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Reducing Product Costs, Increasing Raw Materials Of Non-Controversial Stem Cell Pharmaceuticals By Lean Waste Elimination: A Study With Implications For Reducing Healthcare Costs

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Curriculum Vitae

Janett Gray

Education

Degree	Field	Institution	Year
PhD	Technology Management	Indiana State University	2008
MS	Technical Education	University of Memphis	1989
BS	Biological Science	Arkansas State University	1976

Certifications

Type	Name	Certifying body
CQE	Certified Quality Engineer	American Society for Quality
CQM	Certified in the Management of Quality	American Society for Quality
CQA	Certified Quality Auditor	American Society for Quality

Employment History

Cognate BioServices, Inc. – Director Quality Assurance 2007-Present

- Responsible for the management of quality and regulatory assurance activities of this startup cellular product manufacturer and therapy contract service provider.

CryoCell International, Inc. – Director Quality Assurance & Regulatory 2006-2007

- Led the strategic direction and overall management of the quality system for quality assurance and regulatory compliance of therapeutic products, stem cells and medical devices.

Lifeblood Mid-South Regional Blood Center – VP Quality & Regulatory 2003-2006

- Developed, directed, ensured regulatory and quality policies, goals and procedures that met the organization's strategic objectives of product and process assurance.
- Responsible for anticipating and adapting the regulatory system to changing domestic, global marketplace and intensified regulatory climate.

Lifeblood Mid-South Regional Blood Center –Director Quality & Regulatory 2004-2006

- Responsible for developing, establishing, and maintaining a Quality Assurance and Regulatory system that was consistent with the principles of current good manufacturing practices in healthcare manufacturing of biologics, medical devices, pharmaceuticals.
- Led organization out of risk-from warning letter to zero deficiencies, sustained.
- Quality Awards received, city and state; Baldrige Performance Excellence criteria.

Professional Affiliations

American Association of Blood Banks (AABB)
American Society for Quality (ASQ)
Biomedical Engineers (BME)
International Society for Cellular Therapy (ISCT)

REDUCING PRODUCT COSTS, INCREASING RAW MATERIALS OF NON-CONTROVERSIAL STEM CELL PHARMACEUTICALS BY LEAN WASTE ELIMINATION: A STUDY WITH IMPLICATIONS FOR REDUCING HEALTHCARE COSTS

A Dissertation

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The College of Technology

Indiana State University

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In Partial Fulfillment

of the Requirement for the Degree

Doctor of Philosophy

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by

Janett Gray

August 2008

School of Graduate Studies
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Terre Haute, Indiana

CERTIFICATE OF APPROVAL

DOCTORAL DISSERTATION

This is to certify that the Doctoral Dissertation of

Janett Gray

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has been approved by the Examining Committee for the dissertation requirement for the

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ABSTRACT

A direct cost of a product is the cost of the raw materials used in its manufacturer. When availability of raw materials is high, product cost tend to be lower whereas the inverse occurs when raw materials are low causing product cost to be high. This relationship between product cost and raw material availability holds true regardless of the type of product. The same is true for lifesaving medical treatments produced from stem cells.

Stem cells are used in the production processes of medical treatments where the vast potential continues to remarkably emerge. However, a major problem in advances in stem cell treatments is lack of available raw materials, to include non-controversial stem cell materials affecting production and product costs. An increase in supply could reverse these affects.

This work was used to evaluate balancing measures aimed at increasing the supply of non-controversial stem cells in the production of pharmaceuticals. Reduction in associated product cost was also assessed. The strategy used was the elimination of waste in the manufacturing processes of non-controversial stem cells by application of lean manufacturing. Lean manufacturing is a management technology based on the systemic elimination of waste that has been shown to optimize resources producing high quality products at the lowest cost.

The results of this study examined the influence of the application of lean waste elimination on the availability of raw materials used for production of non-controversial stem cell pharmaceuticals and the associated product cost used for medical treatments in healthcare. The results were positive influences on raw materials with an increase in availability and a significant reduction in the associated cost of the stem cell pharmaceutical product. The latter holds implications of the potential of this study to be used as a point of consideration for evaluating measures to reduce healthcare costs.

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INTRODUCTION

The utility of stem cells has been proclaimed as one of the most significant applications of scientific discovery in recent history. The cells can be used in a multitude of manufacturing systems from the automotive industry in environmental testing, to cosmetics, foods, and drugs (CryoCell, 2006; National Institute of Health, 2007; Policastro, 2006). The most significant and future emerging application of stem cells is in healthcare where remarkable results in successfully treating diseases have been realized. However, the continued research and application of the cells is being jeopardized by the laws of supply and demand of the available raw materials for production affecting costs.

The law of supply and demand developed out of a work by Jean Baptiste Say (1767-1832) in 1803 entitled *A Treatise on Political Economy* which described a relationship of product cost based on its supply or demand (Kates, 1997). As the supply of a product increases, the cost of the product decreases. The direct cost of a product is driven by its supply of the raw materials used in its manufacture. In addition, raw material cost is affected by its supply or availability sharing an inverse relationship with product costs. When the supply or availability of these raw materials is high, the cost of the product tends to be lower. The inverse is true when the availability of raw materials

is low resulting in a limited supply of the product at a higher cost. This inverse relationship between product cost and availability of the raw materials used in production of the product is not affected by the type of product (Jacoby, 2005). Medical products used in the treatment of life-threatening diseases are not immune to the adverse affects that a low supply of raw materials used in their production has on product availability and increases in prices. Stem cells have the ability to treat and cure a multitude of different diseases and medical conditions. Unfortunately, the short supply of the raw materials used in the production of stem cells having negatively affected product costs, limiting treatments for patients in need (Borrow, O'Rourke, & Skirboll, 2000; National Institute of Health, 2007).

Stem cells are at the center of research and development activities, scientific studies and product development in laboratories, biological technologies, medical treatments and production processes around the world, playing a large part in the global expansion of the Biotech industry (Policastro, 2006). The ability to continuously self-replicate and to become any cell type while simultaneously sustaining its original state are defining properties of stem cells, making them versatile in application and use, especially for the treatment of diseases and conditions of the human body (Kadereit & Hines, 2005).

Stem cells are currently being used to treat over 70 different medical conditions and are continuously being studied to treat a multitude of diseases to include heart disease, stroke, diabetes, adult onset leukemia, cancer and diseases of the nervous system to name a few (Borror, O'Rourke, & Skirboll, 2000; CryoCell, 2006; National Institute of Health, 2007). The vast potential of stem cells in medical treatment continues to emerge

yet the lack of available stem cells, and the production processes used in their manufacture, impede wide spread usage of these lifesaving pharmaceuticals (Powell, 2002; International Society for Stem Cell Research, 2007).

This introductory chapter of the research overviews the use of stem cells and the limitation of sources of non-controversial stem cells affecting availability for pharmaceutical medical treatments and product costs, which are the defining aspects of the problem evaluated from this work.

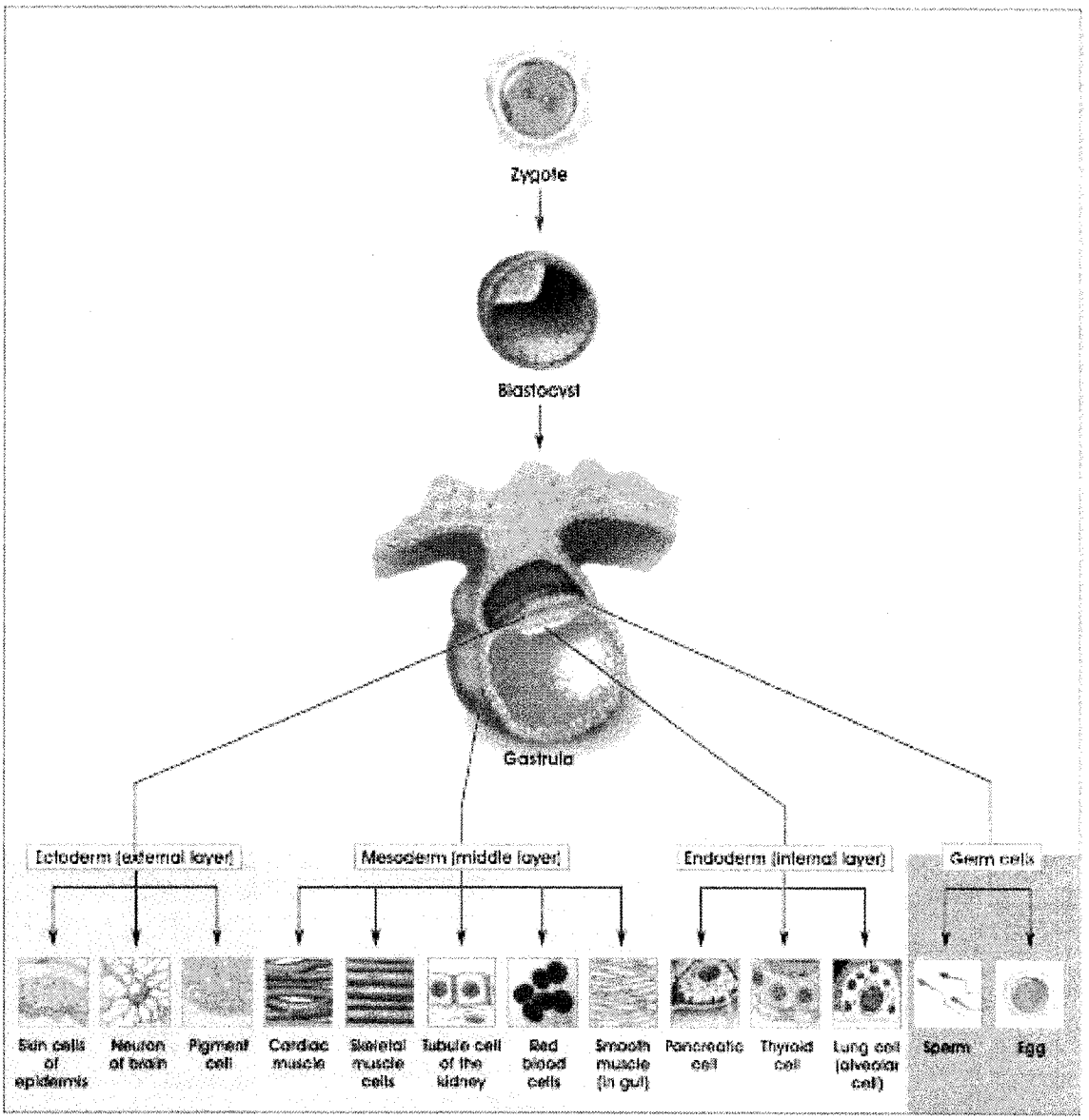
Focus of stem cells

Injury, damage, malfunction, and deterioration of cells of the body are primary causes of diseases and conditions that medical treatment seeks to rectify. Injury to cells results in numerous medical conditions ranging from cuts and scratches to total body paralysis due to spinal cord injury. Cancer stems from the malfunction of cells that cause uncontrolled proliferation or abnormal cell growth producing tumors. Degeneration of nerve cells causes Parkinson's disease and Alzheimer's (National Institute of Health, 2007). Most medical treatments have sought to manage conditions by chemical-based drugs or pharmaceutical therapies, if a treatment is even available. However, these drug therapies are known to be harsh on the body that causes additional adverse conditions; does not eliminate the problem; and may not be effective (Borror, O'Rourke, & Skirboll, 2000). This knowledge has redirected the approach to medical treatments away from chemical-based drug therapy to biological. Treatments are now focused on biological cellular therapies because of their ease of adaptability in the body, the potential to eliminate the medical problem and to find treatments for conditions that were deemed untreatable (Kochar, 2004; National Institute of Health, 2007).

The fundamentals of human development at the cellular level begin with the stem cell. The National Institute of Health (2007) noted that the ability of the primal stem cell to grow and develop into any cell type such as muscle, bone, or nerve cells and on to tissues and organs are reasons that the direction of medical treatments, especially for replacement of damaged or malfunctioning cells, is so focused on stem cells. Pharmaceutical production has evolved to include standard manufacturing systems that consist of stem cell processing. Processing primarily consists of production activities that separates raw material into its components parts, delineating and storage of the cells composing the final product. The entire manufacturing systems of most Biotech companies have been described as cellular processors of biologics such as stem cells (Perkowski, 1989).

Human stem cells are categorized into different types; these are described more fully later in this work. The types of stem cells that have the ability to become every cell type of the human body are those that arise at human development from the fertilized egg or embryo (Kochar, 2004).

The National Institute of Health (2007) defines embryonic stem cells as those that give rise to all of the three primary germ layers consisting of the ectoderm, mesoderm, endoderm from which develops tissues, organs, internal systems and finally the whole complex human being. The germ cells are defined as the egg and sperm that develop apart from the germ layers, yet also from the initial stem cells. These stem cells form approximately three to five days in the embryo or fetus as an inner mass of cells in a structure called a blastocyst; see figure 1 that follows.



(Source: Winslow & Duckwall, 2001)

Figure 1. Differentiation from stem cells into different germ layers.

Embryonic stem cells are obtained, in very limited amounts, from excess embryos from *in vitro* fertilization, aborted embryos, and from embryos where development did not continue or were destroyed (National Institute of Health, 2007). Widespread controversy on the use of these cells resulted from ethical concerns, political issues, and

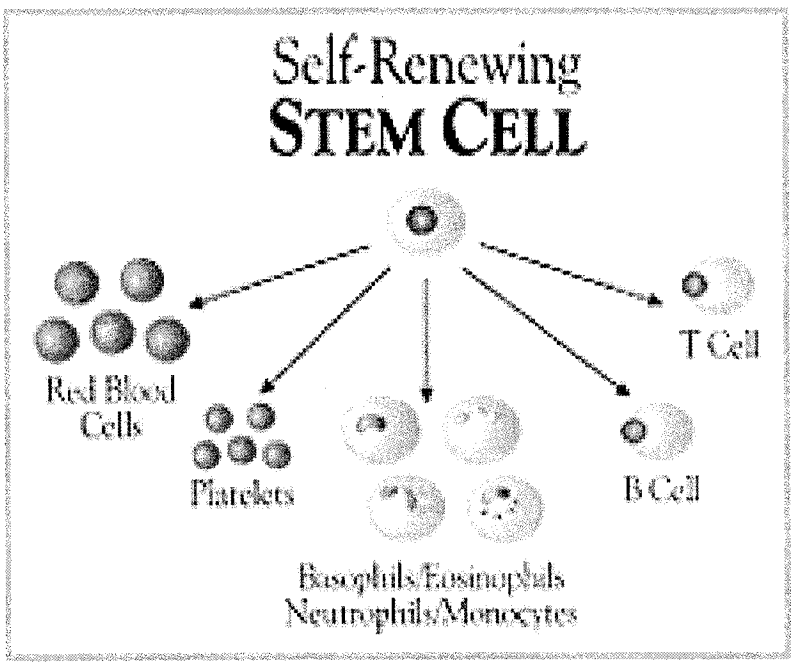
fears of human cloning to include debates on the stage at which the cells develop into the human being. The outcome of public concerns about embryonic stem cells resulted in governmental legislation that enacted federal laws limiting research on embryonic stem cells, critically reducing the availability of these cells. Other sources of cells that do not carry the same controversial issues have been identified, though the supply and availability are also limited (Cord Blood Transplant Study, 2005).

