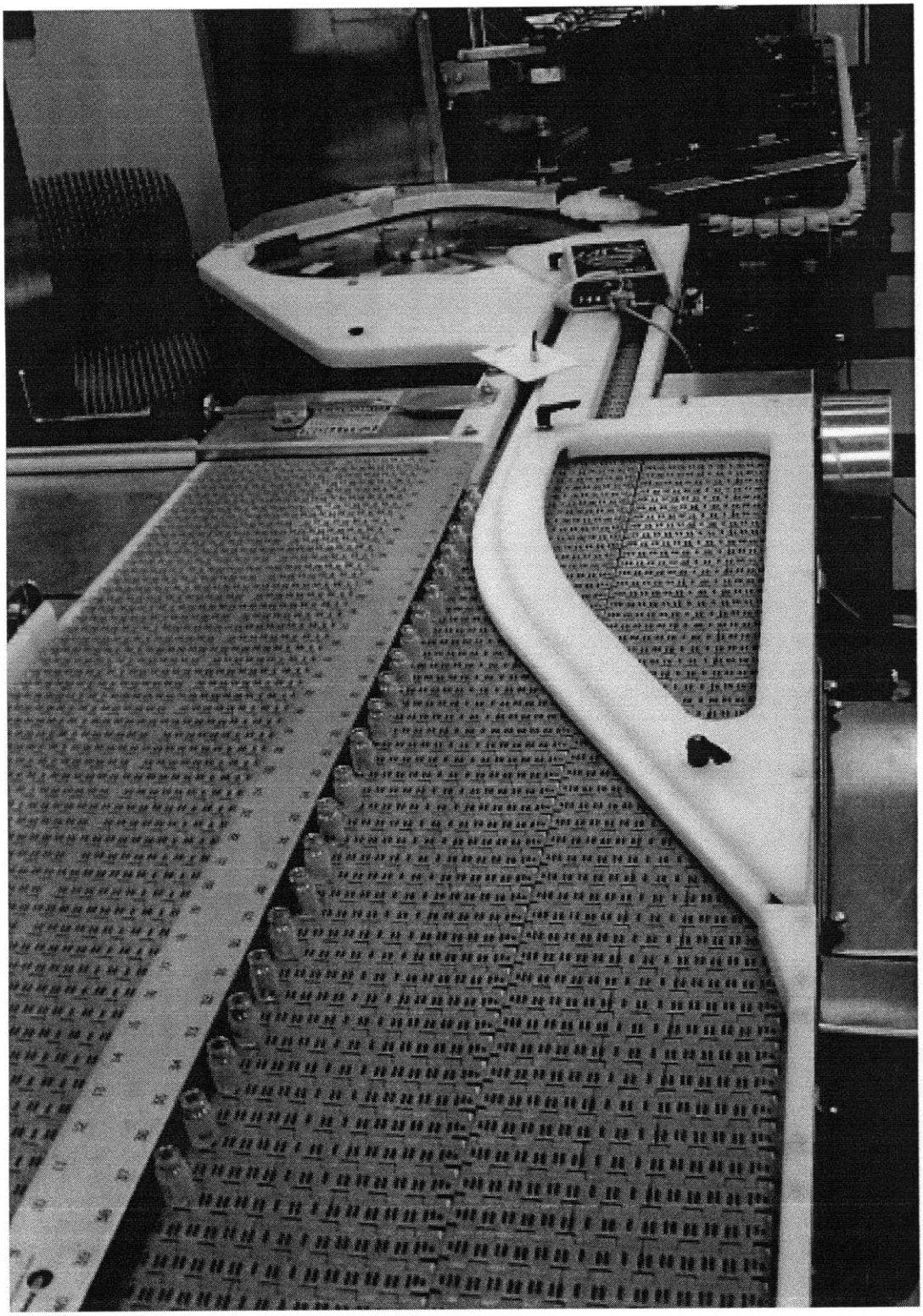

Figure 34: RFID Lab Test Setup

The results of the lab scale RFID test are as follows: 100% read accuracy in every run. What did vary in the results was the total volume of tag reads as the factors changed, though it is not clear that there is relevance to total tag reads. The graph and chart below summarize the results:

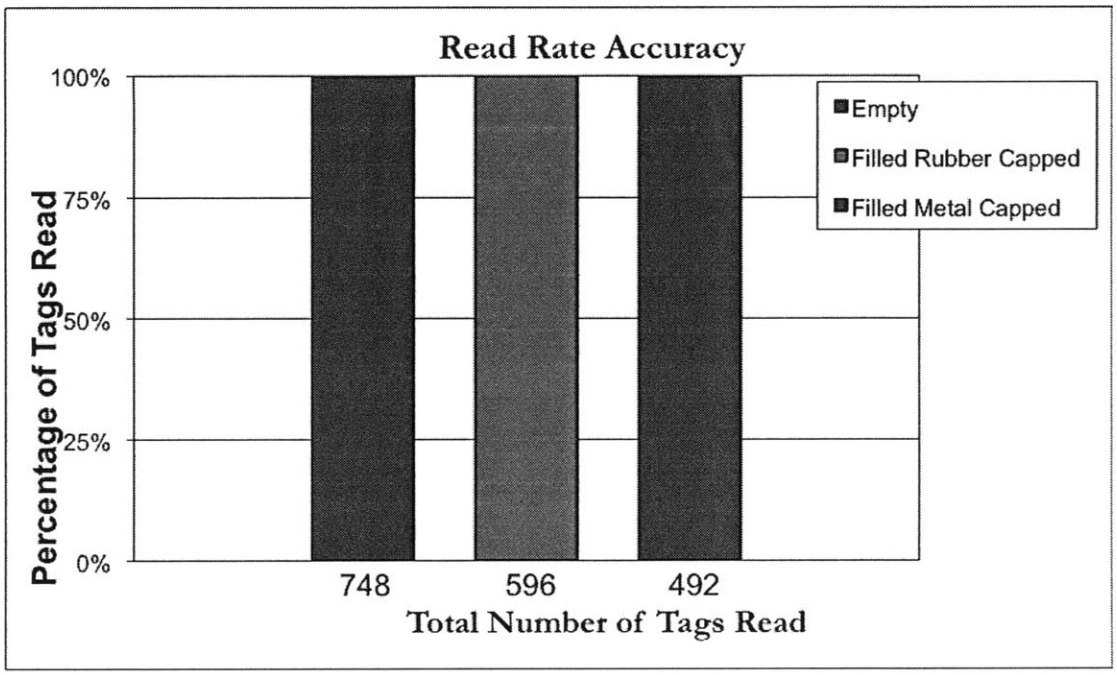

Figure 35: Read Rate Accuracy

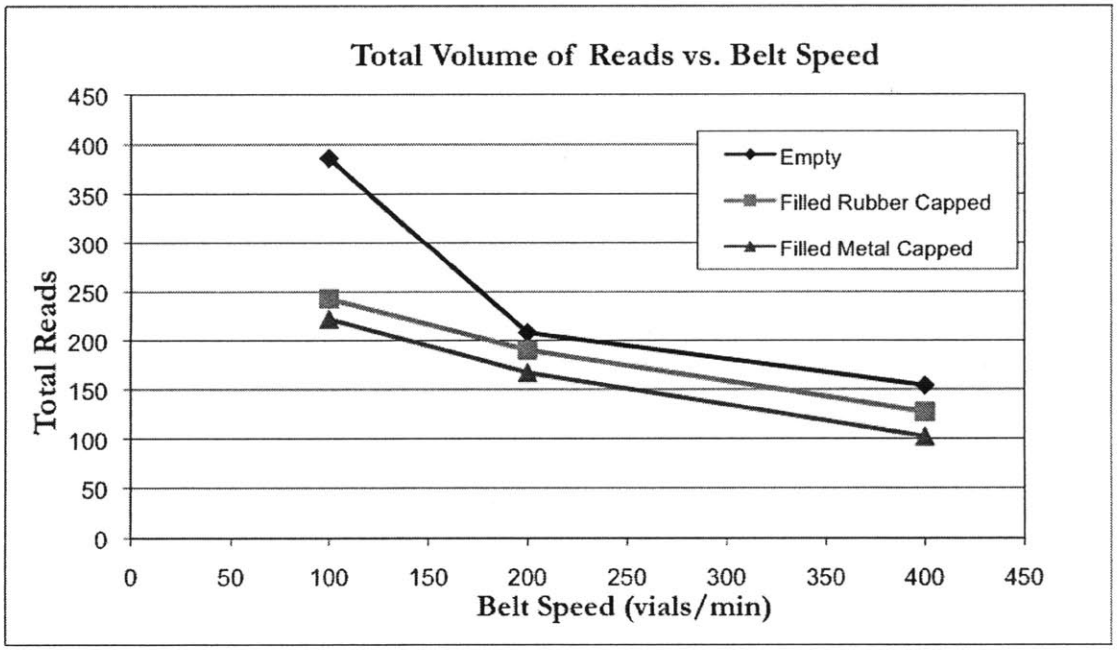

Figure 36: DOE Testing Results

The ThingMagic Mercury 5e RFID reader is rated for a maximum of 170 tag reads per second. The results are clear that 100% read accuracy is possible. As mentioned in Chapter 5, it is important to note the sensitivity of this test. The test is a relatively small number of tag reads compared to volume of product Amgen produces and sells every year. But looking at Figure 36 results, it is clear that belt speed seems to reduce the total volume of reads by a similar amount for all three scenarios. The addition of WFI seems to cause the largest variation in total reads, most notably at the lower speed. Notice that a third and lower speed was tested to check for any added differences.

6.3 RFID Effects on Biopharmaceuticals

The biopharmaceutical industry has an aversion to technological solutions of any kind that could affect the stability or efficacy of their biologic drugs. Although the effects of RFID on biologic drugs are not completely understood, many tests have been completed to specifically determine the thermal effects of the RF field. The FDA, Amgen and the consulting firm Accenture have all completed tests of the thermal effects of RFID on drug temperature and stability.