Stem cells are also located in the biological processes which support human development. Components of the birthing process or "after birth" that consists of the dispelled placenta and umbilical cord, as well as blood in the cord, are rich sources of different types of stem cells. Since the umbilical cord, cord blood, and placenta are discarded after child birth as waste products, use in medical research and pharmaceutical application is deemed non-controversial (Cord Blood Transplant Study, 2005).

The production processes to remove the stem cells from the discarded placenta tissue and umbilical cord require extensive manual tissue digestion techniques. The liquidity of the cord blood makes the production process of harvesting those stem cells easier. These types of non-controversial stem cells do not carry the same capacity to differentiate into every cell type as do embryonic cells, yet the pharmaceutical potential is viewed as substantial (International Society for Stem Cell Research, 2007).

Prindull, Prindull, & Meulen (1978) discovered that the blood that remains in the umbilical cord contain stem cells that are specialized for the formulation of blood cells. Blood cells consist of red blood cells, platelets, basophils, eosinophils, neutrophils, monocytes, B cells and T cells. These cells play critical roles in medical treatments and

are the natural sources for immunological defense systems. Stem cells that differentiate into blood cells are referred to as hematopoietic, see figure 2 that follows.



(Source: CryoCell, 2006)

Figure 2. Stem cell into blood cells.

The non-controversial stem cells from the umbilical cord blood are currently used to pharmaceutically a number of diseases such as leukemia, anemia, Hodgkin's disease osteopetrosis, acute myelofibrosis, and aplasia, to name a few. The cord blood can be readily collected, using standard blood bags, and manufactured into stem cell products. Therapeutic use requires a cell count based on the weight of the patient, which limits its use to a select group of patients. The volume of the cord blood raw material collected and the available volume for processing during manufacturing contributes to the products' cell count and usage. Increasing either has a positive influence on the

therapeutic use of the cord blood stem cells and raw material availability affecting the cost of the pharmaceutical product (Knoppers, Saginur & Kharaboyan, 2004; Mancinelli, et al., 2006).

Pharmaceuticals' Contribution to High Healthcare Costs

Healthcare costs in the United States (U.S.) continue to climb at astronomical rates, with annual costs over $2.3 trillion. Costs are expected to double within ten years (HHS, 2005; Health Insurance Cost, 2008). Data analysis by Davis & Cooper (2003) of The Commonwealth Fund, a foundation started in 1918 to support and facilitate healthcare improvements, show that the U.S. has the highest rate of healthcare spending in the world. The U.S. rate is 69% more than Germany, 83% more than Canada, and 134% more than the average of all industrialized nations. However, people in the U.S. are not by far the healthiest, ranking only 24th by the World Health Organization (British Broadcasting Company, 2000).

Several major reasons for the increase in healthcare costs in the U.S. have been identified, singling out prescription drugs or pharmaceuticals as one of the largest contributing factors (Appleby, 2001; Davis & Cooper, 2003). Most strategies for reducing healthcare costs are aimed at decreasing usage, minimizing health insurance coverage, and increasing premiums, deductibles, and co-pays. These strategies have basically had no effect on reducing healthcare costs (Davis & Cooper, 2001). During Congressional hearings on the subject of increasing healthcare costs, the key to containing costs was identified as the need to make fundamental changes in the supply side of the market (Davis & Cooper, 2001) such as pharmaceuticals. The findings identified that there must be a shift of attention to reducing errors, eliminating waste and

duplication, increasing efficiencies, and streamlining administrative costs. All of these strategies can be directly linked to eliminating wastes.

The elimination of waste is the core of the lean manufacturing improvement technological philosophy (Womack, Jones, & Roos, 1990). The lean manufacturing philosophy is the systematic, continuous, and deliberate elimination of waste throughout an organization (Womack, et al., 1990). Every aspect of a system or process is evaluated, by a set of core principles, to continuously identify and eliminate waste. As noted by Lewis (2002), the aim of lean manufacturing is the optimization of all resources in the most effective manner, by using less human efforts, less materials, less inventory, less time and space; dramatically reducing costs. The result is an economical, efficient business made lean by the elimination of waste.

Lean manufacturing is established by the application of defined technological principles and strategies which have produced dramatic improvement results. These include increased efficiencies, wastes eliminated, defects minimized, errors reduced, optimization of resources, and reduced operating costs (Liker, 2004; Womack, et al., 1990). The application of lean manufacturing to pharmaceuticals, which is a major cause of increased healthcare costs, should be a key focus in reducing costs. Applying lean manufacturing to the production of stem cells directs the assessment to the types of medical treatments that are the current and future approaches to healthcare. Utilizing leans' core principles of identifying and eliminating waste in the production of non-controversial stem cell pharmaceuticals should realize substantial benefits in reducing healthcare costs on the supply side of the healthcare network.

Need for the Study

Stem cells are pharmaceuticals and are the direction of current and particularly future medical treatments (Kochar, 2004). These cells are already in limited supply and the manufacturing processes by which these pharmaceutical products are produced are not generally focused on reducing waste. The pharmaceutical industry in the U.S. has been slow in developing and implementing lean manufacturing principles and strategies that optimize resources (Elliot, 2006). Many attribute this reluctance to the historical regulatory restraints of the industry and also to its manufacturing structure (Holstein, 2006; Thomas, 2005; Radishofski, 2006).

Pharmaceutical regulatory requirements are codified by federal laws such as the Food and Drug Administration's (FDA) Good Manufacturing Practices, Quality System Regulations, and Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) which specify manufacturing standards (FDA, 2006). Numerous other regulatory bodies oversee and regulate the pharmaceutical industry to include the Environmental Protection Agency (EPA), the Occupational Health and Safety Administration (OSHA), the Department of Transportation (DOT), and the Drug Enforcement Administration (DEA), to name a few (Perkowski, 1989). The regulatory environment of the pharmaceutical industry is viewed as complex and stringent. Elliot (2006) describes, in the article *Strong Medicine,* the historical relationship between the pharmaceutical industry and the FDA as being somewhat adversarial and restrictive. In order to make a change in the manufacturing process, the pharmaceutical company is required to submit documented details of the proposed change to FDA and await

approval. The code of federal regulations (FDA, 2005), part 21 CFR 601.12 states that:

1. "Changes that have a substantial potential to have an adverse effect on the safety or effectiveness of the product, require submission of a supplement and approval by FDA prior to distribution of the product made using the change (major changes);
2. Changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product, require submission of a supplement to FDA, 30 days prior to distribution of the product made using the change or, for some changes, the 30 days may be waived (moderate changes); and
3. Changes that have minimal potential to have an adverse effect on the safety or effectiveness of the product are to be described by the applicant in an annual report (minor changes)."

The process of change approval involves back and forth submissions by the pharmaceutical company to the regulatory agency until approval is granted, which may take years. When a proposed change is finally approved by the regulatory agency and made, the pharmaceutical company is very reluctant to make other changes; even changes that they know will enhance productivity. The result has created very long lead times to get pharmaceuticals to market, with most applications requiring 10 to 12 years from development (Elliot, 2006). The FDA (2004b) has developed guidance to reduce approval time, presented in their document *Innovation and continuous improvement in pharmaceutical manufacturing: Pharmaceutical CGMPS for the 21st Century Process Analytical Technology (PAT).* The document consists of policies and procedures to mitigate regulatory restraints that should reduce the time required to market

pharmaceuticals. Unfortunately, the pharmaceutical industry has been reluctant to pursue PAT because of the historical experience to the contrast (Elliot, 2006).

Elliot (2006) and Kardian (2006) also identified that the standard manufacturing structure of the pharmaceutical industry has also contributed to the lack of applying lean manufacturing. Research and development, that include stem cells, is the focus of big pharma, a termed used to describe the top largest pharmaceutical manufacturers, with the manufacturing process taking a back seat. Research is conducted primarily in silos, with the overall industrial structure very departmentalized. The time to research, develop and market a new pharmaceutical takes about 10 - 12 years. The product is protected from being copied or marketed by someone by a patent that expires in about 17 years from approval. The manufacturer then has only 5 - 7 years to recoup expenses and make a profit before copied generics of the same drug may be produced by other companies (Elliot, 2006). In order to sustain and increase profitability after a drug's patent expires, the pharmaceutical company must be well on its way to launching other patented products. This type of strategy positions the research and development component of the pharmaceutical company as the focal point of the manufacturing process. Product manufacturing is minimized, where traditional lean manufacturing originated.

Kardian (2006) explains that the reluctance of the pharmaceutical industry in applying lean manufacturing may also be due to the difficulty of implementation of shared equipment, the high volume product mix, and the volatile demanding environments of the industry. Pressures from international competitive pharmaceutical companies, consumer and federal demands to reduce costs, and product shortages have created an environment that now demands change of the U. S. pharmaceutical industry.

International pharmaceutical companies manufacture under very different conditions, resulting in reduced cost of pharmaceuticals (Crowley, 2006). Labor is cheaper, regulatory restraint are less, and with quality system standards such as ISO, process improvement is a routine part of the manufacturing environment (McAdam & Barron, 2002; Crowley, 2006). These aspects allow international pharmaceutical companies ease of reverse engineering which is analyzing a product and recreating it without the very time consuming research and development processes. The production of generic drugs is a type of reverse engineering (Bansal & Koradia, 2005; Crowley, 2006).

Consumers and the federal government are demanding that U. S. pharmaceutical companies reduce the cost of drugs (FDA, 2004b). Consumers now routinely opt for generics over the higher costing brand name drugs (Crowley, 2006). This method of purchasing generics over brand name drugs is also promoted by federal healthcare funding agencies such are Medicare. Another approach used by consumers to reduce the cost of needed drugs is by purchasing them outside of the U. S. because of the significant cost reduction of international pharmaceuticals (Young, 2003).

The U. S. pharmaceutical industry has also been faced with product shortages due to its manufacturing systems, inventory imbalances of critical materials such as stem cells, and wasted expired inventories. All of which contribute to higher priced drugs. The flu vaccine shortage of 2004-2005 was attributed to a lack of necessary biological raw materials required to produce the vaccine (Elliot, 2006). The manufacturing process, or strategy, used to make the vaccine was based on batch production methods and a push system. Ohno (1988) and Womack, Jones, & Roos (1990) determined that these methods of manufacture are not as efficient as the associated lean manufacturing production

methods of cellular manufacturing and the pull system whereby production is initiated by customer demand. The flu vaccine shortage caused consumers to loose faith in the U. S. pharmaceutical industry to supply the very drugs they need to survive. Consumers responded by looking outside the U.S. for their pharmaceuticals.

Changes to the manufacturing systems of U.S. pharmaceutical companies are needed in order to optimize resources, such as stem cells, for the industry to remain competitive, win back customer loyalty, and survive globally. The industry must meet the challenges of reducing costs by improving efficiencies, reducing cycle time, and eliminating waste (McAdam & Barron, 2002; Elliot, 2006) - all principles of lean manufacturing. Effective systems that better ensure essential raw materials and supplies are available at demand are critical components, as realized by the shortage of flu vaccine incident (Elliot, 2006). One of the most critical, essential, type of raw material used in the manufacture of pharmaceuticals are biologics (American Red Cross, 2005b).

Suppliers of biological pharmaceuticals and biological materials used in the manufacture of pharmaceuticals are daily faced with the challenge of obtaining raw materials (American Red Cross, 2005b). The primary sources of biological materials are human donors. Blood and blood components obtained from donors are essential raw materials used in the production of life-sustaining pharmaceuticals. Unfortunately, blood shortages occur routinely and periodically; specially during holidays and summer.

The summer months are notably a period of blood shortages because people are vacationing, involved in outdoor activities and leisure, and school is out of session (American Red Cross, 2005a). The American Red Cross (2005a) states that from 15 – 20 percent of the overall blood supply is donated by high school and college students at their

schools. When school is out of session for the summer, this source of blood virtually ends. Another element that affects blood donations is inclement weather. Bad weather impedes people from going out to obtain even needed supplies and therefore definitely hinders blood donations. The 2007 year's very harsh winter, for most parts of the U.S., resulted in blood shortages throughout the nation (New York Times, 2007). Supplies were at their lowest with less than a day's supply available. As noted by the Blood Center of the Pacific (2005), "every three seconds someone needs blood." This demand equals 32,000 pints each day. Winter storms can cause such a significant blood shortage that hospitals ration supplies for emergencies only, postponing non-emergency surgeries. When blood shortages occurs affecting medical treatments, other uses, such as pharmaceutical production, is hindered. Waste of these materials has crucial negative impacts on the availability of these pharmaceuticals, causing significant increased costs.

Statement of the Problem

The problem for this research was to determine the influence of applying the principle of waste elimination from lean manufacturing on product costs and raw material availability in the production of non-controversial stem cell pharmaceuticals.

Research Questions and Hypotheses

The research was conducted on the production processes of non-controversial stem cell pharmaceutical products. A single manufacturer was the subject of the research. Two research questions were identified, each of which was related directly to the problem statement noted above. Methods of assessments for each question were based on the type of data collected, whether continuous, variable data or discrete with the former type applicable to statistical analysis for hypothesis testing. The second question includes

hypothesis testing based on the variable data whereas the first question does not since the assessment is a summation of costs.

Research Questions

Research Question 1. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Research Question 2. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Definitions

Aseptic technique. Practices designed to reduce the risk of microbial contamination of products, reagents, specimens, patients, or donors (FDA, 2004a; NETCORD-FACT, 2006).

Aspirate. To draw in or out using suction. (NETCORD-FACT, 2006).

Biologic. Any virus, therapeutic serum, toxic, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives, applicable to the prevention treatment or cure of diseases or injuries of man (FDA, 2007).

Biological safety cabinet. A ventilated cabinet for personnel, product, and environmental protection against biohazards having an open front with inward airflow for personnel protection, HEPA filtered laminar airflow for product protection and HEPA filtered exhaust air for environmental protection (CryoCell, 2006).

Cellular manufacturing. Arranging machines in the correct process sequence, with operators remaining within the cell and materials presented to them from outside (Rooney & Rooney, 2005).

Cryopreservation – The freezing of cells, at very low temperatures between -196°C and -150°C, using devices, supplies, and techniques validated to maintain viability (NETCORD-FACT, 2006).

Error proofing. A process used to prevent errors from occurring or to immediately point out a defect as it occurs (Rooney & Rooney, 2005).

FACT. Foundation for the Accreditation of Cellular Therapy. Develops quality systems standards, with NETCORD, the international organization of cord blood banks, which their memberships are required to follow. The standards are aimed at promoting high-quality patient care and laboratory performance (NETCORD-FACT, 2006).

Flow. The progressive achievement of tasks along the value stream so a product proceeds from design to launch, order to delivery and raw to finished materials in the hands of the customer with no stoppages, scrap or backflows (Rooney & Rooney, 2005).

Hematopoietic progenitor cells (HPC). Self-renewing and/or multi-potent stem cells capable of maturation into the hematopoietic lineages-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source) (NETCORD-FACT, 2006).

in vitro. Outside the living body and in an artificial environment (Merriam-Webster's Medical Desk Dictionary, 1986).

ISO. International Organization for Standardization. Set of global quality system standards for managing business operations (International Organization for Standardization, 2008).

Just In time (JIT). A planning system for manufacturing processes that optimizes availability of material inventories at the manufacturing site to only what, when & how much is necessary (iSixSigma, 2007).

Kaizen. Japanese term of gradual unending improvement by doing little things better, setting and achieving increasingly higher standards (Rooney & Rooney, 2005).

Lead time. The total time a customer must wait to receive a product after placing an order. When scheduling and production systems are running at or below capacity, lead time and throughput time are the same. When demand exceeds the capacity of a system, there is additional waiting time before the start of scheduling and production, and lead time exceeds throughput time (Womack & Jones, 1996).

Lean. Abbreviation for lean manufacturing. Producing the maximum sellable products or services at the lowest operational cost while optimizing inventory levels (Rooney & Rooney, 2005).

Lean manufacturing. Initiative focused on eliminating all waste in manufacturing processes ((iSixSigma, 2007).

Muda. Japanese word for waste (Rooney & Rooney, 2005).

NetCord. The international organization of cord blood banks that meet defined membership requirements of the International NetCord Foundation (NETCORD-FACT, 2006).

Non-controversial stem cells. Stem cells that are obtained from sources other than an embryo or embryonic tissues (CryoCell, 2006).

One-piece flow. The opposite of batch production. Instead of building many products and then holding them in line for the next step in the process, products go through each step in the process one at a time, without interruption (Rooney & Rooney, 2005).

Patent. Grant of a property right to the inventor, issued by the Patent and Trademark Office. The term of a new patent is 20 years from the date on which the application for the patent was filed in the United States or, in special cases, from the date an earlier related application was filed, subject to the payment of maintenance fees. US patent grants are effective only within the US, US territories, and US possessions. The right conferred by the patent grant is, in the language of the statute and of the grant itself, "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States or "importing" the invention into the United States. What

is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention (United States Patent and Trademark Office, 2007).

Perfection. The complete elimination of waste so that all activities along a value stream create value (Womack & Jones, 1996).

Pluripotent. Stem cells that can give rise to cells derived from all three embryonic germ layers—mesoderm, endoderm, and ectoderm. These three germ layers are the embryonic source of all cells of the body (National Institute of Health, 2007)

Pull. System of cascading production and delivery instructions from downstream to upstream activities in which nothing is produced by the upstream supplier until the downstream customer signals a need; opposite of push (Womack & Jones, 1996).

Pull system. An alternative to scheduling individual processes, in which the customer process withdraws the items it needs from a supermarket, and the supplying process produces to replenish what was withdrawn (Rooney & Rooney, 2005).

Stem cell. A cell that has the ability to divide (self replicate) for indefinite periods—often throughout the life of the organism. Under the right conditions, or given the right signals, stem cells can give rise (differentiate) to the many different cell types that make up the organism. That is, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells. Pluripotent stem cells give rise to cells derived from all three embryonic germ layers—mesoderm, endoderm, and ectoderm. All of the many different kinds of specialized cells that make up the body are derived from one of these germ layers as a result of stem cells ((National Institutes of Health, 2007).

Takt time. The available production time divided by the rate of customer demand; the rate that a completed product needs to be finished in order to meet customer demand (iSixSigma, 2007; Womack & Jones, 1996).

Total productive maintenance. A series of methods to ensure every machine in a production process is always able to perform its required tasks. The result is production is never interrupted due to machine breakdowns (Rooney & Rooney, 2005).

Value. A capability provided to a customer at the right time at an appropriate price, as defined in each case by the customer (Womack & Jones, 1996).

Value stream. The specific activities required to design, order, and provide a specific product, from concept to launch, order to delivery, and raw materials into the hands of the customer (Womack & Jones, 1996).

Viability. Living cells as determined or defined by analyses by dye exclusion, flow cytometry, or progenitor cell culture (NETCORD-FACT, 2006).

Waste. An activity that consumes resources and produces no added value to the product or service a customer receives (Rooney & Rooney, 2005).

Work in process. Items between machines or equipment waiting to be processed (Rooney & Rooney, 2005).

Chapter Summary

The cost of raw materials used in the manufacturer of a product directly affects the final cost of the product. Increases in the cost of raw materials occurs based on supply with cost inversely proportional to availability. Product costs tend to be lower when the availability or supply of associated raw materials is higher, with product costs higher when raw material availability is low. This cost versus supply relationship holds

true for products regardless of the type to include medical treatments used in delivering healthcare such as stem cells.

The cost of healthcare in the U.S. is the highest in the world with no associated health benefits. Costs have significantly and consistently increased for years, negatively impacting the economy, businesses, and each person, directly or indirectly. Root causes of increased healthcare costs have been identified, determining that the cost due to pharmaceuticals as a primary factor.

A major component of critical pharmaceuticals is stem cells which are also the primary direction for the future of medicine. Stem cell raw materials are limited in availability increasing the cost of the pharmaceuticals which are already a major contributing factor of the increased cost of healthcare. Current measures to reduce healthcare costs are known to be ineffective. These measures have only redirected funding without reducing costs. New measures and approaches are needed that are aimed at elimination of waste and increased efficiencies.

Stem cell products used in the treatment of medical conditions are pharmaceuticals and are so classified by the FDA. The manufacturing processes of the pharmaceutical industry are known to be inefficient, wasteful, and antiquated, primarily as a result of a focus on research and development with little attention to the production side. The effect has caused waste of product and raw materials resulting in drug shortages, further increasing costs. With stem cells in short supply, measures to offset product shortages are warranted.

Lean manufacturing is a management technology based on the elimination of waste proven to enhance productivity, reduce cost and optimize resources. This work

investigated the influence of applying the principle of waste elimination from lean manufacturing on product costs and raw material availability in the production of non-controversial stem cell pharmaceuticals based on the research questions identified above. A comprehensive study of the lean manufacturing concept began the research, presented in the review of literature that follows.

Chapter 2

REVIEW OF LITERATURE

The aim of this research was to determine and evaluate the influence of applying the lean manufacturing strategy of waste elimination to the production of stem cell pharmaceuticals in reducing the cost of manufacture with optimization of resources. The effect of waste elimination from lean manufacturing on end-product costs and availability of raw materials were the specific factors of consideration for evaluating influence. The cumulative assessment of the influence of waste elimination from lean manufacturing relative to the stated questions has potential in discovering additional approaches or methods for evaluation in reducing healthcare costs from pharmaceuticals.

A comprehensive understanding of lean manufacturing was needed to investigate the applicability of the technology to pharmaceutical production of stem cells. This chapter of the research presents a study of lean manufacturing followed by a review of stem cell manufacturing. An overview of measures in reducing healthcare costs and the use of lean manufacturing in traditional pharmaceutical manufacturing are included. The chapter ends with a review of the key factors addressed through the research questions by applying lean manufacturing to pharmaceutical production of non-controversial stem cells; evaluating raw material availability and end-product costs.

Lean manufacturing is a technological concept that could have a significant impact on reducing the costs of pharmaceutical production affecting resources. Womack, Jones, & Roos (1990) describe lean production or manufacturing as a technological business strategy that is focused on the systemic and methodological elimination of waste to provide high quality goods and services at the lowest cost. VerDuft (1999) adds that in lean manufacturing the total enterprise is assessed for waste.

Every aspect of a system or process is evaluated, by a set of core principles and strategies, to continuously identify and eliminate waste (McVay & Cooke, 2006). The term waste is defined as an activity, product, or process, which does not add value to the customer where value is defined from the perspective of the customer (George, 2003). Thomas (2005) points out that value is the opposite of waste and waste is the opposite of value. Daley (2003) defines lean manufacturing as strategies that define the value stream by the identification and elimination of waste. Liker (2004) notes that from product manufacturing to customer service, throughout production, purchasing, supplied parts, and design, the lean manufacturing methodology is applied to identify and eliminate waste. The result reduces manufacture to only value-adding components. May (2005) describes the core principle of lean manufacturing as clearly to do more with less. One of the more comprehensive definitions of lean is provided by McVay & Cooke (2006): "Lean is a combination of organization, management philosophy, tools, and techniques to deliver greater value to the customer in the form of the right service, at the right time, in the right place, at the lowest possible price, with no defects."

The available literature on lean manufacturing is extensive. An Amazon.com book search on the topic of lean manufacturing listed 52,301 sources. Library searches,

with search specifications limited to full-text articles from scholarly journals, listed over 164 articles. A complete literature review of lean would include background information, concepts, and applicability to this research. These elements serve as the framework of the discussion on lean manufacturing that follows. The first part of the following literature review serves as a study of the lean manufacturing philosophy. A discussion of stem cells is presented next that includes the production process. Strategies and applications of lean in the pharmaceutical industry follow. The review concludes with a summary of consequences as a result of high healthcare costs of which pharmaceuticals is a major contributor with stem cells the direction of advances in healthcare.

History of Lean

Womack, Jones, and Roos (1990) in the book *The Machine that Changed the World* describes the history of lean manufacturing and coins the phrase lean production. As production of goods changed from being individually built by skilled craftsmen to mass production of goods marking the industrial revolution, the end of World War II (WWII) also changed production methods. Liker (2004) notes that after the war many countries were faced with limited resources of both raw materials and supplies. This effect was drastically seen in the Asian world especially in Japan. The aftermath of the war reduced the Japanese economy to rations of products. Their consumer market was open for massive incursion of foreign products, especially automobiles, for that very large population of consumers (Womack, et al., 1990).

Womack, Jones, & Roos (1990) continue the history by describing the Japanese manufacturing environment during WWII and post. During WWII, most Japanese automotive companies produced vehicles for the military as part of the governmental

requirements of that society. The vehicles manufactured were large, built for transport of military troops and equipment. The post war automotive needs of the average consumer in Japan were for very different types of vehicles. Individual transport vehicles were the demand as well as vehicles to carry small loads and for farmers to transport their produce to market. Consumer transportation vehicles also had to be small to maneuver their narrow streets. The Japanese automotive manufacturing systems, at the time, were not ready for the changing customer base and their needs. The necessity for a radical manufacturing change was apparent (Womack, et al., 1990; Liker, 2004).

The work life of the Japanese laborer before the war was that of very long hours with limited benefits. Workers were routinely fired without cause creating an environment of hostile mistrust. The post war era of Japan saw rise to labor unions and employee rights groups that restricted the length of the work day along with other changes (Womack, et al., 1990). Additional demands of the workforce resulted as the automotive industry in Japan faced lagging sales that threatened industry survival. One Japanese automotive company owned by the Toyoda family, founders of the company *Toyota*, attempted to resolve the labor problems and lagging car sales by firing one fourth of their labor force. Workers revolted by physically taking over occupation of the company (Womack, et al., 1990). Aggressive negotiations ended the standoff between the owners of Toyota and employees with significant benefits to workers agreed upon. Compensation to workers included implementation of a system of financial increase based on bonuses and seniority, and provision of life-time jobs. The latter benefit clearly gave workers ownership in the success or failure of the company. The owners realized that these workers were there for life and they would need to invest in, and optimize, their

human resources to survive. Toyota's management decided to benchmark one of the top automotive companies in the world. At that time, these were Detroit's Big 3 in the U.S. - Ford, Chrysler, and General Motors. Toyota selected Ford to benchmark in order to understand, learn, and hopefully transfer the company's successful automotive manufacturing technology back to Japan (Womack, et al., 1990; Lee, 2003; Liker, 2004).

The Ford Motor company had pioneered the assembly line with the first mass production of the Model-T Ford. The process worked as a result of standardized, interchangeable parts that were easily assembled on a moving line (Ford, 1926). Workers performed only one task, separating labor into defined areas. Mass production evolved to a state of standardization of work tasks, tools, equipment, supplies, and even management activities. The outcome was high-volume production of standardized cars at reasonable prices, although there was limited flexibility in car styles and amenities, with little innovation (Womack, et al., 1990). During their several visits to Ford, Toyota's management recognized these limitations and also noticed that mass production required stock-piles of raw materials waiting to be processed with workers also waiting to process. Taiichi Ohno, one of Toyota's top engineers who visited Ford, saw that this mass production system consisted of large amounts of *muda*, a Japanese term for waste (Ohno, 1988). He saw waste in materials, cycle times, and human work due to separation of labor. At Toyota, Ohno analyzed and re-engineered the manufacturing process used by the U.S. automotive industry in such a way that was adaptable to the Japanese lifetime worker and with process improvements (Womack, et al., 1990; Liker, 2004).

Major differences between workers in Japan and the U.S. caused Ohno to decide to structure his workforce into teams that did not specialize in just one activity but many

to include housekeeping, equipment repair, decision making, and problem solving (Womack, et al., 1990). Ohno also noted that the product quality assessments done only at final inspection by U.S. producers were extremely costly due to having to correct the cumulative defects of the product at the end stage. Toyota transformed the inspection process to become a continuous assessment with corrective action throughout the manufacturing process. This inspection enhancement reduced the cost of rework due to poor quality dramatically. Ohno understood that errors could be predicted and were not just a result of random causes as the U.S. industries saw them. Predicable errors could be anticipated and their causes eliminated. Ohno developed a method to determine root-causes that consisted of asking and answering *five whys* of a problem. The employee or team traced the problem back to root-cause by assessing the whys at each layer of manufacture. Corrective actions were developed and implemented.

The initial teams progressed as Ohno continued to add other responsibilities. He charged the teams to make, discuss, and implement suggestions to improve the production process (Manos, Sattler, & Alukal, 2006; Womack, et al., 1990). Ohno supported the initiative by allocating scheduled time for the teams to work on a problem, make suggestions, and implement associated improvements. The teams, called quality circles, made continual incremental improvements; a process known as Kaizen.

The redesigned Toyota production floor included supplies that were obtained or *pulled* only when they were needed. There were no large inventories of materials as seen in mass production processes. Parts on the production floor were stored in limited quantities, in size specific containers, so that no more than the parts needed for a operation were available. This philosophy extended to suppliers to align Toyota's supply

flow on a day-to-day basis. The flow of supplies, which was controlled by the amount of need, was later termed *kanban*, or Just-In-Time (Womack, et al., 1990).

The multiple strategies of optimization of resources, time, and human activity, were based on the elimination of waste that also increased the rate of production (Lee, 2003). These composite strategies developed into the Toyota production system that formed the manufacturing process of lean. The innovative strategies produced cars faster, of high quality, imparted reliability, and were more economical (Womack, et al., 1990).

Today lean manufacturing is an established improvement technology that increases production rate and process flow. The elimination of waste caused the increases in flow and speed of production by removing delays and barriers that resulted in time wastes (Womack, et al., 1990). However, increased speed is just one of the benefits of lean manufacturing. The foundation of this technology management process is proactive problem-solving that is focused on waste elimination through the lean manufacturing philosophy. Potential problems are anticipated and resolved with solutions sustained by strategies employed from lean manufacturing (Finchbaugh, 2005).