To better understand the variables involved with specific dielectric heating, consider that "the volumetric power (P) is proportional to the square of the electrical field (E) and the conductivity (σ) of the medium and can be expressed by the following equation[28]:

$$P = \sigma \mid E \mid^2 = 2\pi f \varepsilon_o \varepsilon'' \mid E \mid^2$$

Using the energy conservation equation assuming all of the electromagnetic energy is absorbed by the sample as heat,

$$\rho C_p \Delta T = P \cdot t$$

where C is the heat capacity of the material and ρ is density.[29]

Substituting the first equation into the second and rearranging for the change in temperature over the time yields,

$$\frac{\Delta T}{t} = \frac{2\pi f \varepsilon_o \varepsilon'' \mid E \mid^2}{\rho C_p}$$

Solving this equation for the rate of heating ($\Delta T/t$) for a 4W UHF RFID system yields the result of 1.12×10^{-10} degrees Celsius per minute. Thus, theoretically, a standard RFID system

should not impart much heating to a vial or syringe contents over the amount of typical exposure to the RF field, which is usually measured in seconds.[27]

Industry tests completed saw no thermal effects from the tested UHF RFID equipment on vials positioned close to the antennas where the RF field strength is the highest. The FDA saw a temperature rise of 0.3°C but the vial was exposed to a 22W UHF field for 7 hours. Also, Accenture saw a 0.5°C but again the vial was exposed longer than Amgen's exposure time of 4 hours. Accenture's vial sample was exposed to a 4W UHF field for 16 hours. Despite the FDA and Accenture seeing a temperature rise even in their worst case scenario's, these are not temperature deviations that of concern to the stability of their drugs. It was also reported that neither Amgen nor the FDA and Accenture saw any changes in non-thermal factors of any drug tested. Although the studies seem to suggest that that RFID is completely safe on biologic drug products, FDA approved stability studies can take several years for conclusive evidence.

6.4 Potential RFID Supply Chain Benefits

Because RFID allows for NLOS (non-line of sight) reading and has the ability to store more information than a barcode, it's application to manufacturing and operations can many times lead to savings from reduced labor, inventory and stock-outs. In other industries, these savings come from a reduction in total inventory and reduced supply chain issues like obsolescence, shrinkage and stock-outs. Because biopharmaceutical industry operations are dominated in a large part by risk mitigation protocols, the potential RFID supply chain benefits don't really apply (except in the case of some labor reduction). Even if an RFID system showed the possibility of reduction of inventory, a biopharmaceutical company would probably not reduce its total inventory, which it keeps to mitigate any possibility of running out of product. This is an industry that strives to operate with a "lead capacity policy". Under this type of capacity strategy, "capacity is added before it is needed, so on average there is excess capacity and demand is always met."[30] Therefore, although some savings could be seen, the value proposition of RFID implementation is not as strong for a biopharmaceutical company like Amgen.

6.5 Technical Summary of RFID

RFID technology offers many benefits over other solutions: the ability to read tags without direct sight, the ability to store significant amounts of information and potential for small labor savings involved with reading barcodes. Regulatory bodies such as the California State Board of Pharmacy and the FDA "envision a drug supply chain in which security is enhanced by a *universal* electronic pedigree requirement with full-system track and trace, and mass serialization *at the unit level* with standardized unique numerical identifiers. Both the FDA and California prefer, and assume this system will utilize, RFID technology."[31] Despite the benefits, regulatory pressures and technological advances. RFID as a solution is still unlikely to be accepted by biotechnology companies due to the per-unit cost as well as the lack of an ideal application form to vials and syringes.

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7 Clear Label Application: A Technical Evaluation

This chapter presents the strategy and tests performed during the evaluation of clear label application as a potential solution to identify syringes and vials at the unit level. The tests were completed at Amgen's clinical labeling facility.

7.1 Clear Label Lab Scale Evaluation Strategy

The objective of this chapter is to determine the feasibility of clear label application as a solution for marking or distinguishing unit level vials or syringes. The success factors listed in Chapter 5.1 are again valid here with the focus on cycle time of the labeling operation as well as the added labels effect on the overall diameter of the syringe. The reason this is of concern is due to Amgen's use of a needle safety device generically called a needle guard. Amgen uses two types of needle guards for their products depending on the regulatory requirements: a manual needle guard and an automatic needle guard. For a complete tolerance analysis of a syringe and needle guard, see Appendix 2.

The strategy for the testing was to apply the clear label to a syringe and then run it through the standard labeling operation to examine the performance of the labeling with an additional label present. There were concerns the clear-labeled syringe would not fit into the labeler and additional concerns the clear label would prevent proper adhesion of the final label. The lab scale testing was designed to attempt to answer these concerns about the technology as a solution.

7.2 Lab Scale Testing

The label supplier for the lab scale testing was CCL label, which provided custom labels designed specifically for testing. The custom label was small in all directions. It was designed to be about 0.002 inches thick and with length and width such that the label did not overlap itself when wrapped around the syringe. It was also designed to be completely encapsulated by the second label. Of particular relevance to this testing is the fact that Amgen completed an over-labeling project on one drug product to extend the expiration date in accordance with regulatory requirements. There are several issues with over-labeling a syringe with a commercial label already present. Label manufacturers apply a coat of varnish over commercial labels to prevent smudging of the text on the label. That varnish creates a surface that is non-ideal for proper label adhesion by lowering the surface energy. Also, the

original label placed on that syringe has to be designed to be over-labeled from a size perspective. The registration of the second label has to be perfect in order to match up with the original label. In the process of the over-labeling project, label flagging, wrinkling and scuffing can be an issue. The design of new clear label sought to minimize these issues by eliminating the varnish and by its thinness. Below is a picture of syringes with a clear label applied:

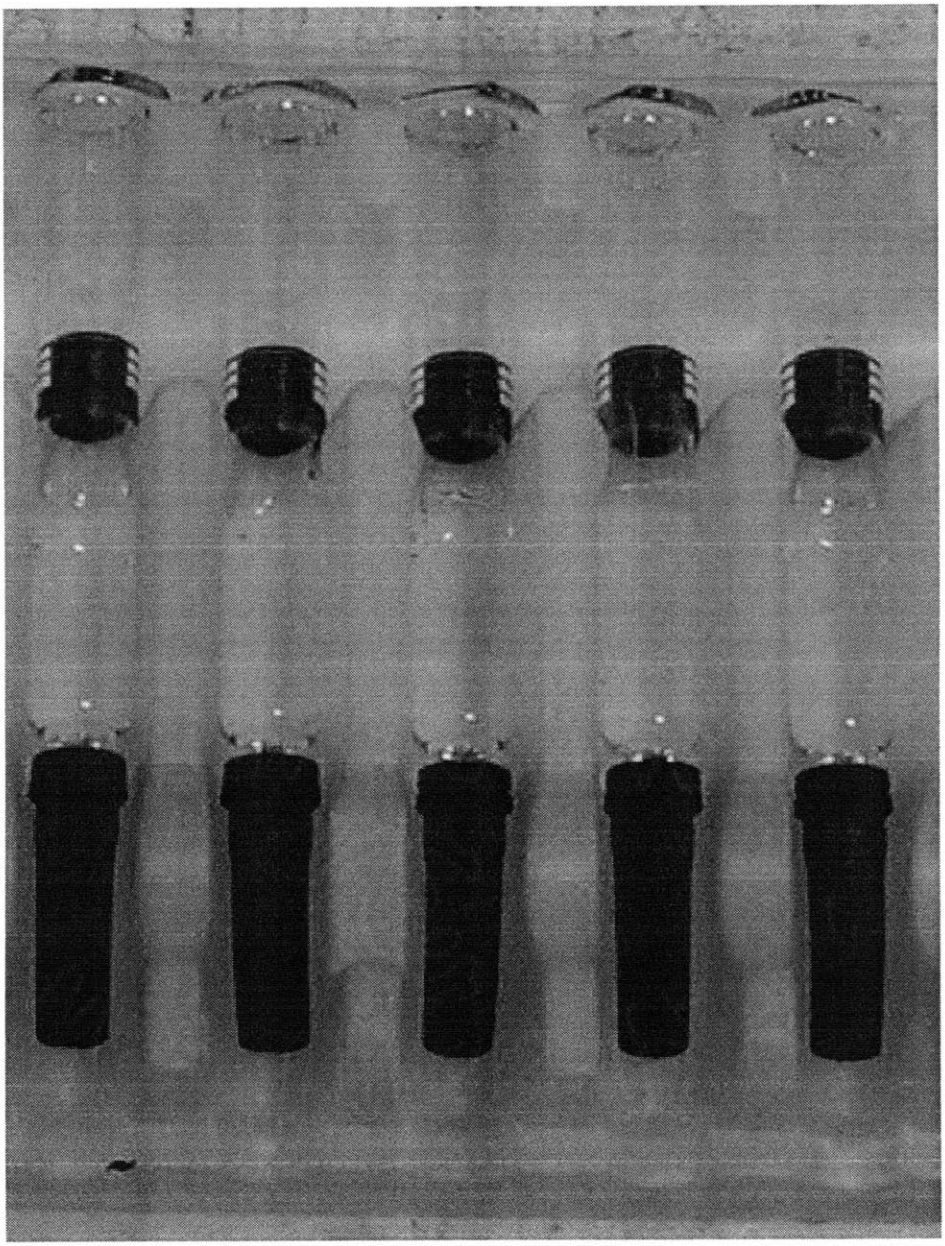

Figure 37: Clear Labeled Syringes

The label by itself does not distinguish or mark the syringe or vial. Two options are considered for marking.

1.) UV ink 2D matrix barcode pre-printed by the label supplier

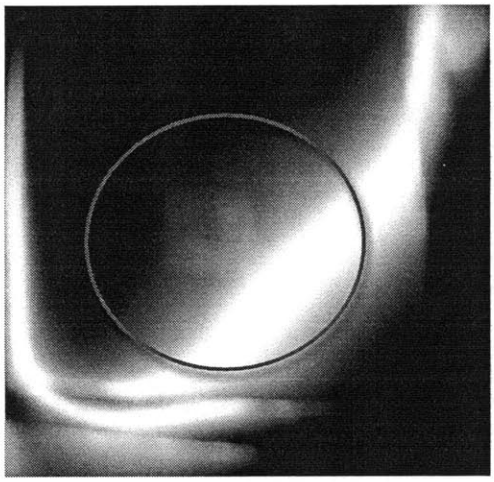

Figure 38: Clear Label with UV 2D Matrix Barcode

2.) Fluorescing yellow ink washed across the entire label only visible with UV light called *Radflour 2040* made by a company called Radcure.