Principles of Lean Manufacturing

Womack & Jones (1996) defines five core principles of lean manufacturing from which lean thinking is generated. Value, the value stream, flow, pull, and perfection are the five principles of lean thinking, manufacturing, or enterprise. VerDuft (1999) supports the same five principles as the core of the lean manufacturing enterprise. Applying each principle sequentially optimizes performance resulting in continuous improvement.

Value is defined from the viewpoint of the customer and created by the manufacturer (VerDuft, 1999). Womack & Jones (1996) describes value as customer specified capabilities of a specified product, provided at the right time and appropriate cost. VerDuft (1999) denotes that value is specific to the associated product which is defined by the external customer. The focus of value is external as opposed to internal operations. These definitions of value are focused on the customer and, as a result, can only be defined by the customer. Both Deming and Ishikawa, leaders in the field of Quality, declared that quality can only be defined from the perspective of the customer. Ishikawa makes the point that quality is all encompassing; it is quality of work, quality of products, and quality of management in terms of the customer (Ishikawa, 1985). Deming, in his book *Out of the Crisis* (1982), stated that quality must be aimed at the needs of the customer. Quality and value may be viewed as synonymous terms defined from the perspective of the customer

The second principle of lean manufacturing is the value stream. The composition of the value stream starts at product concept through to design, manufacturing, and launch that includes the activities of problem-solving, information management, and physical product transformation (Womack & Jones, 1996). Value stream analysis identifies the value-adding activities. These activities include tasks that may not add direct value but are necessary due to requirements or capabilities. The analysis also includes activities that are of no value, which are wastes (Crabtree, 2006). The assessment should be conducted both internally and externally to include assessment of raw material suppliers in order to obtain an entire view of the production system for the

systemic elimination of waste. After waste has been removed from the system, valued flow can be created (Introduction of lean manufacturing, 2005).

The principle of *flow* is based on viewing the whole product concept at each manufacturing step. The focus is on the finished product regardless of what production task is being performed at a given activity (George, 2003). The result is a process flow whereby all value adding steps are conducted continuously until the final product is achieved. This concept is the reverse of mass production or assembly line processing. The principle of flow requires consolidating organizational departmentalization into a common work team with a consistent focus on the specific product. Continuous flow reduces inspection time waste, the number of defects, and allows for real-time improvements due to the ability to view the whole system. When the whole system or product is consistently being taken into consideration, improvement opportunities can be identified and realized directly.

The foundation of the *pull* principle of lean manufacturing is production that is initiated, or pulled, at customer demand. Design, scheduling, and manufacture of the exact product that is pulled by the customer results. This type of production stabilizes fluctuating product demand challenges of the manufacturing process (Womack & Jones, 1996).

The last principle is *perfection*. When value is specified, the value stream generated, flow unobstructed, and production by customer demand, a cycle results that continues to identify opportunities for improvement. It is at the time of continuous realization of those opportunities that perfection is achieved. Womack & Jones (1996) notes that during the perfection principle the totality of a product's cycle is made

transparent, from the quality of raw material suppliers through to customer satisfaction levels. This type of clarity readily identifies value that can be consistently increased for product perfection.

Establishment of these five principles of lean manufacturing results in an organization that is focused on the product from the perspective of the customer, targeting and eliminating waste to produce the exact product that the customer requires at the time required. Figure 3 that follows graphically illustrates the hierarchical principles of lean manufacturing, starting with the determination of value, followed by identification of the value stream, determining production flow, assessment pull and ending with perfection.

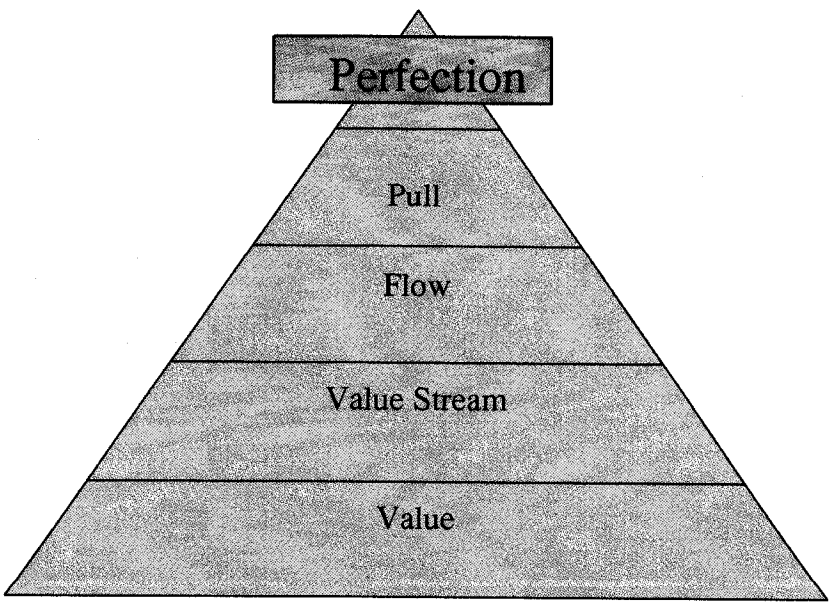


Figure 3. Principles of lean manufacturing from value to perfection.

Strategies of Lean Manufacturing

There are six primary strategies used in applying lean manufacturing (Womack, et al., 1990; Environmental Protection Agency, 2005), which may be used individually, consecutively, or concurrently:

1. Kaizen
2. 5S
3. Total Productive Maintenance (TPM)
4. One-piece flow production: Cellular Manufacturing
5. Point of use storage: Just-in-time (JIT)
6. Control of variation: Six Sigma

Kaizen, pronounced as "ki-zen," is a process of making gradual, yet constant improvements, accomplished by making small incremental changes focused on eliminating or reducing waste (Venables, 2005). The continual small improvements of Kaizen have a synergic affect that results in significant improvements. The term "kaizen" comes from the Japanese, where "kai" means change and "zen" is to become good or improve. The philosophy of Kaizen is a way of life that assumes every aspect of life should and can be constantly changed for the better. The Kaizen strategy in lean manufacturing directly includes all employees, for a multi-functional team approach that works together to solve problems or improve a particular process involving waste elimination (University of Dayton, 2006). As a result, application of Kaizen in lean manufacturing also serves as a problem-solving element for continuous process improvement. This problem-solving aspect is one of the many benefits of the lean management technology.

Key components of the Kaizen team-based strategy are effective communication, personal discipline, teamwork, participation, suggestions for improvement, and quality circles. A significant benefit of Kaizen is improved morale (McNichols & Hassinger, 1999). Workers from all levels of the organization are formed into teams to apply lean manufacturing strategies, to implement suggestions for improvement, for problem solving, or to cut the "fat" from a process making it "lean." In addition, the team may be charged to identify areas where there is waste. Analytical tools, such as value stream mapping, a type of flow-charting, are used to visually map the flow of a process, part or system to identify waste. This flow-charting or mapping activity uses standardized icons for types of activities, materials, and processes.

Value stream mapping is used in the Kaizen strategy to chart the flow of information, materials, and processes, from supplies to the customer, to identify waste, for communication, and to design solutions (Womack & Jones, 1996; Rother & Shook, 1999; VerDuft, 1999; George, 2003; Daley, 2003). There are numerous benefits of the value mapping process. As noted by Kenneth Daley (2003) in his *Lean manufacturing Handbook*, value stream mapping determines dependent activities and improves the understanding of complicated systems, serving as a communication tool. Value stream mapping also identifies areas appropriate for specific tools or strategies, locates constraints, and prioritizes improvement efforts.

There are different types of value stream maps based on the process to be mapped. For example, production maps chart the process from raw material to final product, to the customer; design maps, from concept to launch; and administrative maps depict order taking to delivery (Rother & Shook, 1999; Stratego, 2005). Regardless of

the type of map, they generally consist of the process activities, cycle times, materials, flow, and staging or downtime. In most mapping activities two maps are developed: the current state and the desired or future state. The process of value stream mapping is similar to flow-charting with differences in action symbols used. The value stream map also depicts the flow of information. Examples of the symbols used in value stream mapping are presented in figure 4 that follows.

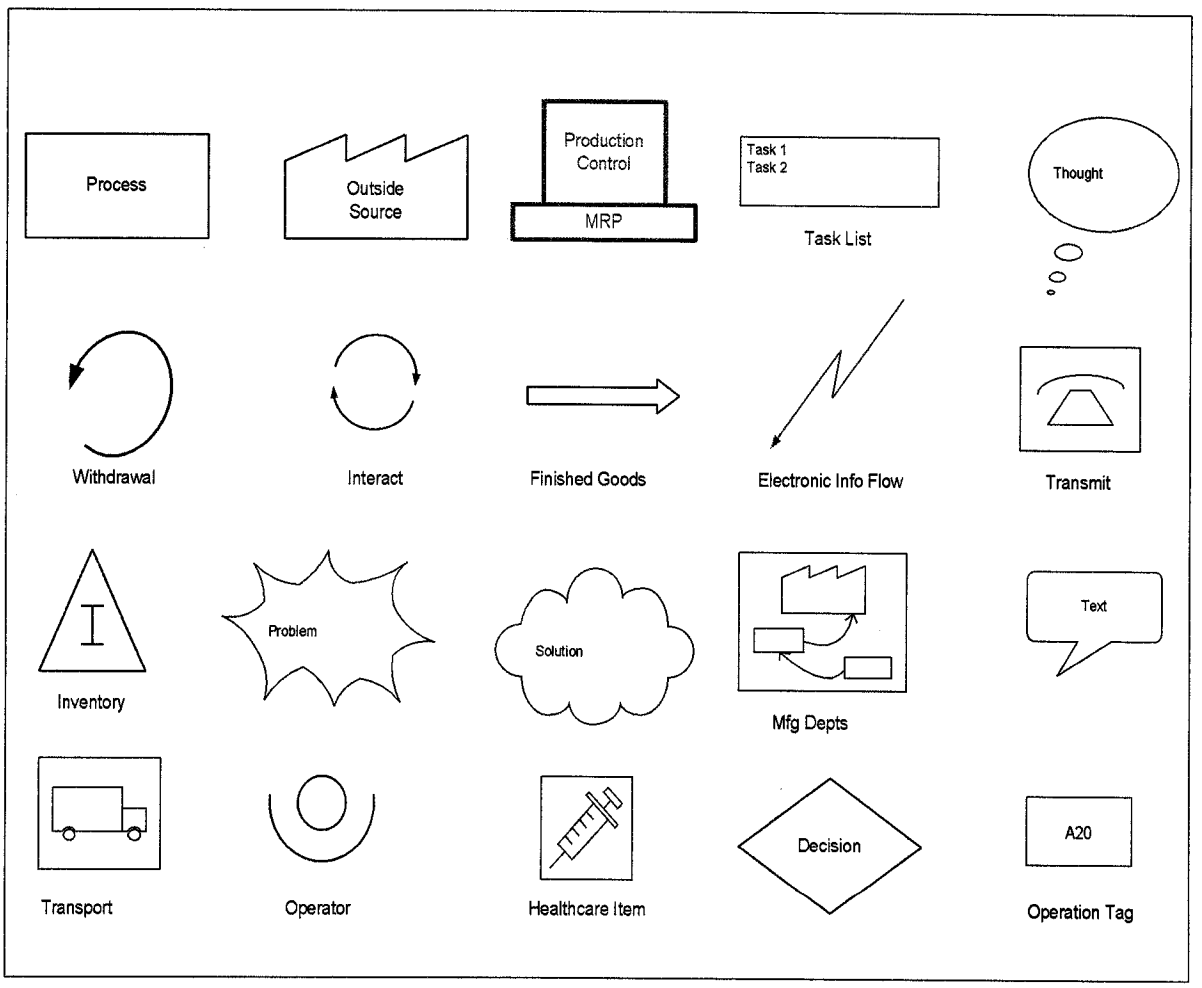


Figure 4. Value stream mapping symbols.

The fundamental goal of the mapping process used in the Kaizen strategy is the identification of waste. The Toyota Production System, lean strategists, and technologists have identified eight general types of waste (Evans, 2005; Daley, 2003; George, 2003; Introduction to lean manufacturing, 2005; Manos, Sattler, & Alukal, 2006; Rooney & Rooney, 2005; Thomas, 2005; Womack, et al., 1990):

1. Overproduction - produces more than is needed or not at the time of need. The results of overproduction waste are the costs of increased lead times, work-in-process (WIP), and storage costs. Identification of defects occurs later in the production process which also increases waste and associated costs. Thomas (2005) notes that excessive lead times between product manufacture to customer purchase results in product deterioration and/or product expiration, which is a routine problem in the pharmaceutical industry. Overproduction also reduces the amount of raw materials that may be needed for on-demand production. If there are quality problems, large quantities of materials are at risk and supply problems occur, especially with, for example, critical or short supply raw materials.
2. Waiting - time wasted. When employees are watching an automated machine, waiting on the next batch to work on, idle from lack of raw materials to be processed, or from delays in processing, waiting waste occurs (Liker, 2004). Essentially the waste of waiting occurs whenever employees are on the clock, e.g., being paid, yet no work is being done. Daley (2003) determined that waiting waste is a result of processes not being synchronized.

3. Excess inventory or WIP – materials waiting between processes, or WIP, is waste, and includes waste from an excess of raw materials and from finished products waiting on a customer order or demand. These types of waste also produces other waste as a result of obsolescence, damage, cost of transportation, storage, and delays (Liker, 2004). Excess inventory or WIP causes longer lead times and tends to mask problems of late deliveries, long set-up times, production imbalances, and equipment downtime. The primary waste from excessive inventory is its carrying cost which is money spent without a return on investment.
4. Making defective products - classical waste. Other associated wastes from producing defects are time required to correct defects or from scrape when corrections are not possible. Inspection, handling, transport, and damage costs are also part of the waste of making defective products.
5. Transportation - adds no value. Moving parts or products from storage to the next process, especially long distances, is transportation waste. Time and energy are wasted in transportation that carries associated costs.
6. Motion - of materials, people, and/or equipment due to, for example, inappropriate location to the activity to be acted upon. Reaching, walking, stacking, and twisting are degree related wastes of motion that adds no value to the product or process.
7. Processing waste - unnecessary steps and activities. Processing waste include rechecks, testing that adds no value, inefficiencies from improper manufacturing designs, and even producing higher quality products than

needed or required by the customer. Redundant activities are a primary source of processing wastes (Daley, 2003).

8. Under-utilizing people - inadequate knowledge management of human abilities. Ideas are lost, utilization of skills are not optimized, creativity missed and wasted time are results of under-utilizing human resources.

In principle, eliminating these eight types of waste results in the lean operation (Alukal, 2003). The types of waste to look for may be used to direct the focus of waste elimination. A Kaizen team is generally formed for a selected aspect to develop and implement solutions to eliminate the waste and to follow-up to ensure improvements are effective and sustained.