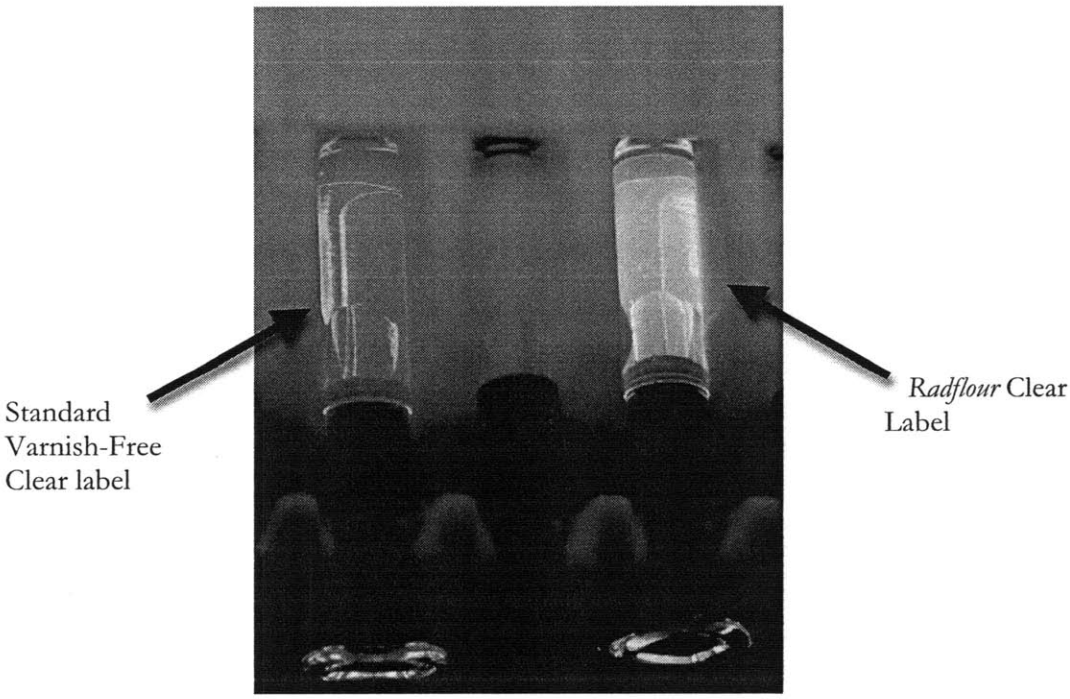

Figure 39: Standard Clear Label versus *Radflour* Yellow Label

An important point to note is the innovation in the design of option 2. Option 1 requires a sophisticated and capital-intensive multi-camera vision system to check for presence and read the 2D matrix barcode. The ink technology in option 2 has never been applied to biopharmaceutical labels before but it can be read by a simple, inexpensive vision system that does a binary check for the particular ink color that can be proprietary for each product the company produces.

The laboratory test consisted of 100 clear-labeled syringes to be labeled with a final test label. Following the labeling step, each syringe is to be checked for visual defects including flagging, wrinkling and scuffing. The labeling machine used is a *Groninger*, the same machine used in commercial labeling facilities.

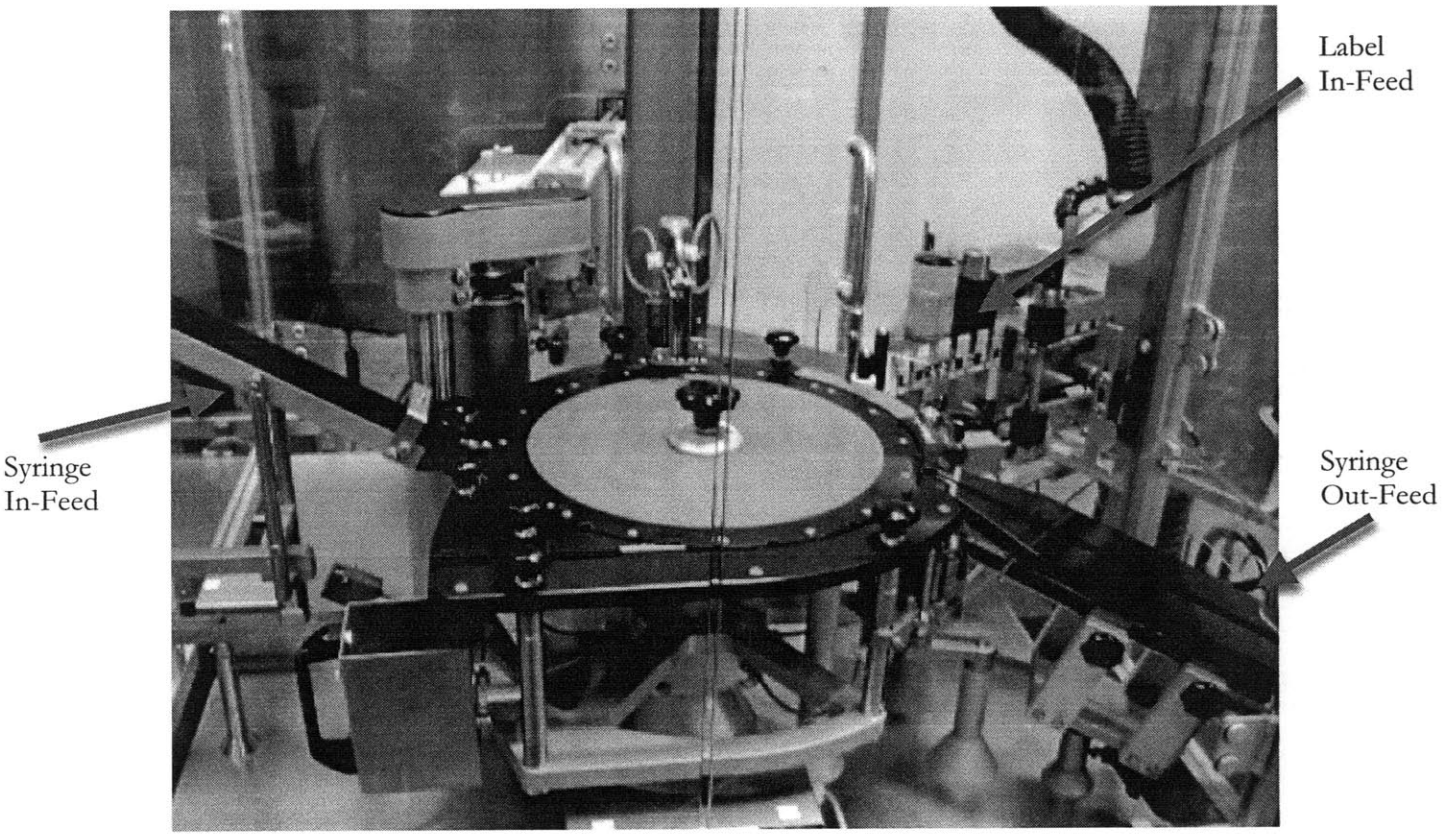

Figure 40: Groninger Labeler

7.3 Results and Discussion

The results of the clear label test are shown below in Table 5. Label flagging occurs when the edge of a label peels up due to lack of perfect adhesion. A label scuff is any foreign mark on the label that occurs during label operations and handling. A label wrinkle is an

enclosed bubble in the label after the label is applied. The automatic needle guard fit was a hand fit test where each double-labeled syringe is inserted into the device to check for acceptance fit.

Clear Label Test Results	
Syringes Labeled	100
Label Flagging	2
Label Wrinkling	0
Label Scuffing	0
Automatic Needle Guard Fit	100

Table 5: Label Application Results

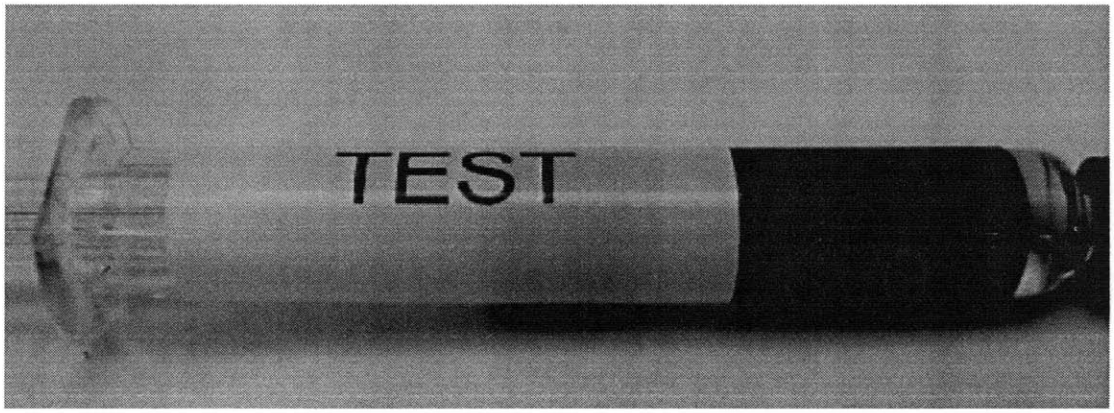

Figure 41: Clear Label and Test Final Label Applied to a Syringe

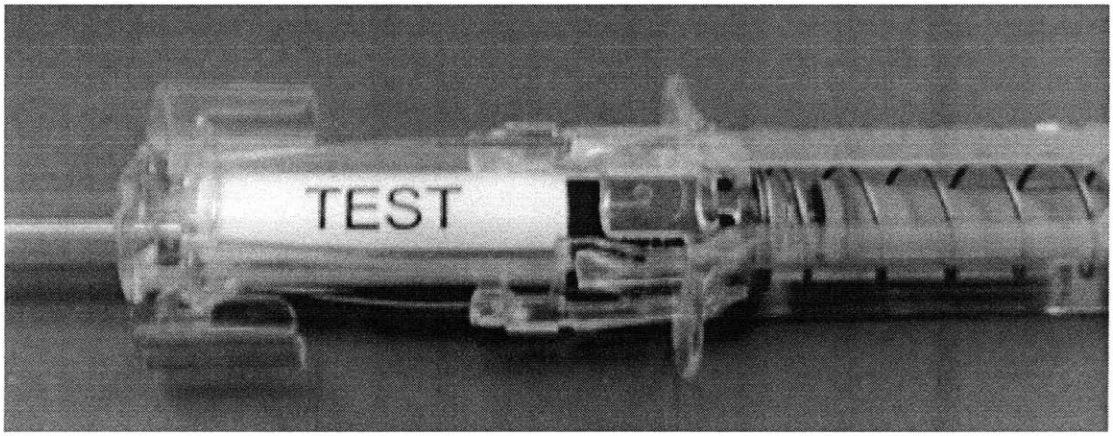

Figure 42: Automatic Needle Guard Fit Test

Several important notes about the results must be discussed. First, the test was successful. The testing showed that is indeed possible to place a distinguishing mark on a clear label and apply a commercial label over the first label. Also, despite the concern of automatic needle

guard fit, all 100 syringes passed a fit test into the device. Second, although there was a 2% incidence of flagging, the likely cause was human error in placing the clear label.