Some Kaizen projects, or events, are rapidly implemented to quickly show results which aides in acceptance and support of the strategy (McNichols & Hassinger, 1999). Each small incremental change is defined as a Kaizen event (Value, 2004). The Kaizen team works on a targeted Kaizen event that contributes to the Kaizen methodology. There are some Kaizen events that are implemented within 72 hours; however, generally 2 - 10 days, characterizing them as rapid improvement processes (Environmental Protection Agency, 2005). A Kaizen blitz is the intentional quick implementation of a successful solution that is dramatic and clear. The implementation is so rapid that there is no time for resistance to change, initiating the paradigm shift toward lean through Kaizen (Venables, 2005). There is a major difference between the philosophy of Kaizen and a specific Kaizen event or blitz. The continuous small incremental improvements made over time that results in significant improvements, as a way of conducting business, is the Kaizen philosophy; simply put Kaizen is continuous improvement.

The outcomes of Kaizen are the elimination of waste, standardization, increased efficiency, and an organized system (George, 2003). It is this last benefit, organization, which has evolved into a separate lean manufacturing strategy referred to as 5S.

Chapman (2005) defines the 5S strategy as a system composed of an orderly workplace that increases productivity through the reduction of waste from disorganization. Time is wasted when searching for materials, tools, documents, and the like. Disorganization is a direct cause of waste of motion. Disorganization causes increases in downtime, safety hazards, mistakes, late deliveries, longer lead times, low productivities, and does not optimize space (Chapman, 2005). There are five parts to this system, each starting with the letter S, developed in Japanese and translated to English. The acronym 5S consists of the five elements that achieve organization in the workplace:

1. Sort - (Seiri, in Japanese)
2. Set in Order - (Seiton)
3. Shine - (Seiso)
4. Standardize - (Seiketsu)
5. Sustain - (Shitsuke)

The first element of 5S is Sort. Clutter and extraneous items are removed from the workspace resulting in enhanced flow and an increase in available workspace. The next element, Set in order, consists of organizing the workspace with only needed materials and parts. Space is provided for items which are placed in their proper space. Items are easily located adding a clear visual of missing items. Shine is the element of 5S that addresses cleanliness. How, what, when to clean and by whom are addressed. This

element also involves assessment of conditions to trigger replacements before wear out occurs, stopping work. Proper supplies, amounts, and visual aids makeup the basis of the element of Standardization of the 5S system. Checklists are commonly used tools to standardize an activity. The last element, Sustain, is the establishment of the 5S strategy as a routine way of work. Involvement of all levels of employees is an essential aspect of sustaining change, especially when organizing the workplace (Chapman, 2005).

The 5S method consists of developing and ensuring a clean, organized workspace that reduces wasted time looking for items and unplanned downtime, providing smooth work flow with efficient use of in-process inventory. The benefit to the employee of the organization that 5S brings are jobs made easier and frustration removed that was caused by searching for items. The benefit to the employer of the organization that 5S brings is increased productivity and reduced cycle times which reduces the cost of manufacture.

Total Productive Maintenance (TPM) is a strategy aimed at optimizing equipment utilization by establishment of a process of maintenance that avert breakdowns, product loss, work stoppages or idle time, and reduce step-up time. Manos, Sattler, & Alukal (2006) define the process of TPM as simply maintaining equipment so that it is always available for use. TPM involves all levels of staff taking responsibility for maintenance. Workers are comprehensively trained to take care of equipment and tools and also to anticipate problems for preventative action. The process includes optimizing work layout designs, mistake-proofing equipment, use of redundant systems and equipment that need little or no maintenance. Equipment is then always ready and available when needed to better ensure a continuous production flow (Evans, 2005). The TPM system components are preventative maintenance, corrective maintenance, and break-down maintenance.

The entire production life-cycle, using TPM, is focused on prevention of accidents from equipment and reducing defects, downtime, and production losses (Environmental Protection Agency, 2005).

Cellular manufacturing or one-piece-flow is a strategy of manufacturing that arranges work in a composite sequence of units to benefit process flow by minimizing material transport, motion, and delays (Manos, Sattler, & Alukal, 2006). Visual controls may be used to identify a systems' status; floor layouts arrange machines and processes in the best operational sequence. Each production piece moves through the manufacturing process one at a time, as opposed to traditional manufacturing which produces numerous parts at one operation or batch that waits in cue for the next operation. This one-piece process flow of cellular manufacturing allows more flexibility in production changes with the rate of flow dependent on customer needs. These needs are initiated at customer demand for the product, pulling the production into action.

Changing manufacturing from traditional work flow design to cellular manufacturing work units require replacing large-high volume production equipment with smaller machines that are capable of signaling cycle completion and when problems occur. Work methods would also be standardized to reduce waste, to include wasted human motion (Evans, 2005; Manos, Sattler, & Alukal, 2006). The work units of cellular manufacturing allows workers to spend less time watching the equipment or waiting on the next batch and more time better spent on activities such as preventative maintenance or TPM.

The next strategy of lean manufacturing is point of use storage or Just-in-time (JIT). JIT is a process of staging materials at the space they will be used (Manos, Sattler,

& Alukal, 2006). It is a production control technique of producing the necessary products or services at the time and quantities needed - no excess products or supplies. The two primary direct costs in manufacturing are supplies and processes used to make products, referred to as unit order costs and caring costs, respectively. Most unit costs are due to setup costs. Setup costs are higher than production costs yet equalizes somewhat as the number of units produced increases. Carrying costs result from capital being tied up in inventory (Daley, 2003). Optimization of the production process requires stabilization of caring and unit order costs. Since the major portion of unit cost is setup time, reduction would decrease that cost. This may be accomplished by several techniques such as 5S and eliminating wasted time identified from the process of value stream mapping.

Carrying costs are proportional to inventory; reducing inventory reduces caring cost. JIT systems use physical inventory cues, referred to as kanbans that defines the need for more raw materials or components from a previous process. Re-useable containers used in kanban are limited by capacity to control manufacturer to only what is needed. Organizations with JIT systems may also require the same type of system from their suppliers. This network of JIT substantially reduces waste of excess inventory. The JIT strategy forms a smooth production system that evenly spreads manufacturing flow among processes (Strategos, 2005). Customers, manufacturers, and users all *pull* from the system. Womack & Jones (1996), in their book *Lean Thinking,* describes the JIT system as a process whereby the customer downstream initiates the production upstream by their demand for product. Production flows only when pulled, resulting in a system that optimizes cycle times.

Control of variation, the last lean strategy, can be accomplished in several ways. An optimum standard is Six Sigma, as noted by George (2003). Six Sigma is a statistical methodology to reduce variation with prediction of the rate of defects defined and controlled to a target or value. The term Six Sigma is defined as a process that results in a value stream flow of only 3.4 defects per million units produced. This is accomplished by establishing a stable system that minimizes variation, progressively promoting high quality lower cost products as a result of the low defective rate. Six Sigma, and the strategy of variation control, are process improvements aspect of lean manufacturing.

Establishment of the lean manufacturing strategies provides a production system that continuously improves, reduces errors; limits capital tied up in inventory, minimizes defects, and increases efficiencies. The lean environment is one that identifies potential problems and implements preventative measures for sustainable solutions (Womack, et al., 1990; George, 2003). Lean manufacturing is also a technology of effective problem solving with proven tools to affect change, establishing an organization that does not just react to problems but anticipates them by design. Each strategy of lean is focused on value adding activities, flowing production that is pulled by the customer. The result of the lean environment is a culture of flexibility that quickly responds to customers' changing needs and expectations, consistently eliminating waste, aiming at perfection.

Implementing Lean Manufacturing

There are numerous different ways of implementing or applying lean manufacturing. This literature review presents the basic elements of implementation. The method of implementation may depend on resulting expectations, e.g., the value desired. Value should be defined to direct the implementation process and to better ensure a

common understanding of what the primary goals are. Initiation activities of lean manufacturing start with a value stream analysis, which may include defining the value of implementing lean and specifically determining process value streams to identify waste (George, 2003). The full benefits of the lean manufacturing philosophy may be obtained when all of the principles are applied systemically. Full implementation of lean generally starts with the selection of an implementation consultant and/or team.

A team is formed and trained on the basic lean principles, strategies and techniques to establish and deploy the technology. The first activity in implementing lean is value stream mapping of processes to identify where value is added and where there is waste. A current state value stream map is generated. Future state value stream mapping is also conducted for definition and visualization of goals. A gap analysis is performed between the current state value stream map and the future map. Results of the analyses are used to develop and/or re-engineer processes and systems accordingly, using the lean strategies. Expansion of the scope of application of lean to external affiliates such as suppliers should be considered when a process change occurs. Change must also be managed that include education, illustration, and incentive programs; preparing the organization's culture to think lean. It is also important to quantify and develop metrics for each aspect of the transformation to lean to give stakeholders solid results.

Implementation of lean may be viewed as a series of improvement steps that are put into action, as illustrated in the graphic that follows at figure 5. The first step is development of human resources through training, team building, transfer of knowledge, facilitation through a change agent, and creation of the process value stream map. Staff development during this first step of lean implementation provides an understanding of

the concerns of the organization and how each member contributes to the company's success. Motivation and pride of workman are commons elements that evolve as lean manufacturing is implemented. Step 2 of the process consists of a focus on lean process methods such as JIT, TPM, and cellular manufacturing. Lean manufacturing requires change management for lean thinking. These elements are step 3 in the climb to lean manufacturing. Step 4 includes quantification, standardization, policy development, and rewards systems, evolving to in the final step 5 lean realization.

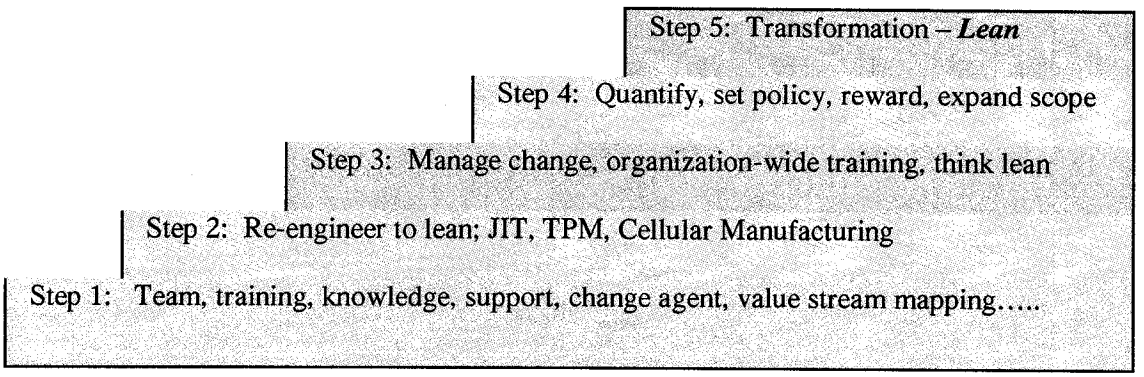


Figure 5. Steps to lean manufacturing

Of course, full implementation is not that simple and does require comprehensive project management including the cultural change to lean thinking (Womack & Jones, 1996).

As with major business endeavor, support is required from senior management in order to succeed and sustain improvements (George, 2003). Needs and values must be determined from their perspective of the customer, whether the customer is internal or external. An effective strategy for obtaining senior management's support of lean manufacturing associates what their organizational needs and values are. A common

approach is association of the organizational strategic plan, such as product development or enhancements, with proposed improvement efforts that specify strategic goals with defined lean manufacturing initiatives (George, 2003). Some strategists start with an aspect of the strategic plan and consider application of a Kaizen blitz to gain senior management's support. This strategy obtains positive results quickly proving leans' effectiveness at the onset of implementation.

A Kaizen blitz may or may not be used. However, in order to better ensure success for quality improvement efforts, they must be aligned with the values of senior management. Management is then provided the technological business strategy of lean manufacturing that achieves strategic goals, directly contributing to the success of the organization and gaining senior management's support. This strategy, as with others of lean manufacturing, is generic to product type, being applicable, for example, to household goods as well as life saving pharmaceuticals production such as biological stem cells.

Stem Cells

The term *stem* cells derived from the fact that all other cells of the body evolve or *stem* from these types of cells. Kadereit & Hines (2005) describes stem cells as unspecialized cells that self replicate and differentiates into defined specialized cell types such as nerve cells and muscle cells. Cell division of stem cells is different from normal cell division which results in two identical cells that are progressively differ from the original cell. The process of cell division in stem cells results in two non-identical cells. One of the cells continues to remain a stem cell and the other is the more progressive or specialized cell.

Stem cells are defined by the number of different cell types they can differentiate into (National Institute of Health, 2007). Totipotent stem cells can produce every type of cell in the body, giving rise to the entire organism or human being. Development of the entire organism requires the capacity of the cells to produce all cell types of the body and cells outside of the body that supports development such as the placenta, umbilical cord, and other extra-embryonic tissues (Kadereit & Hines, 2005). Pluripotent stem cells can also produce every type of cell in the body but cannot give rise to the entire organism because these cells cannot produce the life supporting tissues such as the placenta. These cells are the embryonic stem cells that form from the fertilized egg at the union of sperm and egg. Borror, O'Rourke, & Skirboll (2000) explain that the pluripotent stem cell evolves from the totipotent stem cell with the multipotent cell from the pluripotent. Multipotent stem cells can produce several different types of cells to include mature or adult stem cells found in different tissues of the completed organism. Cells that can produce only one type are referred to as unipotent (Borror, O'Rourke, & Skirboll, 2000; Kadereit & Hines, 2005)

Categories of Stem Cells

Stem cells are categorized into two types: Embryonic stem cells and adult stem cells. The origin of the cells and the level of maturity define the two types. Embryonic stem cells are derived from the embryo and are immature cells; whereas adult stem cells are the most mature, given the name adult. Adult refers to the developed cell found at completion of human development at childbirth (National Institute of Health, 2007).

Embryonic stem cells are those formed in an early stage embryo that is about four days old, consisting of 50 – 100 cells, forming in the inner cell mass of the blastocyst.

The cells are pluripotent giving rise to all cells of the human body from the formation of the three primary germ layers consisting of the ectoderm, endoderm, and mesoderm. These germ layers form all the other tissues, organs, and biological systems that culminates into the whole organism or human being (Borror, O'Rourke, & Skirboll, 2000; National Institute of Health, 2007).

Adult stem cells are more tissue-based specialized stem cells found in limited areas of the body to include the bone or bone marrow, brain, and some muscles. These cells are also called somatic stem cells, a Greek term for "of the body." Adult stem cells renew cells of the body that are routinely deleted or damaged such as blood cells, bone marrow, and cells of the muscles and eyes (National Institute of Health, 2007).

Adult stems cells have been used in medical treatments for some years. Leukemia and other blood or bone formed cancers have been treated by using transplanted stem cells from bone marrow. Stem cells from umbilical cord blood are also being used in similar treatments. The adult stem cells that give rise to the cells in blood are referred to as hematopoietic. Hematopoietic stem cells develop into all of the cells of blood such as red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, macrophages, and platelets (National Institute of Health, 2007).

Production Process of Non-controversial Stem Cells

Embryonic stem cells are at the core of ethical and political controversy as a result of their origination from fertilized eggs that starts the development of the human being. Non-controversial stem cells are defined as those obtained from sources other than the embryo. These types of stem cells include those that are obtained from waste by-products

of the birth process that are discarded such as the placenta, umbilical cord and blood (Cord Blood Transplant Study, 2005).

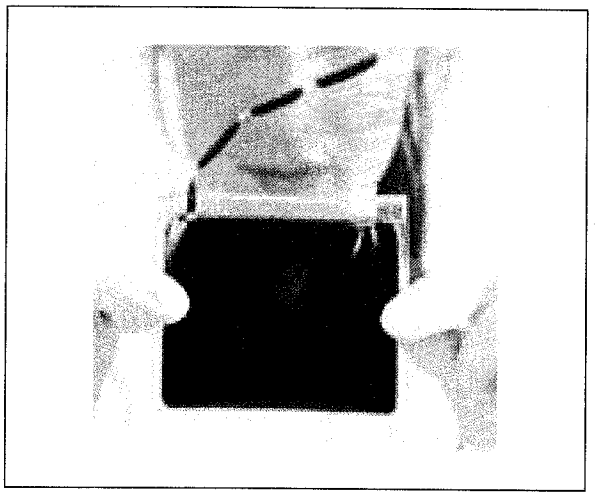
Cord blood is a rich source of hematopoietic stem cells. CryoCell International, Inc., a leader in the harvesting of stem cells from cord blood, describes the overall manufacturing process as starting with the source of collection. Whole cord blood is obtained from the umbilical cord following child birth after the cord has been clamped. The cord is first cleansed with alcohol and iodine. A blood bag system consisting of integrally connected bags with an attached needle is used to collect the cord blood. The needle of the bag system is inserted into the cleansed area of the cord. The blood in the umbilical cord is collected through the needle, filling at least 1/3 of the bag. The collection process takes about 3 to 5 minutes to complete.

The cord blood is processed generally by addition of hydroxyl ethyl starch known as hespan (HES) to enrich for the total nucleated cell population that includes the hematopoietic stem cells identified as $CD34^{+}$. These cells are subsequently cryopreserved frozen in 10% dimethyl sulfoxide (DMSO) and dextran as the cryoprotectant. The cells are stored safely in liquid nitrogen vapor phase at temperatures under $-135^{0}C$ to preserve viability. The products are usually stored in a 25 ml bag with two (2) compartments; one part holding 20 milliliters (mL) and other 5-mL. An attached tubing segment allows for three separately labeled quality control samples that are integrally connected to the stem cell unit (CryoCell, 2006).

The specifics of processing umbilical cord blood into stem cells occur by a separation of the stem cells from the other components in the blood raw material (Cord Blood Transplant Study, 2005). The volume of the raw material is reduced by removing

most of the plasma, red blood cells and other components, then storing the remaining stem cells.

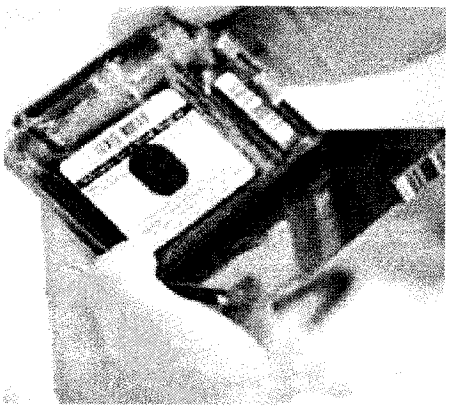
The production process starts by determining the volume of the incoming bagged cord blood. The resulting weight, converted to volume, is used to determine the amount of the hespan reagent to inject into the bag at 20% of the volume, providing a 1:5 ratio of reagent to cord blood. Hespan, the expander reagent, is used to facilitate the agglutination of the red cells to aid in their separation from the stem cells (Cord Blood Transplant Study, 2005). Centrifugal force is used to further separate the blood components by placing the hespan containing blood bag in a balanced centrifuge, processing approximately six minutes. The result is a density gradient of the blood product with heavier components at the bottom and lighter progressing to the top. The lighter portion is expressed off into an attached separate bag and again centrifuged. This second centrifugation is at a longer processing time and harder gravitational pull to better separate the lighter remaining components. Again, a density gradient result with the heavier components settled to the bottom and lighter on top. In the middle rests the layer of stem cells, that are transferred to another attached storage bag, for a final product volume of 25-mL of stem cells. The final package is illustrated in figure 6 that directly follows.



(Source: CryoCell, 2006)

Figure 6. Stem cells in final package with attached segments.

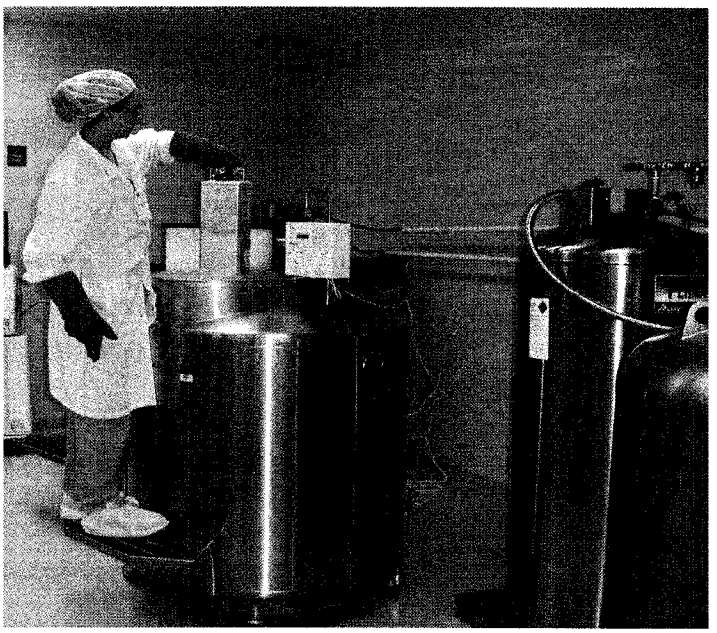
The last step of the production process is the cryopreservation of the stem cells for storage. Cryopreservation is the process of storage at very low temperatures, less than -135^{0}C or -211^{0}F, to preserves the stem cells for future use. The standard sustained average temperature of cryopreservation storage is -190^{0}C or -310^{0}F. The cells are first protected by addition of a mixture of DMSO and dextran. Initial freezing occurs by gradually lowering the temperature of the bagged stem cells using a controlled step-wise method to a temperature of -90^{0}C or -130^{0}F by liquid nitrogen. The frozen bag of stem cells is placed into a metal cassette holder for further protection and transferred to the final storage tank. Internal tank temperature averages -190^{0}C or -310^{0}F (CryoCell, 2006; Cord Blood Transplant Study, 2005); see figure 7 that follows.

Stem cells into metal cassette holder	Final freezing storage
	

(Source: CryoCell, 2006)

Figure 7. Final stem cell product and storage.

The cells are engulfed in the gaseous vapor of the liquid nitrogen that is at the bottom of the storage tank. Viable stem cells can remain at this frozen cryopreserved state for at least 15 years or more with some researchers hypothesizing that the cryopreserved cells can remain viable indefinitely in this cryogenic frozen state. The permanent storage tanks, shown in figure 8 that follows, are automatically filled with liquid nitrogen as needed to ensure an average constant temperature of about -190^{0}C or -310^{0}F. The tanks remain unopened until a medical need arise for use of the stem cells. Stored in metal racks, the stem cells are removed and prepared for transport to the transfusing facility.



(Source: LifeBank, 2007)

Figure 8. Cryopreservation at -190^{0}C of non-controversial stem cells.

The Dilemma of Rising Healthcare Costs

The applicability of using lean manufacturing to identify, eliminate and/or reduce wastes in healthcare, to include the high cost of pharmaceuticals such as stem cells, requires an understanding of the contributing factors. The following describes the history of rising healthcare costs, consequences, and opportunities for lean waste elimination.

Healthcare spending in the U.S. has consistently increased each year since the turn of the century (HHS, 2005; Cooper & Davis, 2003; Cowman & Hartman, 2005). Economists for the Centers for Medicare and Medicaid Services (CMS), one of the largest healthcare payers in the U.S., states that in 2007 costs increased for the eleventh straight year in a row to $2.3 trillion. At the turn of the century in 2000, costs were $1.3 trillion; in 2001 costs exceeded $1.4 trillion; and in 2002 costs increased 9.3% over 2001

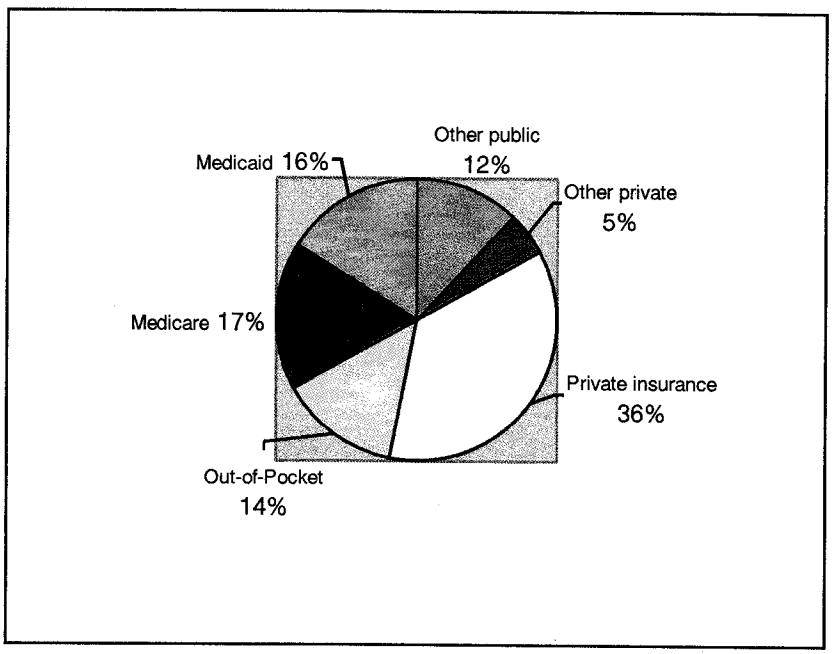
figures to $1.67 trillion. Healthcare spending in 2004 reached over $1.9 trillion. This trend continued with healthcare cost in 2007 at $2.3 trillion (Health Insurance Cost, 2008). It is estimated that within the next ten years costs are expected to almost double if there are no significant interventions. These consistently increasing healthcare costs have negatively affected the economy, businesses, households, and each and every one of us (Borger et al.., 2006).

The U. S. Department of Health and Human Services (HHS), in its document *Effects of Healthcare Spending on the U.S. Economy* (2005), reports that there is a 9.3% growth in healthcare spending compared to only a 3.6% economic growth. The 5.7% difference represents an increase in resources going to healthcare with an offsetting decrease in the purchase of other goods and services, negatively impacting the economy. Internationally, U.S. exports are less competitive because of their increased costs from balancing healthcare spending. In addition, the federal budget has been adversely impacted by healthcare costs, resulting in discontinuance of sponsored projects, reduced funding of others and non-funding of new proposed programs. As one of the largest employers, the federal government has cut jobs accordingly, as have private employers, lowering overall employment while raising inflation, due to funding of healthcare.

In order for government to pay for its portion of healthcare spending from health programs such as Medicaid and Medicare, its source of funding, through taxation, must be increased causing increases in the individual tax burden. The individual portion of the $2.3 trillion healthcare cost amounts to about $7,600 per person. Another alternative that the federal government may use to pay for health programs is through increasing long-term debt. This results in increased interest rates limiting funding for activities and

potential expenditures for companies and households. Companies that would have expanded because of federal funding, for example, increasing staffing from new jobs, could no longer do so due to increased interest rates from higher federal debt. Families that would have purchased homes, resulting in construction increases, moving the economy, would have to potentially reconsider due to increased interest rates by the federal government. Of note, the major source of healthcare funding is not the federal government. It is the private sector that pays for the largest portion of healthcare costs.

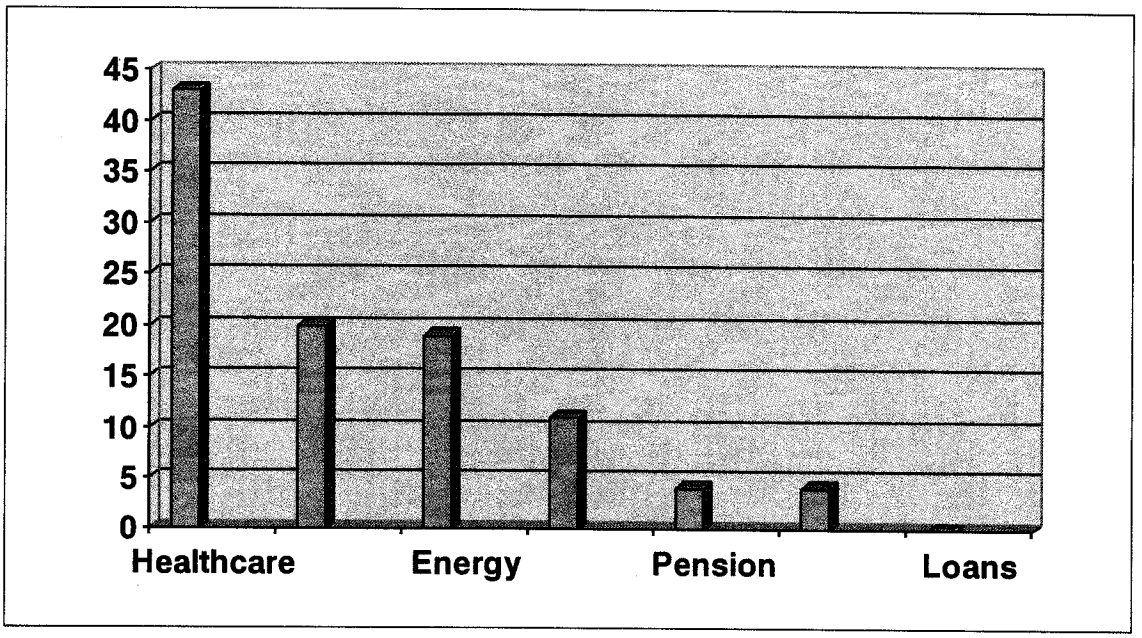
Thirty-six percent (36%) of the total cost of healthcare is paid by private insurance; the largest portion of funding (HHS, 2005). Medicaid, healthcare funded by states, pays 17% of total costs; Medicare, from federal funding, pays 16%; individual out-of-pocket accounts for 14% of the funding; 12% comes from other public funding programs such as workers' compensation, the Department of Defense, or Veterans Affairs. The remaining 5% of healthcare funding comes from other private sources such as philanthropy; see figure 9 that follows. These percentages show that the private sector pays over half of the entire cost of national healthcare, with $828 billion, that 36%, coming from private insurance (HHS, 2005; Cowman & Hartman, 2005). Figure 9 that follows depicts the percentages of total healthcare cost paid by different payers.



(Source: HHS, 2005)

Figure 9. Payers of healthcare costs by percent of share of total.