From a business perspective, the clear label solution offers some key advantages over the other solutions. The cost of the extra label at large volume (>3million) is about 0.5 cents per label. That cost is especially low when considering this clear label would only need to be applied to product being shipped intra-site for sale in the EU or potentially for labeling and packaging by another company. Add to that the fact that the competency for labeling already exists within the company, the solution is attractive, especially from a short-term perspective. Other technologies may improve and eclipse this solution but in the next few years, this may be the most ideal solution to solve the issue of shipping unmarked vials and syringes.

7.4 Technical Summary

Clear label application is a feasible and attractive solution for marking syringes that are unlabeled in the supply chain. Testing showed that, at least at a lab-scale, over-labeling of a custom designed clear label is possible and repeatable. The business implications of this solution are also positive. Both the cost per label and the cost of the reading equipment (for option 2) are inexpensive. The competency for labeling exists within Amgen and can be leveraged to make this an optimized solution, especially in the short-term. Specifically for syringes, the clear label technology could be applied to vials too. From a technological maturity perspective, it is more reasonable to apply an inkjet to the vial process as commercial-off-the-shelf systems are available and are being used for vial marking throughout the industry.

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8 Technology Advancements

In Section 2.5.7, technology advancements were summarized, showing the direction of future of the marking industry. In order to fully analyze the entire solution space, two advanced technologies were looked into with greater depth. This chapter will touch on LaserJet technology and a few lab scale tests performed to understand the current capabilities of the solution. The chapter will also consider the future of parenteral primary packaging, specifically in relation to the potential movement towards plastic.

8.1 LaserJet Technology Analysis and Testing

The purpose of this chapter is to dive deeper into the technology referred to as LaserJet. The value proposition of this technology is clear. The technology vendor claims that it is a robust, low-cost, serialized code that does not affect the glass or external dimensions of the syringe or vial. Working with the supplier, 30 syringes were procured for some basic testing. The reason the technology is not currently being considered as a potential solution is due to the status of the intellectual property. The technology was co-developed between two companies and it looks as though a glass supplier bought a limited-time right to the technology.

LaserJet is a technology in which a laser is fired at a ribbon that is in front of the substrate or glass. The laser ablates the ribbon and deposits the ink by-product on to the syringe or vial. The 2D matrix code looks like the following picture:

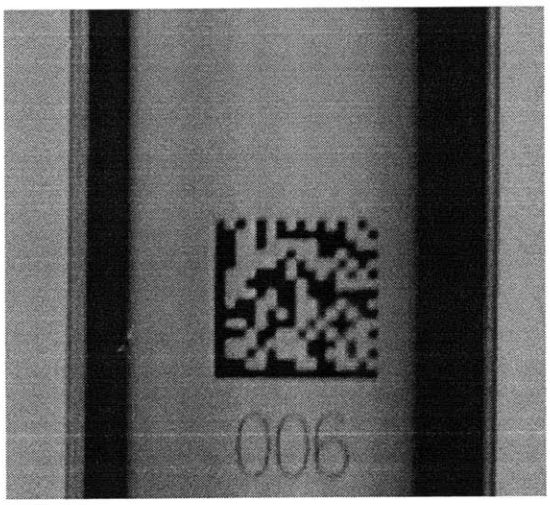


Figure 43: LaserJet 2D Matrix Barcode with Human Readable Code

Although the syringes in Figure 10 and Figure 43 look similar and are both ink marks, there is an important difference. Both marks are made with ink, but as will be shown below, the laserjet mark is virtually indelible whereas the inkjet mark has issues sticking to glass in the presences of silicon oil.

A significant concern with the technology is the ability of the code to survive the rubbing and chaffing of processing and shipping. In order to test the robustness of the code, a laboratory scale test was designed using the *Sutherland Rub Tester 2000* pictured below:

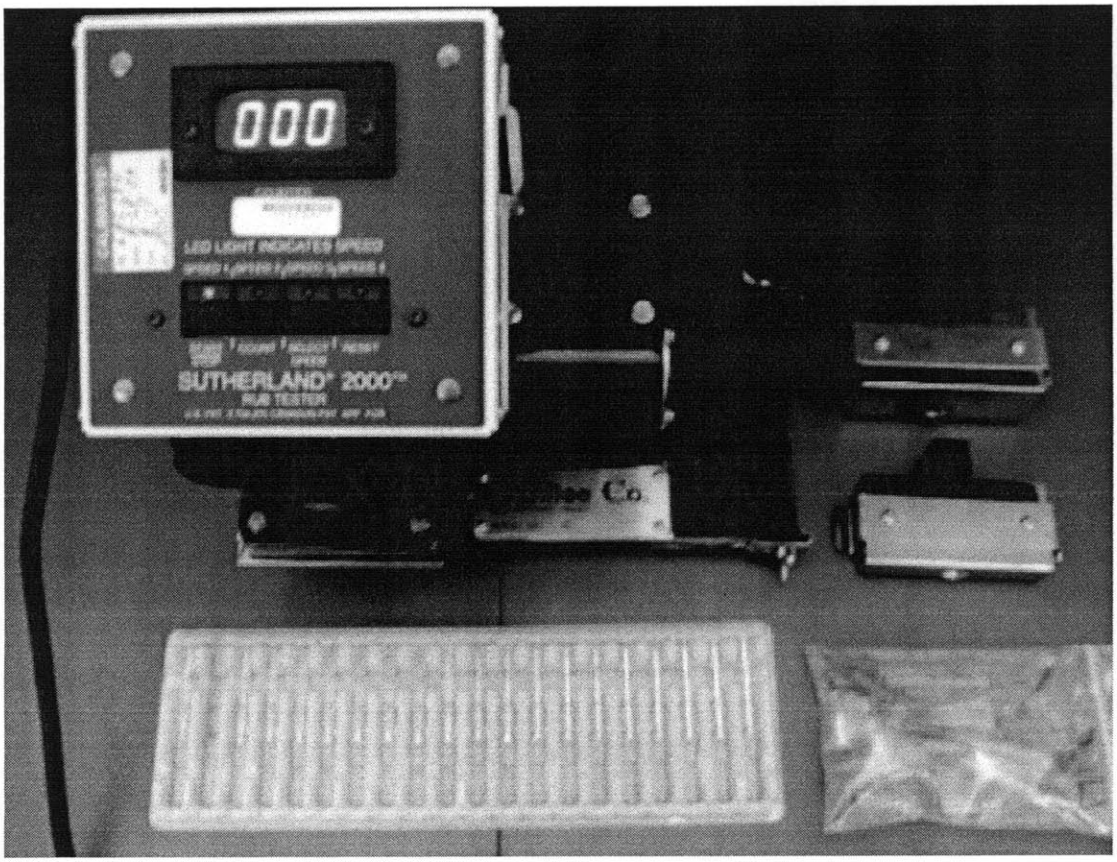


Figure 44: Sutherland Rub Tester

Each of the 30 syringes was rubbed for a total of 120 seconds and this was compared to a standard inkjet mark on a syringe. The results, shown in the graph below, prove the robustness. After two full minutes of direct on-the-mark rubbing, the code looked exactly the same as compared to the standard inkjet, which was unreadable after the rubbing. It is important to note that the graph in is a qualitative expression of the results of the rub test.

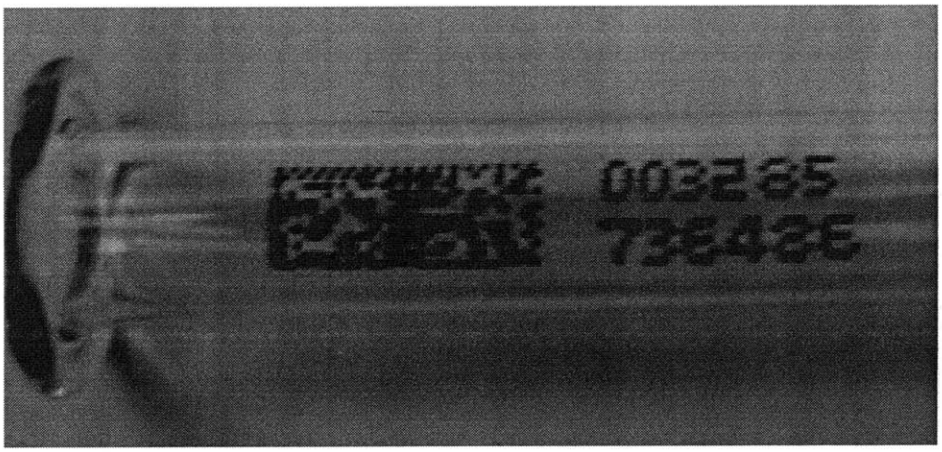


Figure 45: Standard Inkjet Mark before Rub Test

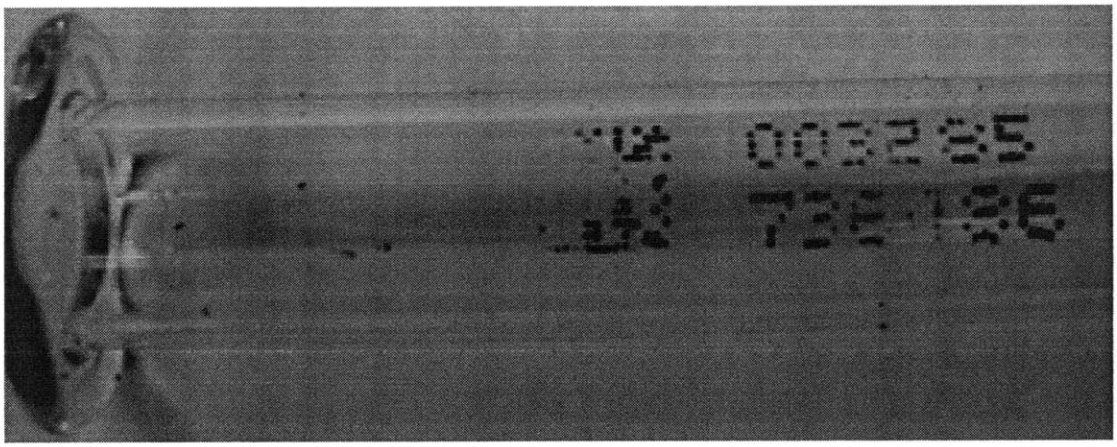


Figure 46: Standard Inkjet Mark After Rub Test

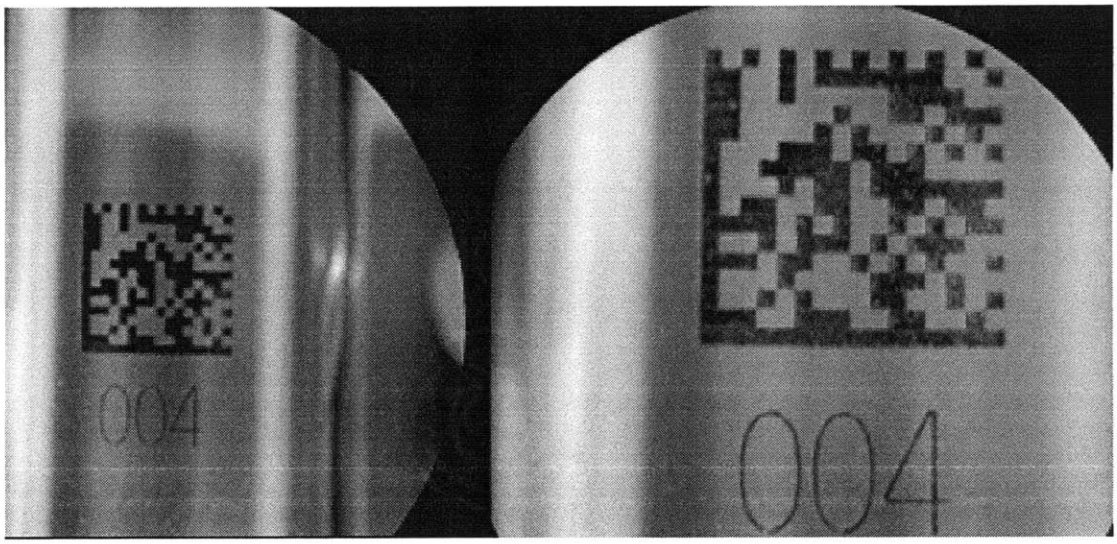


Figure 47: LaserJet Mark Before (Left) and After (Right) Rub Test

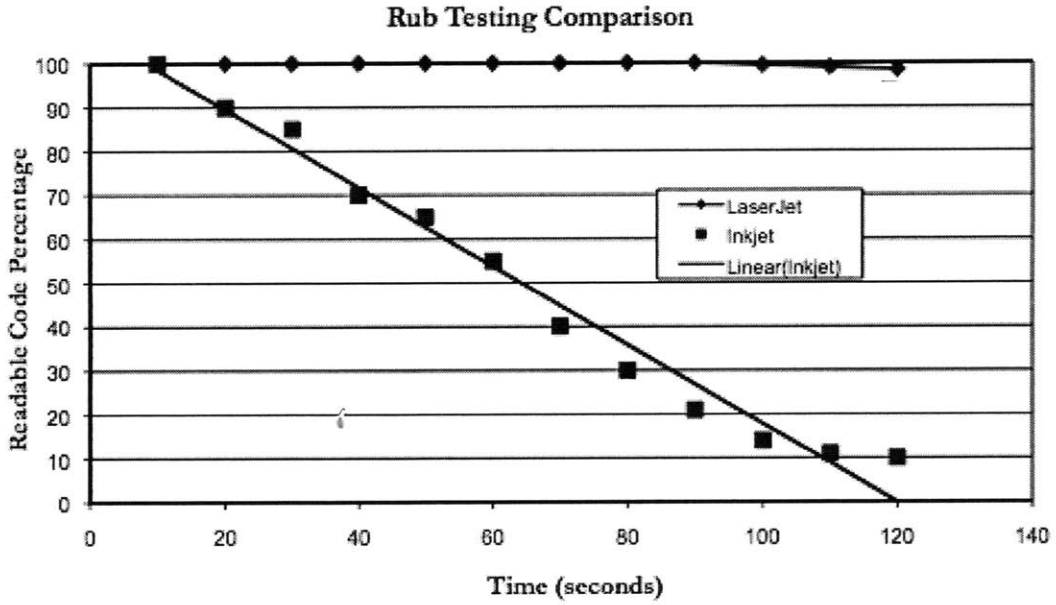


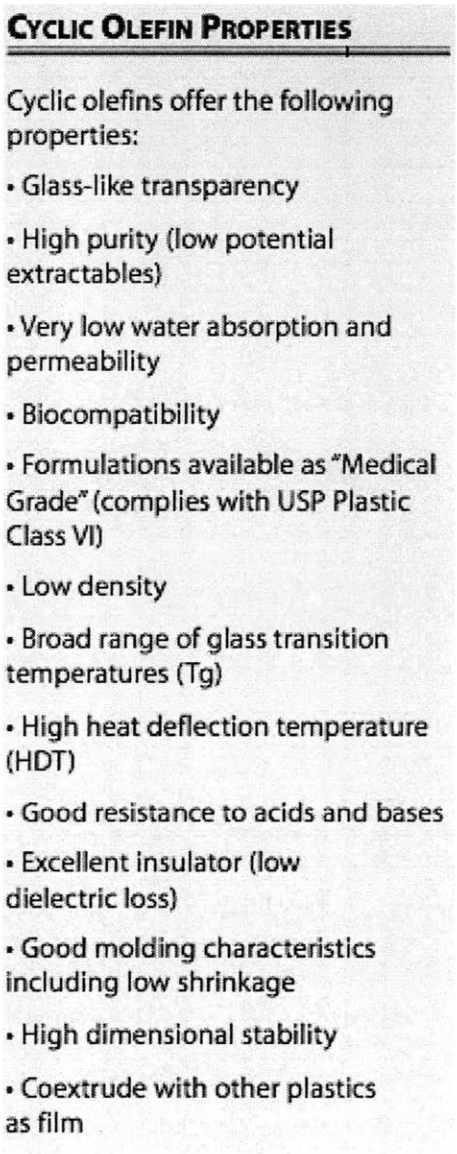
Figure 48: Rub Testing Qualitative Results

LaserJet technology is extremely robust and a standard, inexpensive reader can easily read the code. Even when exposed to an alcoholic solvent, the code showed no degradation in quality. LaserJet technology is certainly a solution that industry should continue to monitor in the future.

8.2 Plastic Parenteral Primary Package

In the last few years, there has been increased interest from biopharmaceutical companies in new formulations of plastic compounds used to make syringes and vials. The 'new' compound is a 50-year old plastic composition called cyclic olefin polymer; it is 'new' in its application to parenteral packaging. Many of largest glass syringe and vial manufacturers such as Schott and Becton Dickinson have plastic syringes and vials available. "It is the combination of their clear optical properties and low moisture permeability, high purity, and bio-compatibility that contribute to their attraction for primary pharmaceutical packaging."[32] (See Figure 49 below.) Indeed, these factors are key in the consideration for use at a company like Amgen. From an operations perspective, plastic syringes and vials offer two key advantages over the current glass packages. First, plastic syringes are break resistant during processing, handling, shipping or even in use by the patient. This prevents costly errors that create scrap and also potentially eliminates certain quality steps that check for

glass cracks in the current fill-finish process. Second, a plastic syringe would allow for complete freedom to apply many marking technologies. Laser marking, inkjetting and even molding in a mark are all options for plastic that do not suffer from the same restrictions as glass due to the material properties of plastic. It will be important for Amgen to follow the regulatory movements for plastic syringes, which may be the last big hurdle for their acceptance. If plastic syringes and vials become a commonplace part of Amgen's process, their ease of marking nude vials and syringes will greatly increase.



CYCLIC OLEFIN PROPERTIES

Cyclic olefins offer the following properties:

- Glass-like transparency
- High purity (low potential extractables)
- Very low water absorption and permeability
- Biocompatibility
- Formulations available as "Medical Grade" (complies with USP Plastic Class VI)
- Low density
- Broad range of glass transition temperatures (Tg)
- High heat deflection temperature (HDT)
- Good resistance to acids and bases
- Excellent insulator (low dielectric loss)
- Good molding characteristics including low shrinkage
- High dimensional stability
- Coextrude with other plastics as film

Figure 49[32]: Attractive Cyclic Olefin Polymer Properties

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9 Financial and Implementation Analysis

In the previous chapters, the different solutions were analyzed from a technical feasibility standpoint. Although certainly an important first step, it doesn't take into account the financial and operational aspects of each solution. This chapter will focus on the methodology used to calculate the financial impact of each of the solutions on the business as well as the issues related to actual implementation. The financial analysis will compare the solutions with each other, utilizing a method of financial study called risk-adjusted net present value. The implementation analysis will focus on the application of the solution presented in Chapter 7 to the biopharmaceutical process.

9.1 Methodology for Financial Analysis

Financial data associated with cost modeling is not an actual or perfectly accurate representation of the costs incurred in applying each solution. Rather, it is a method to obtain general costs using assumptions to simplify the scenarios. The data obtained here is a combination of non-binding verbal quotes from suppliers as well as estimates from the manufacturing and finance departments at Amgen.

Because of the goal of financial analysis is to determine approximate cost numbers for each solution, the scope of the analysis is limited to processes related to marking and reading of the coded syringe or vial. The costs that make up the analysis include:

- Capital costs associated with the procurement of equipment needed for making the mark onto the vial or syringe
- Ongoing operation costs associated with consumables in relation to the marking solution or technology
- Maintenance costs associated with the upkeep of marking equipment
- Additional labor costs needed to perform the marking step

Additionally, because unit level marking has never been performed at Amgen, several assumptions had to be made as to the level of additional labor or the cost of maintenance. Although attempted, peer biotechnology companies were, without surprise, unwilling to share this type of financial data with Amgen. Other assumptions surround the risk adjustment of the net present value as well as the number of units being shipped unmarked between sites.