Private health insurance is usually obtained by employees through their employers. The HHS (2005) determined that 60.4% of Americans have employment-based health insurance with cost to employers well over $330.9 billion or about $3.80 per hour for each employee with the health benefit. As health spending continues to climb, employers have been faced with finding ways to finance health care benefits for their employees. A survey of Chief Operating Officers (CEOs) conducted by the Business Roundtable organization (2004) identified that the number one cost pressure U.S. businesses faced is funding healthcare benefits for their employees. Figure 10 that follows is a graph showing that the cost of healthcare is the highest concern of the CEOs.



(Source: PricewaterhourCoopers Health Research Institute, 2005)

Figure 10. Business cost pressures communicated by CEOs.

Employers pay $4,400 each year for single health coverage for an employee, whereas family coverage averages $10,712. The National Coalition on Health Care (2008) states that for a family of four, insurers charge employers $12,100. Retirees', inactive employees, coverage is also funded by employer healthcare plans which have seen 12.7% annual increases due to increasing healthcare costs.

A survey of large U. S. companies, published in Biotech Law Weekly (2005), reported that half of the companies stated increased healthcare costs have resulted in lower profits. General Motors, one of the Big-3 automobile manufacturers in the U.S., estimates that $1,400 of the cost of each car it produces is a result of providing employee and retiree healthcare coverage, illustrative of the direct negative effect of rising healthcare spending has on the cost of goods. Companies have also attempted to

mitigate healthcare costs by increasing the amount employees contribute to health insurance; reduced the amount of wage increases to employees; not replaced employees who quit; put off hiring of new permanent employees; and increased the use of part-time or temporary personnel. The benefit of using part-time and temporary personnel is due to these groups having limited or no health insurance benefits/expenses from the company that uses this type of personnel (HHS, 2005). Some employers have also reduced the amount of healthcare coverage to employees and some no longer offering the benefit.

The most common strategy used by employers to reduce the cost of paying for employee-based healthcare is through cost-sharing (Coates, 2004; Davis & Cooper, 2003; Cowman & Hartman, 2005). The cost is passed on to the employee by consistently increasing the amount that the employee contributes to the insurance plan (Davis & Cooper, 2003; Cowman & Hartman, 2005). In addition to paying for the plan, employees contribute increasing amounts for co-pays and deductibles; are allowed shorter hospital stays; and have varying increased costs based on the type of prescription or drug; for example, generic versus brand (Health Insurance Cost, 2008). The average household in 2002 spent $2,350 or 4.8% of its income on healthcare. The average employee contribution to their health insurance plan has increased more than 143% since 2000. The average out-of-pocket expenses paid for healthcare has increased 115% since 2000 (Hewitt, 2004), affecting household financial stability. However, these cost-sharing strategies by employers do little to contain the rate of healthcare cost (Davis & Cooper, 2003; Marshall, 2006). These methods only shift the costs of healthcare from the employer to the employee (Simmons, 2002). In 2003, 20 million families reported financial problems due to paying for healthcare (HHS, 2005; National Institutes of

Health, 2004). Monies targeted for savings for education or retirement must now be used for healthcare. In addition, money that would have been used on consumer products is being used to pay for healthcare, negatively affecting the national economy.

The increasing cost of health insurance has caused numerous employees to forego carrying health insurance because of the expense (National Institutes of Health, 2004). In August of 2006, the U.S. Census Bureau reported that 46.6 million people do not have health insurance. Without health insurance, people do not routinely use preventative healthcare but utilize healthcare only during crisis. Crisis treatment or critical care is the most expensive and increased utilization is a major contributor to rising healthcare costs. As more people become uninsured, healthcare spending increases because of the need for more critical care. In a report by the National Academy of Sciences' Institute of Medicine (IOM), the cost to the country from poorer-health, uninsured people averages $97.5 billion per year, to include about 18,000 associated, preventable, deaths (Coates, 2004). These costs are paid through taxation. Regardless of the direct source of funding, whether through state Medicaid, federal Medicare, or especially from private insurance and philanthropy, the burden of rising healthcare costs is on each tax paying or contributing citizen (Pauly, 1995). As noted by Cowan and Hartman (2005), each individual pays for increasing healthcare through higher taxes and reduced wages from paying increased insurance premiums, deductibles, and co-pays. Each person also pays for healthcare costs as a result of paying more for goods and services which cost more to offset healthcare costs to employees provided by employers.

The backlash of the rising number of uninsured is increased healthcare costs. Other reasons for increased costs as previously noted are increased use of prescription

drugs, hospital expenditures, newer expensive technologies, increased utilization of healthcare due to the larger number of aging population, and administrative costs (Davis & Cooper, 2003). The largest contributing factors to healthcare cost are from prescription drugs and hospital expenditures, with hospital expenditures the most costly (Appleby, 2001). Hospital costs also include prescription drugs dispensed in the hospital, making prescription drugs or pharmaceuticals the largest contributing factor.

The foundation of medical treatment in the U.S. is based on pharmaceutical or drug-chemical based therapies. These include the use of drugs or pharmaceuticals for stabilizing patients as intermittent treatments, and for improving and sustaining overall health (Holstein, 2006; Institute, 2006). To critically evaluate approaches to healthcare cost reductions, drug utilization should be an essential part of the assessment.

Davis & Cook (2003) testified, during Congressional hearings on the subject of increasing healthcare costs, that the key to containing costs is to make fundamental changes in the supply side of the market. They pointed out that there needs to be a shift of attention to reducing errors, eliminating waste and duplication, increasing efficiencies, modernizing administrative functions and streamlining costs. This statement clearly identifies waste elimination and reduction as essential elements for reducing healthcare costs. The focus should be directed on the suppliers of healthcare. Since pharmaceuticals are a leading cause of healthcare expenditures, suppliers of drugs used in medical treatments such as stem cell therapies, should be a key focus in reducing costs.

Identifying and eliminating waste is the core of the lean manufacturing concept. Applied to the production of pharmaceuticals, the primary driver of increasing costs, lean manufacturing should prove to be a significant contributor to reducing healthcare costs.

The aim of this study was to apply lean manufacturing strategies to the production of pharmaceuticals. The specific focus was on critical, short supply pharmaceuticals which fundamentally are higher in cost. Non-controversial stem cells are being used more frequently, are the direction of future medical treatments, and are in short supply. Lean manufacturing principles and strategies of waste elimination was applied to evaluate its influence on these types of healthcare suppliers.

Review of Healthcare Costs and Lean

Literature on the application of lean manufacturing in healthcare is primarily limited to enhancing care in the hospital setting. Reducing medical errors, limiting patient wait times, evaluating length of stay, obtaining medical records, reducing in-hospital infections, improving release techniques, and reducing patient transport times are some of the standard metrics in hospital care identified from employing lean manufacturing principles (Leslie, Hagood, Royer, Reece, & Maloney, 2006; Nolan & Bisognano, 2006). These same efforts have been applied in private medical practices with significant improvement results (Weber, 2006). Conversely, the applications of lean efforts by healthcare suppliers have been limited to a few large pharmaceutical manufacturers based on reactionary measures.

Merck, a large U.S. pharmaceutical manufacturer and a major player of big pharma, initiated its path to lean manufacturing upon the heels of near company disaster. As described by Stanley (2004), in the article *Merck's Lean Mission,* the company recalled their popular drug Vioxx from the market as a result of a study of 2,600 users identified increased risk of heart attack and stroke. Merck's response was the development and implementation of a quality management system that encompassed

quality system elements of lean manufacturing, Six Sigma, and Overall Equipment Effectiveness (OEE). Termed the Merck Production System (MPS), the foundation was based on core lean manufacturing principles of waste elimination, continuous flow, demand based on a pull system, and value manufacturing. Because of the recall, customers were faced with no supply of the product and resultantly lost faith in the pharmaceutical supplier's ability to provide the drug treatments needed. As previously noted, this same consumer concern from lack of needed pharmaceuticals was a result of the flu vaccine shortage (Elliot, 2006). Alternative medications were identified to replace Vioxx causing the cost of those healthcare alternative pharmaceuticals to rise substantially. One such alternative, Celebrex, a product of Pfizer, which is the largest drug manufacturer in the world, significantly increased in demand. Of note, Celebrex was also later pulled from the market because of the same risk of heart attack and stroke (Stanley, 2004; Elliot, 2006), resulting again in product shortages.

The flu vaccine shortage previously referred to has occurred more than once. Ashley (2005) points out that the flu vaccine shortage has occurred for several straight years in a row. The major cause of the shortages was due to lack of the raw material to produce the vaccine. The availability of antibiotics and antimicrobial pharmaceuticals has also resulted in numerous drug shortages. Thirty-eight percent (38%) of the drugs listed on the FDA web site of drug shortages are anti-infective agents; see the Appendix A. Other causes of drug shortages were due to recalls caused by manufacturing deficiencies, unexpected increase in demand, and damage to a drug, directly linking waste as a significant factor.

Jensen, Kimzey, & Goldberg (2002) also attribute drug shortages, per their discussions with FDA, to manufacturing problems, limited production capability, and lack of availability of drug substance, which is the raw material from which the finished product is made. When drug shortages occur due to a lack of raw materials, interruption of production of the drug from all suppliers may be affected. Of note, a drug under patent protection is usually supplied from one company. If manufacturing problems occur, to include a lack of drug substance or raw materials, the supply of that drug may be entirely stopped. As described by the FDA, even if there are multiple pharmaceutical manufacturers of a particular drug, usually one manufacturer has the more dominant market share. If that dominant manufacture has production problems, supply problems result which cannot be balanced by other manufacturers of the drug due to their lack of capability. Their capability is based on their direct market share and cannot readily gear up to fill the gap from the larger market share. This situation was the case, as described by Jensen, Kimzey, & Goldberg (2002), for shortages of the drugs naloxone hydrochloride, used to treat addiction, and diazepam, better known as valium. On the other hand, if there are alternative drugs that can be substituted for the shortage or manufactured in enough quantity to meet the needs, the cost of the drug is significantly increased. Potential solutions to manufacturing problems and resource limitations that cause drug shortages and increased costs may very well lie with the technology of lean manufacturing.

The literature on applying lean manufacturing principles and strategies to specialty healthcare and raw material suppliers to pharmaceutical companies are also

limited. This is especially true for suppliers of biological pharmaceuticals and materials, to include stem cells, which are routinely in critically short supply.

Biological pharmaceuticals are composed of materials supplied from mainly human donors. These pharmaceuticals include blood needed for direct transfusions, but also include a host of innovative new biopharmaceuticals, to include stem cells. As previously noted, the non-controversial type of stem cells have proven to be much more beneficial in treating illnesses compared to harsher standard chemical-based drug therapies (American Red Cross, 2005a). Non-controversial stem cells are those not associated with embryos. These non-controversial stem cells are found throughout the body for regeneration, although the amounts are very small. Umbilical cord blood, a biological material which is discarded after child birth, contains a wealth of stem cells, and is now being collected and used for medical treatments but also in limited supply (Kadereit & Hines 2005).

Biological materials used for the manufacture of pharmaceuticals are rare, short supply commodities, adding to the pharmaceuticals' cost. This aspect is especially true for stem cells (CryoCell, 2006). Over 30% of all treatments in hospitals include some type of biological pharmaceutical, primarily some type of blood transfusion (America's Blood Centers, 2005). With the success of treatments using stem cells, a pluripotent biologic, these biopharmaceuticals are in more demand with the future direction of medical treatment the driver (CryoCell, 2006; Kochart, 2005). As identified by Norvis, Renner, Friedberg, Walsh, & Saladino (2002), much of the raw materials used for the manufacture of these essential pharmaceuticals are wasted, in addition to consistently being in short supply.

Raw materials for biological pharmaceuticals, to include blood and stem cells needed for life-saving transfusions, are obtained from human donors. The American Red Cross (ARC) in conjunction with the American Association of Blood Banks (AABB) estimates that eight million volunteers donate blood each year. According to the National Blood Data Resource Center about 15 million units of whole blood and red blood cells were donated in the United States in 2001 (American Red Cross, 2005a). In times of disasters, such as the Katrina and Wilma hurricanes, and the war, the need for blood has dramatically increased. Each day, averages of 38,000 units of red blood cells are needed (American Association of Blood Banks, 2005a). Blood transfusions often are needed for trauma victims, to treat accidents and burns, heart surgery, organ transplants, and patients receiving treatment for leukemia, cancer or other diseases such as sickle cell disease and thalassemia. In 2001, nearly 29 million units of blood components were transfused. The aging population, advances in medical treatments and procedures requiring blood transfusions, demands for blood continues to increase (Association of Blood Banks, 2005a). It is estimated that 1 in every 3 persons will contract cancer. The most promising treatments and prevention measures for cancer are biological cellular therapies such as stem cells and the development of a cancer vaccine derived from stem cells; both treatments use biological raw materials.

The availability of non-controversial stem cells is in more of a critical short supply than other biologics. The vast potential of stem cells in treating a multitude of medical conditions and other applications can no longer be denied. Cell International, Inc. (2007), a major processor of stem cells, states that stem cells are now used to treat over 70 diseases and have been used in over 6,000 transplants. In addition to the value of

stem cells today, research is ongoing for a multitude of potential medical treatments in the future. Current research has established the capability of stem cells in successfully treating heart attacks, the one number killer of adults in the U.S., and in the treatment of neurological diseases (National Institute of Health, 2007; CryoCell, 2006; Kochart, 2005). The potential of stem cells to treat a multitude of diseases and usage of the cells in a host of applications seems limitless. Of note, the flu vaccine storage previously discussed is being addressed by development of new manufacturing methods utilizing stem cells that prove to dramatically increase production speed, to alleviate vaccine shortages (Elliot, 2006).

The shortage of available stem cells continues to be a major problem for healthcare providers and contributes to increased healthcare costs. Measures that may have the potential of optimizing resources and eliminating waste, such as lean manufacturing, would be of great benefit in optimizing the stem cells that are available.

Numerous other biological pharmaceuticals are made from blood or blood components and stem cells. These medicines are used to treat numerous conditions such as burns, shock, emphysema, hemophilia, immune deficiency, multiple sclerosis, and hepatitis, to name a few (PlasmaCare, 2007). The use of specialized blood-based pharmaceuticals, such as oral anti-platelets used as blood thinners, has increased over 75% in less than six years. The production of immune globulin products which are made from blood plasma and used in vaccinations to treat viruses and infections has increased annually by 15% (Siegel, 2006). Due to the harsh, negative side affects and limitations of chemical or traditional drug treatments, the direction of medical treatment is with biological therapies such as blood-based and stem cell pharmaceuticals (Monroe, Potter,

Millares, Barrueta, &Wagner, 2006). Blood is also used in diagnostic applications, test kits, and are used in a host of other healthcare applications as well. Shortages in the blood supply adversely impacts production of blood-based pharmaceuticals. As described previously, human blood shortages occur routinely due to periodic shifting supply, weather conditions, and regulations that result in an increase in blood donor deferrals (American Association of Blood Banks, 2005b; American Red Cross, 2005a). Measures to reduce or eliminate waste of the blood supply and other biological materials especially stem cells are essential.