9.2 Net Present Value Analysis

Net present value is "defined as the value—in today's dollars—of the cumulative annual after-tax net cash flows directly stemming from the project or product deal."[33] In mathematical terms, NPV looks like:

$$NPV = \sum_{t=0}^{n} \frac{(Benefits - Costs)_t}{(1 + r)^t}$$

where:
r = discount rate
t = year
n = analytic horizon (in years)

Figure 50[33]: NPV Equation

The assumptions for the model include a 3% inflation rate; a 38% corporate tax rate and a constant year-to-year wage merit increase for labor headcount. Cash outflows were discounted using the standard rate at Amgen for capital investment projects. Depreciation of the capital equipment occurred over 5 years using a straight-line method.

Cost estimates for clear label applications are well understood as labeling is a core competency across the industry.. Laser marking and RFID require slightly larger estimations given the lack of fully accurate information available for costs related to ongoing operations, maintenance, and labor. Because of this information shortfall, two cases are considered for each NPV calculation: a base case and a worst case, where costs are assumed higher for RFID and laser marking.

Risk adjusted NPV is "adjusted for risk by multiplying cash flows by the probability that those cash flows will actually occur"[33]. The normal use for this type of analysis is for the valuation of biopharmaceutical products in the pipeline and the probability that the product will be approved for commercialization. In this case, the risk adjustment will be in terms of an adverse event related to product mix-up, assuming the unit level mark prevents that adverse event from occurring. An adverse event is defined here as a product mix-up that is caught either in house or in the field. Because of the large difference between the costs associated with an in house find versus an in the field failure, two cases are analyzed. Rather than product success or failure then, the analysis is focusing on cost avoidance of an adverse event occurring.

Marking Technology Option	Base Case NPV ($millions)	Worst Case NPV ($millions)	Risk Adjusted NPV Low	Risk Adjusted NPV High
Laser Marking	-3.09	-4.61	-2.06	1.91
RFID	-0.74	-1.67	-0.56	4.33
LaserJet	-0.67	-1.41	-0.52	3.94
Clear Label	-0.49	-2.24	-0.35	4.50

Table 6: Net Present Value Analysis for All Scenarios

(Note: Numbers have been altered to protect sensitive data. However, the basic significance has been preserved)

The risk adjustment was made in terms of a best guess scenario for an in house mix-up discovery where product must be scrapped and for an in the field mix-up where product has to be recalled. The valuation of those different scenarios in based on industry data as well as Amgen understanding of internal costs. As previous mentioned, the numbers have been altered to protect sensitive data.

9.3 Financial Discussion of Technology Options

As can be seen from the analysis above, the clear label technology has the least negative NPV. The reason the base case for clear label application is the lowest is that it utilizes current infrastructure. For more discussion about the different options for clear label technology, see chapters 9.4 and 9.5. Laser marking has the highest expenditure because of the high cost of capital equipment. Outside of the capital purchase, the laser marking option could be one of the lower cost options as the per unit costs and maintenance costs are extremely low.

The business driver for the marking project is risk mitigation with product mix-up. The costs involved with a mix-up result from scrapped finished goods but also from potential product recalls. Product safety concerns are most important for the long-term sustainability of the company's reputation. Therefore, Table 6 shows all negative NPVs for the base and worst-case scenarios. The project is about risk and cost avoidance, which is taken into account in the risk adjusted columns.

9.4 Methodology for Implementation Analysis

The purpose of the implementation analysis was to determine the feasibility of the application of the solutions to the biotechnology manufacturing process. Specifically, the

analysis focused on the fill-finish process. It is important to understand the potential implementation issues surrounding a particular solution, especially as two of the solutions would be completely new technologies for Amgen. The focus of the implementation analysis was on the one solution with most promise for short-term application. That solution, clear label application, is analyzed given current Amgen space and capital constraints, looking at product flow throughout the plant.

9.5 Implementation Exercise: Clear Label Technology

In analyzing the application of clear technology to a current manufacturing facility, two implementation options resulted as potential solutions:

1. Use of existing labeling equipment taking into account capacity constraints and material flow. Because syringes would come from the fill-finish area in a rondo tray, the syringes would have to be un-trayed before clear labeled. Also, in this option, the syringes would be loaded back into rondo trays manually (although the option exists to re-tray the syringes using a machine).

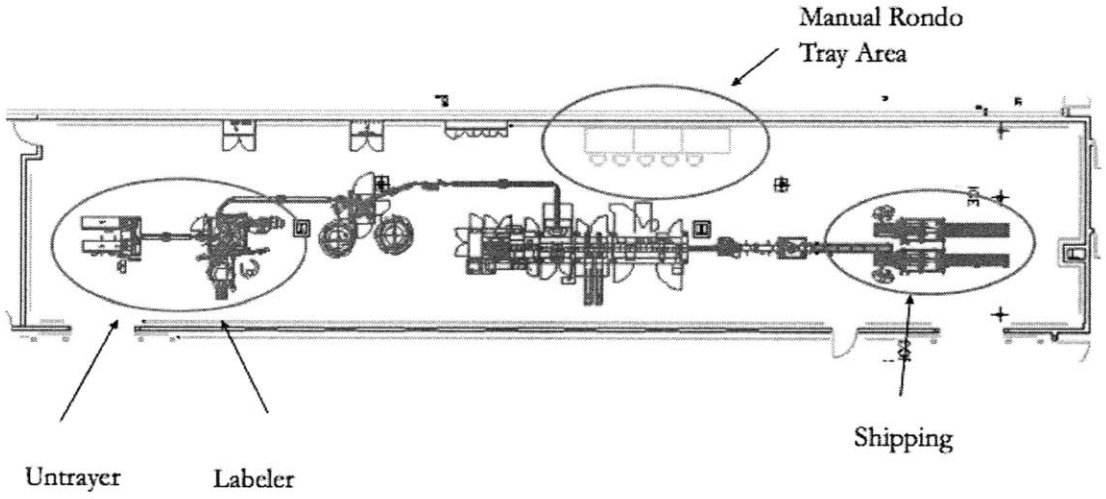

Figure 51[34]: Implementation Option #1 for Clear Label

2. Creation of an entirely new, small clear labeling line. Space would need to be made available for an area that would be specifically for product that required a clear label. The benefit of this option is that it would make material flow much simpler as all products needing a clear label would

simply move to this new line as opposed to using existing equipment. The drawback is the higher cost of capital as compared to option one above.

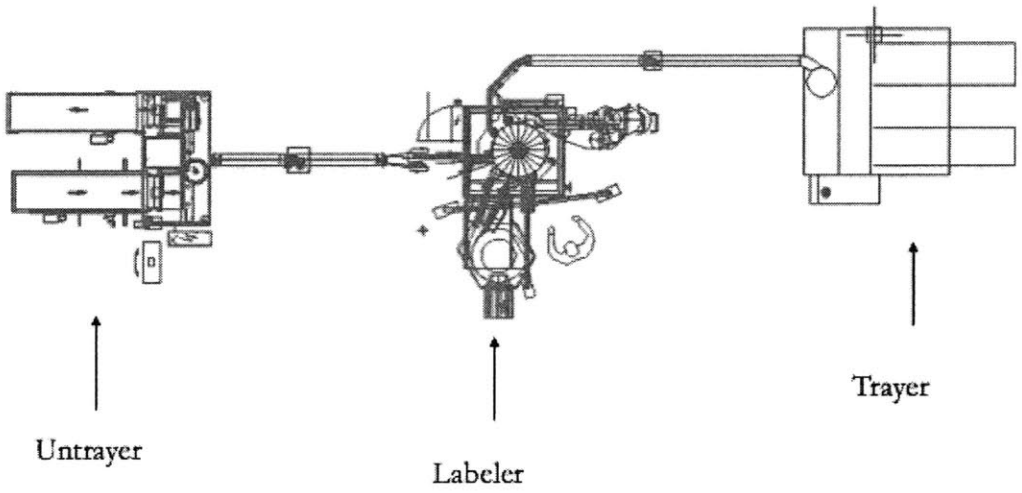

Figure 52[34]: Implementation Option #2 for Clear Label

The implementation exercise shows that not only is the clear label option feasible from a technological perspective but from a manufacturing perspective as well. Implementation study fleshes out all of the small yet important details involved with a new process such as material flow, space constraints and labor requirements. Without such an analysis, the likelihood of actual implementation is much lower. This analysis gives the solution a much needed depth and understanding of the reality of the actual variables involved at the manufacturing site.

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10 Conclusion

In a complex manufacturing industry like biotechnology with uncertainties in product approval and success, risk management is a key component of sustainable survival. Amgen has proven its success by remaining one of the few biopharmaceuticals who hasn't gone through a merger or acquisition in the last decade. Nude product in the supply chain, although current cGMP mechanisms serve Amgen well in ensuring product movement across its network, presents a potential risk that has implications for product safety and quality as well as corporate reputation. With a new product about to be successfully brought to market, other promising products in the pipeline, and increasing international growth, the need for a solution has never been clearer. In looking at the marking industry, several solutions are attractive options. Three specific options were analyzed for their feasibility from a technical, financial and implementation perspective. From that analysis and discussion, it is apparent that the clear label technology is the most realistic option for short-term implementation. It offers a low-cost solution that relies on internal competencies but utilizes new ink technology. Although technological advancements may become more readily applicable, it properly mitigates the risk without being prohibitively expensive. Applying the clear label at the point of manufacture mitigates the risk of mix-up as well as reduces regulatory pressures going forward.

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Appendix 1

Regulatory Frame Work

• CGMP Regulations (FDA) 21 CFR 211)

§ 211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and crosscontamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations.

Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

Appendix 2
Automatic Needle Guard Tolerance Analysis

Automatic Needle Guard
Inner Diameter: 8.6mm ± 0.1mm (0.340in ± 0.004)
Range of **8.5** – 8.7mm

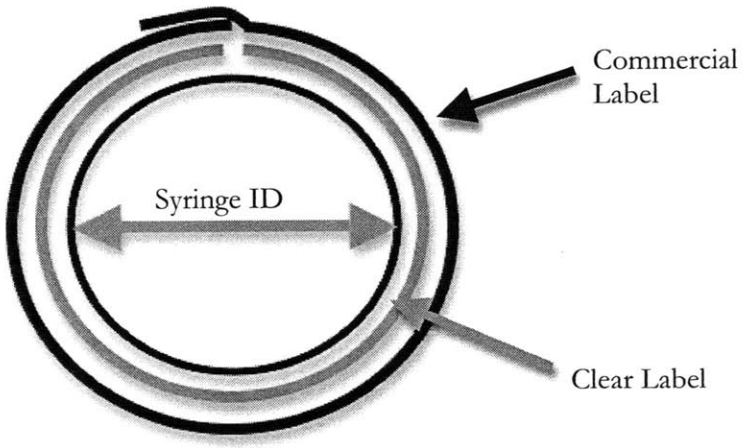
Manual Needle Guard
Inner Diameter: 8.63mm ± 0.25mm (0.34in ± 0.01)
Range of **8.38** – 8.88mm

Syringe Barrel
Outer Diameter: 8.15mm ± 0.1mm
Range of 8.05 – **8.25**mm

Clear Label Thickness: 0.06mm (blue)
Commercial Label Thickness: 0.09mm (maroon)

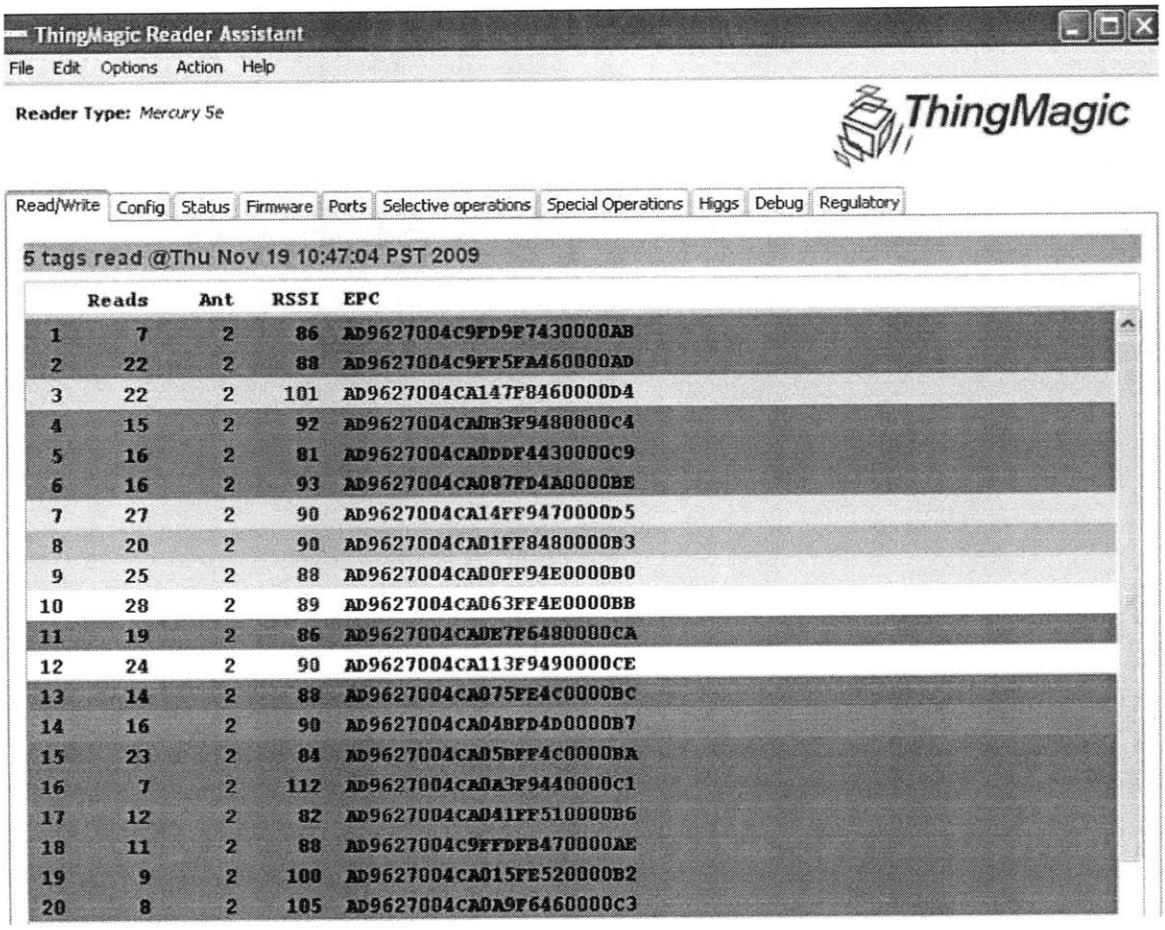
Total Label Additional Thickness = 0.06mm + (0.09mm x 2) = 0.24mm

Therefore, total barrel thickness being inserted into needle guard (worst case) is about 8.5mm.



Appendix 3

ThingMagic Reader Assistant Software Output



	Reads	Ant	RSSI	EPC
1	7	2	86	AD9627004C9FD9F7430000AB
2	22	2	88	AD9627004C9FF5FA460000AD
3	22	2	101	AD9627004CA147F8460000D4
4	15	2	92	AD9627004CAD83F9480000C4
5	16	2	81	AD9627004CADDDF4430000C9
6	16	2	93	AD9627004CA087FD4A0000BE
7	27	2	90	AD9627004CA14FF9470000D5
8	20	2	90	AD9627004CAD1FF8480000B3
9	25	2	88	AD9627004CAD0FF94E0000B0
10	28	2	89	AD9627004CA063FF4E0000BB
11	19	2	86	AD9627004CADE7F6480000CA
12	24	2	90	AD9627004CA113F9490000CE
13	14	2	88	AD9627004CA075FE4C0000BC
14	16	2	90	AD9627004CAD4BFD4D0000B7
15	23	2	84	AD9627004CAD5BFF4C0000BA
16	7	2	112	AD9627004CADA3F9440000C1
17	12	2	82	AD9627004CAD41FF510000B6
18	11	2	88	AD9627004C9FFDFB470000AE
19	9	2	100	AD9627004CA015FE520000B2
20	8	2	105	AD9627004CADA9F6460000C3

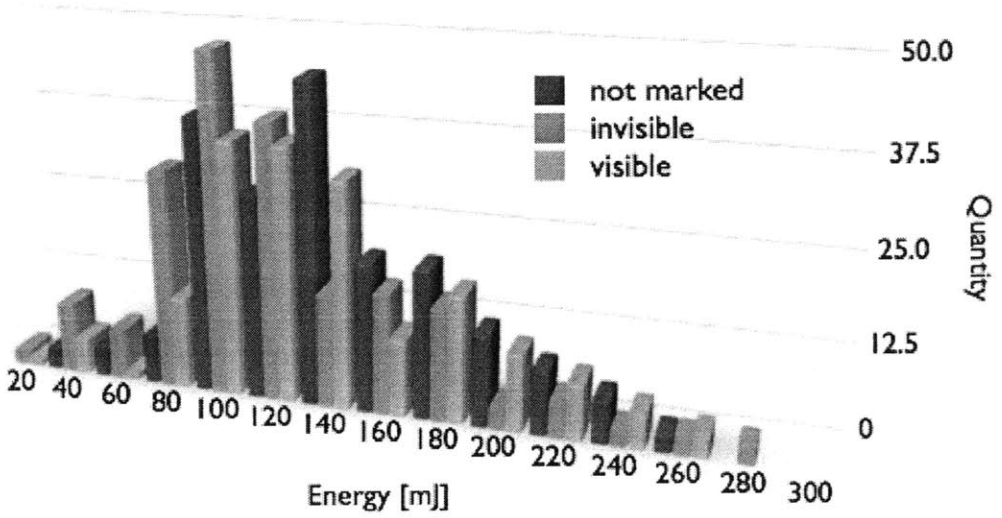
Appendix 4

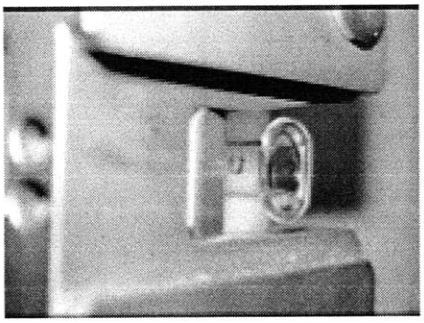
Frewitt Laser Mark Shock Testing Results

FREWITT Printing

Shock

	not marked	invisible	visible
average [mJ]	132	131	131
deviation [mJ]	44	52	53





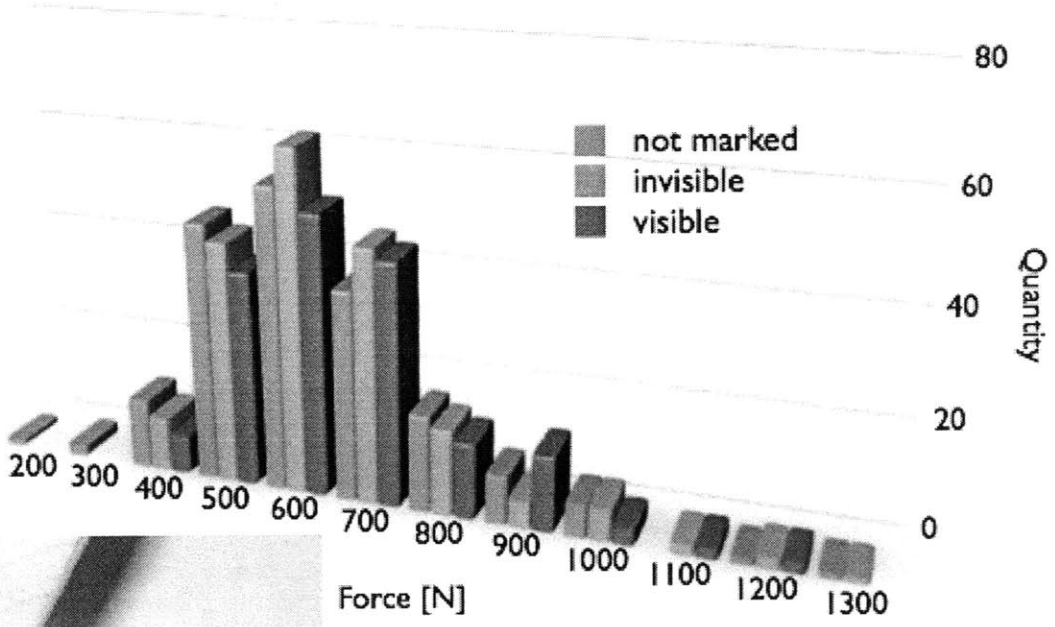
Appendix 5

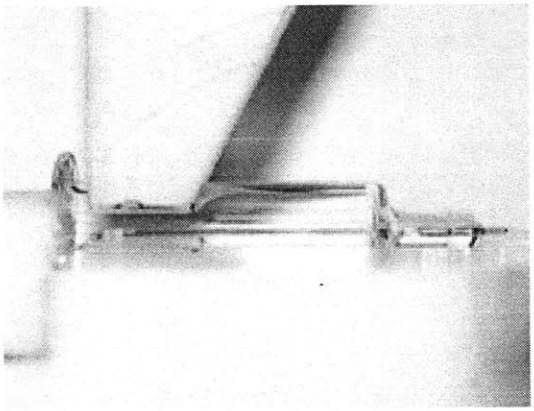
Frewitt Laser Mark Compression Testing Results

FREWITT Printing

Compression

	not marked	invisible	visible
average [N]	579	593	601
deviation [N]	159	151	152





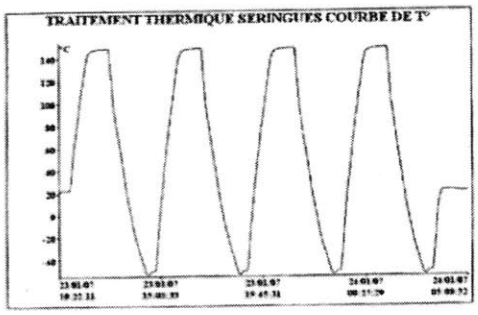
Appendix 6

Frewitt Laser Mark Thermal Cycling Results

FREWITT IF
Printing

Thermal cycle

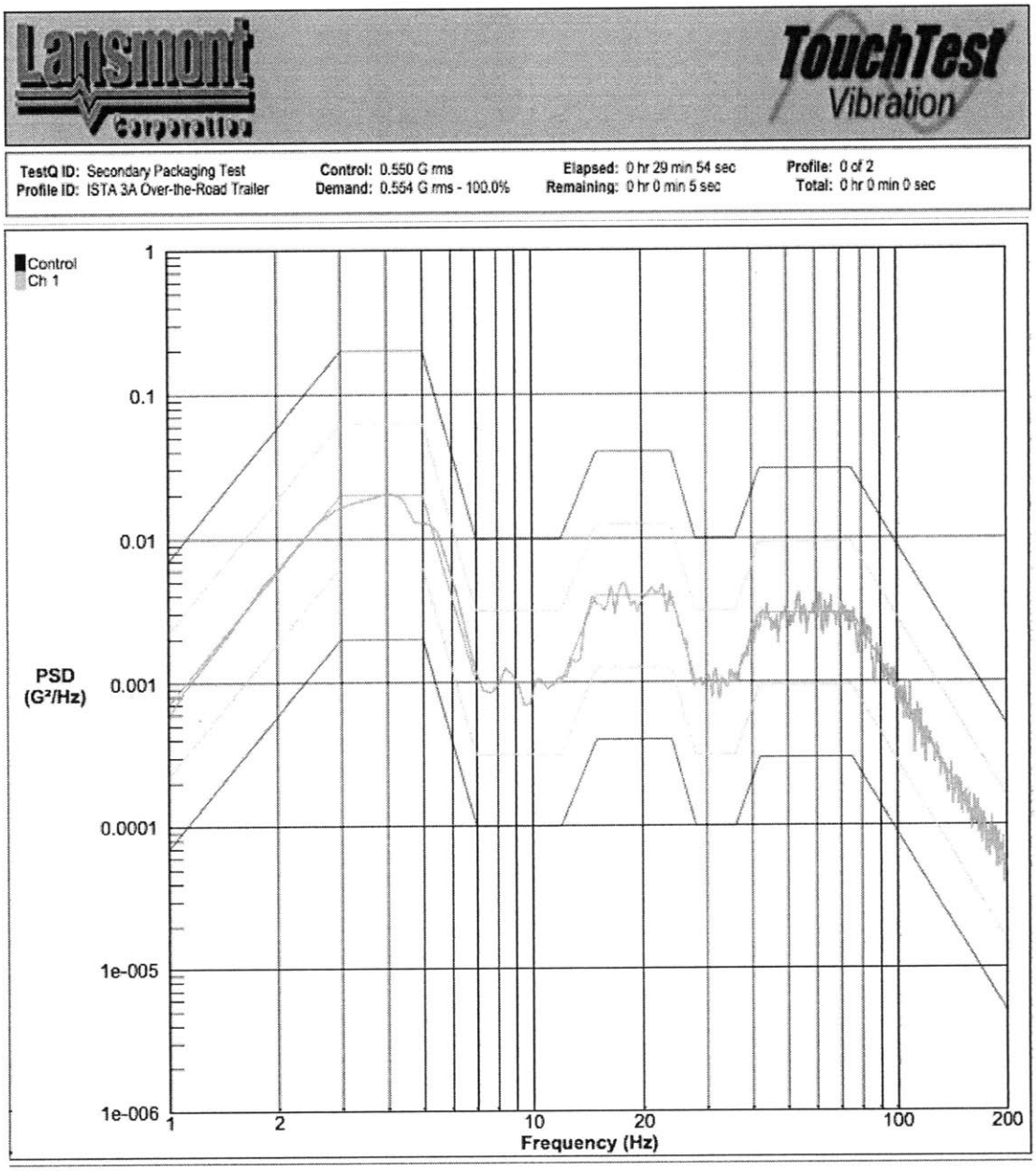
- 10 syringes
- -50°C for 30 min
- +150°C for 60 min
- repeat 4x
- no visible effect



Appendix 7

Vibration Cycling Chamber Settings and Output

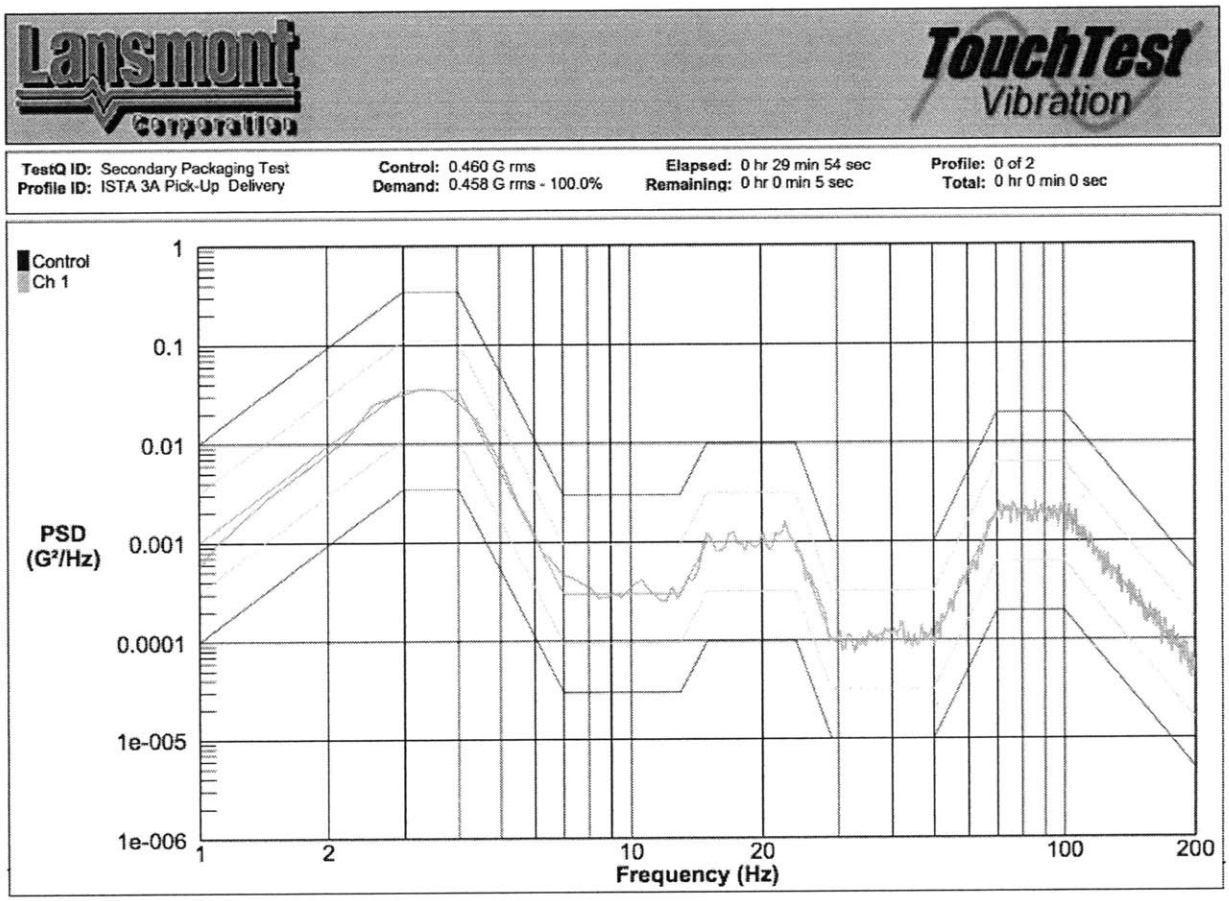
Over-the-Road Trailer



Appendix 8

Vibration Cycling Chamber Settings and Output

Pick-up and Delivery



Appendix 9

Bar Codes versus RFID

Bar Code Tags	RFID Tags
Bar codes require line of sight to be read.	RFID tags can be read or updated without line of sight.
Bar codes can only be read individually.	Multiple RFID tags can be read simultaneously.
Bar codes cannot be read if they become dirty or damaged.	RFID tags are able to cope with harsh and dirty environments.
Bar codes must be visible to be logged.	RFID tags are ultra thin and can be printed on a label, and they can be read even when concealed within an item.
Bar codes can only identify the type of item.	RFID tags can identify a specific item.
Bar code information cannot be updated.	Electronic information can be overwritten repeatedly on RFID tags.
Bar codes must be manually tracked for item identification, making human error an issue.	RFID tags can be automatically tracked, eliminating human error.

Appendix 10

Multi-Attribute Utility Theory Model Output

The Utility of Marking Technologies

	Attribute							
Alternative	Marking Efficiency	Capital Cost	Ongoing Cost	Supply Chain Effect	Ease of Implementation	Scalability	Risk	*Overall Utility*
RFID	35	67	25	85	75	67	50	56.15
Laser Marking	67	25	85	50	35	67	15	49.45
LaserJet	85	50	35	50	45	75	85	64.25
Clear Label/Inkjet	55	67	45	50	80	40	90	61.95
Importance Weight	0.25	0.1	0.1	0.15	0.15	0.1	0.15	