An outcome of the lean manufacturing process of eliminating and reducing waste is improved processes and procedures in production affecting both product costs and raw materials (Womack, et al., 1990; Lewis, 2006); issues which are major concerns in pharmaceutical manufacturing. As described by Thomas (2005), pharmaceutical industry leaders recognize that the industry has made very little improvement in process enhancements in the last ten years. The cause was attributed to inadequate data management, inefficient business processes, and conservative approaches. Gottlieb, Deputy Commissioner for Medical and Scientific Affairs at the FDA, pointed out that the pharmaceutical manufacturing industry has developed numerous innovative drugs; however, using dated manufacturing techniques (Chiarello-Ebner, 2006). Modernization of processes in drug development and production is necessary. Improvements would result in elimination of drug impurities and reduced research and development time resulting in faster times to market and lower drug costs. The relationship between quality, safety, and efficiencies require the necessary balancing for process and resource optimization. Gifford (2007) suggests that balancing resource availability, profit margins,

quality requirements and operating costs, which reduces product costs, can be achieved through the application of lean manufacturing. Commissioner Gottlieb also noted that the pharmaceutical industry must get past the perceived concept of regulatory constraints and uncertainty in order to move forward with essential process improvements (Chiarello-Ebner, 2006). A new way of thinking is necessary, which is also a prerequisite for lean manufacturing, as noted by Womack and Jones (1996) in their book on the subject entitled *Lean Thinking.*

In addition to the need for improved processes on the production side of pharmaceutical manufacturing to reduce drug costs with increased availability of raw materials, the distribution of the manufactured pharmaceutical at the end of production needs efficiency improvement. Harrington (1999) determined several deficiencies in product transportation that causes distribution processes to contribute to increased product costs. Increased competition, limited resources, delivering to multiple areas within a facility, shipping products directly to customers instead of intermediaries such as wholesalers, and working with limited or exact inventories has decreased efficiency of the traditional product transport methods. Gifford's (2007) evaluation of process issues in supplying drug products determined that the most cost-effective method would consist of implementing lean manufacturing strategies. Specifically, processes would be enhanced by reducing large inventories currently activated or transported by pushing the product on the customer and changing to smaller, more distributed inventories with product pulled by the customer on-demand.

The research and literature on applying lean manufacturing principles and techniques of waste elimination to the manufacturing processes of critical biological

medical suppliers, of which the vast majority are blood banks, to include blood banks for transfusion and umbilical cord blood banks for production of non-controversial stem cells, is limited. Stanley (2004) in the article *Applying Lean manufacturing in the Blood Center* briefly described implementation of lean at Stanford Medical School Blood Center in this two page article. Five principles of what was denoted as a leaner operation were defined: utilization of one-piece flow, establishment of prescribed work performance, associated measures, distribution and balancing of work, and use of visual controls. The article stated that implementation of lean manufacturing resulted in a 60% reduction in equipment needs; a 40% reduction in production staff; and a 50% decrease in facility needs. No details were provided on how these improvements were achieved.

Davey (2006), in the article *Applying Lean manufacturing in the Component Lab*, provided more detail on utilizing lean manufacturing in product production at a blood center. One-piece-flow was the technique employed, with a well described overview of push versus pull systems of manufacturing. The report did not include metrics or specific results but only summarized steps to assure in implementing one-piece-flow. Myers (2006) describes implementation of lean at the South Texas Blood & Tissue Center that focused also on the component processing laboratory and included the blood collection process. With a project focus, a core team was developed and trained. The group identified value by a gap analysis between current and future desired states. Employing lean strategies of reducing batch sizes, standardization, 5S, work modules, and use of visual aides, improvement results of increases in available raw materials, reduction in motion waste and operating costs, with a decrease in expired materials and enhanced production flexibility were obtained. Production cost per unit was reduced significantly

by 21%. Mand (2006) of the Blood Center of Wisconsin, reported gains through the application of lean manufacturing from reduced cycle times, elimination of waste, work balancing, establishing a pull production system, and 5S organization. The results were cycle time reductions of 33%, a supply inventory reduction of up to 32%, transportation reduced by 47% and defects by 12%. The latter reduction alone created a direct increase in production proportionately. Driving the lean concepts and strategies of flow, pull, waste elimination, and 5S, Memorial Blood Center realized organizational benefits of increased efficiency, reduced operational expenses, increased employee morale and a cultural shift to lean thinking for sustained improvements (Klawitter, 2006) With few publications on the application of lean manufacturing by raw material suppliers of blood used in pharmaceutical production and no publications by suppliers of stem cells, there is a significant need for further study, which was the aim of this work.

Chapter Summary

Lean manufacturing is a technology based on the systemic elimination of waste through the application of established principles and strategies. The five principles are value, value stream, flow, pull and perfection. The primary strategies of lean manufacturing are Kaizen, 5S, total productive maintenance, one-piece flow, point-of-use storage, and control of variation. From product concept to the acquisition of raw materials, development of production processes, through to manufacturing, finished product, transport and distribution, lean manufacturing is applied, with the initiation of production at consumer demand. The result is an efficient system of production that reduces time, waste, and inventory, for the optimization of resources, producing high quality products at their lowest costs. These concepts should prove beneficial to reduce

the high cost of healthcare to include from stem cell pharmaceuticals.

Stem cells are being used to treat many different medical diseases and conditions and are the direction of future advances in healthcare. The cells are produced from biological raw materials and stored in a frozen cryopreserved state. The raw materials used to produce stem cells are in critical short supply, contributing to the high cost. Measures to optimize raw materials and reduce the cost of the product are warranted.

The cost of healthcare in the U.S. is the highest among all industrialized nations, without associated health benefits. Costs have continued to increase at astronomical rates for over eight years in a row, now at $1.9 trillion, negatively affecting the economy, businesses, households, and each of us. Measures to reduce healthcare costs have focused on shifting funding sources without cost reductions.

Pharmaceuticals make up primarily one of the largest portions of healthcare costs. The pharmaceutical industry is marked with inefficient processes, raw material shortages, and waste throughout the system, producing higher costing products. Drug shortages have occurred causing consumers to loose faith in U.S. pharmaceutical companies to supply their life-saving drugs, especially at a reasonable cost. The industry has been reluctant in apply lean manufacturing. Manufacturing changes are necessary in order for the pharmaceutical industry to remain competitive and to win back customer loyalty.

The evolution of pharmaceuticals is consistently and continuously moving to biologically based drugs such as stem cells as opposed to traditional chemical based drugs due to their ease of acceptance by the human body. Biological raw materials to include stem cells are the sources of these drugs, which are in short supply. Optimization

of these materials is critical to ensure availability for pharmaceutical production, aimed at reducing associated healthcare costs.

A leading cause of increased healthcare costs is pharmaceuticals which are not generally produced optimally. The emerging use and effectiveness of stem cells in medical treatment and, their scarcity, demands production processes that are resourceful. Lean manufacturing is a production technology that is proven to eliminate waste, reduce cycle times, inventory, and optimize resources for cost efficient production with a focus on continuous improvement. The application of lean manufacturing in the production of non-controversial stem cell pharmaceuticals is a potential approach to healthcare cost reduction that may realize significant results with continual systemic use.

Chapter 3

METHODOLOGY

The purpose of this study was to determine the affects of applying lean manufacturing principles and strategies of waste elimination to the manufacturing processes used in the production of non-controversial stem cell pharmaceuticals. The aim of the study was the discovery of new methods to enhance the amount and availability of the short supply of stem cell raw materials and potentially reduce the associated product cost of the pharmaceutical. The cost of pharmaceuticals is a primary factor in increasingly high healthcare costs. Reductions in pharmaceutical product costs should correlate with a potential reduction in overall healthcare costs.

The activities of this research examined the influence of lean manufacturing on a single type of stem cell pharmaceutical supplier. The most conducive type of research strategy for this type of examination is the case study design. Yin (2003) defines a case study as an empirical inquiry that investigates a phenomenon within its real-life context. It is a comprehensive investigation of a single event or influence. The case study design was selected as the research strategy since the cumulative influence of eliminating waste by application of lean manufacturing on a single pharmaceutical supplier of non-controversial stem cells was examined in-depth.

Yin (1994) identifies five elements of a case study as the study questions, propositions, unit of analysis, linking of data to propositions, and criteria for interpreting the findings. The five elements defined relative to this research follows.

Study Questions

Research Question 1. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Research Question 2. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Lean manufacturing principles of waste elimination were applied to the manufacturing processes and evaluated, with measurements collected and recorded, proceeding and after application to answer these questions. The research was guided by the following specific test and measurement criteria. Data assessment included statistical analyses with the specific type of analysis based on the collected data. Statistical analyses were performed consisting of a paired t-test and analysis of variance (ANOVA).

Propositions

Management support of initiatives plays a critical role in its success. Therefore, for this research, management commitment to the project was assured at the onset of the endeavor. Following, the processing systems used to manufacture the non-controversial stem cell pharmaceutical products were comprehensively examined, focusing on waste in application of lean manufacturing. The direction of the examinations was the identification of processing waste of the raw material, to include waste in motion and

time, materials, labor and overall production costs. Examinations included direct observations, a review and alignment of procedures, time studies, and record reviews.

The principles of lean manufacturing were used to investigate production processes as they relate to raw material usage, efficiencies relative to production costs, and overall product costs as the cumulative evaluation. Lean principles of value, value stream, flow, pull, and perfection were the key components for assessing waste in the production system. Upon completion of a thorough understanding of the processes, value stream mapping of the current state was performed and documented.

The value stream map includes the production activities from raw material receipt to finished goods output. Within the map, above the documented production processes, depiction of the management and information system's flow were included. In addition, the value stream map includes volumes, amount of materials, in-process inventory, and cycle times (Daley, 2003; Rother & Shook, 1999). A future state value stream map was developed, and a gap analysis conducted between the two maps. Gaps were documented and corrective action, to close the gaps between current and future states, developed. Corrective actions employed lean manufacturing strategies and techniques based on the collected data and the type of waste identified. Specific testing, assessment protocols, and data collection tools for the questions proposed follow.

Research Question 1. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Specific focus of testing protocol

Cost analysis was conducted upon elimination and assessment of waste eliminating strategies. The cost of production before waste was eliminated and after serves as the initial mathematical evaluation. The cost of a unit of product before and after process changes was the approach used to evaluate reduced product costs.

Research Question 2. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Specific focus of testing protocol

The volume of raw materials was determined for each process of the examination. Identification of waste of raw materials was the focus, to include concentration on defects, scrape, and rework in that these elements are traditional areas of material waste (Crosby, 1988). Measures to eliminate raw material waste were determined and analyzed to evaluate potential raw material savings as a result of waste elimination.

Research Methodology

The following describes the method employed for collecting data and conducting the research. The control and test groups are defined in table 1 that follows. Information pertaining to the associated groups as defined was used for the evaluation.

Table 1.

Test Groups

Item	Description
Control group	Data, information, and other statistics collected from the current production state prior to interventions; before waste was eliminated.
Test group	Data, information, and other statistics collected from the production state after interventions; after waste was eliminated.

General data collection

1. Manufacturing procedures were obtained and reviewed for the product under study. The procedures are listed on the data collection form. These procedures include set-up, manufacturing steps, quality control requirements and inspection points.

2. After a comprehensive review of the associated documented procedures was completed, the actual production processes were observed. The data collection form served as the record for documentation that includes a process description, the number of employees, as well as reagents used, type of equipment, what records were generated and the set-up process.

   2.1. Observation of the production process was conducted several times to completely document elements noted. Individual processes were also viewed in stages to better capture and verify information.

   2.2. Identification of waste was a key focus during observations and data collection. Findings were recorded on the data collection form for further evaluation.

      2.2.1. The eight types of wastes, listed below, described in the lean philosophy, were used to guide the waste identification process:

         - Overproduction
         - Waiting
         - Excess inventory or Work-in-Process (WIP)
         - Defects
         - Transportation
         - Motion
         - Processing
         - Under utilizing people

3. A value stream map of the current process was created and is presented with the results, in chapter 4, which follows. The map includes, but is not limited to, process tasks, materials, flow, cycle times, information sharing, and staging areas.

4. The information gathered was used in the assessments of the amounts of available raw materials for manufacturing and product cost evaluations.

Raw material availability evaluation

Relative research question: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

1. Completed data collection forms which list process steps were reviewed to identify activities where non-controversial stem cells, as raw materials, are used. Also, procedures were reassessed and work activities observed again, concentrating on those tasks where the stem cell materials are used. Results were recorded on the raw material data collection form.
2. Manufacturing records were evaluated to determine starting volume and processed volume of the cells. These were recorded on the raw material data collection form. The differences were calculated to determine volume of raw materials/stem cells used.
3. Potential waste of raw materials/stem cells, identified from the above assessments, were recorded and described including possible opportunities to reduce the amount of stem cell material used.
4. Lean manufacturing strategies for process improvement were identified and protocols for application developed.
5. The difference between the volumes of stem cells/raw materials used before proposed process changes and after were quantified. The significance of the difference was determined by statistically evaluating the two population means. The statistical

technique used was an analysis of variance (ANOVA), evaluating the null and alternative hypotheses:

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

6. A statistical analysis of factorial design using a one-way ANOVA was used to assess the significant differences in the means of materials before and after process interventions by application of lean manufacturing principles of waste elimination to answer the null and alternative hypotheses. A paired t-test was used to further evaluate statistical significance.

Product cost evaluation method

Relative research question: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

1. The cost of production was evaluated by delineating costs of reagents, supplies, and labor per unit produced, documented on the production cost per unit data collection form. A comprehensive description of the product/unit started this assessment.

2. Waste identified from the above assessments of product cost, raw materials, and from the general data collection activity were factors used in cost reductions.
3. Lean manufacturing strategies for process improvement were identified and protocols for application developed.
4. Eliminations of wastes were tallied and associated costs applied. The sum of the cost savings generated from elimination of waste was subtracted from the cost per unit before process changes occurred to eliminate the waste. The results were defined as reduction in cost per unit due to application of lean waste elimination.
5. The costs of production, after improvements, were evaluated by delineating costs of reagents, supplies, and labor per unit produced.
6. Product cost evaluation relative to productivity
    6.1. Process evaluation started the assessment. Process steps were characterized, recording the type of operation, the materials used to include volume or amount, as well as the type of equipment utilized for the process operations. The information was recorded on the productivity data form.
    6.2. Cycle time was a focus of the productivity evaluation. The time required for a process step associated with potential waste was determined and recorded on the collection form. The time was recorded in hours and minutes.
    6.3. Process time was further delineated between machine/equipment time and employee time. The work being performed by each was described. Employee waiting time was recorded and denoted as a type of waste. Other wastes identified were documented and assessed.

6.4. The distance traveled by the employee during performance of a step would be determined and recorded on the data collection form. The distance traveled by materials used in an operation would also be denoted on the form.

6.5. Takt time and WIP were evaluated for process steps. Using the operation time determined above, process or cycle times were elements that were used to calculate potential savings by subtracting WIP and re-assessment of takt-time.

6.6. Wastes associated with productivity identified from the general data collection process, and other wastes noted, were further evaluated, repeating steps above.

6.7. After evaluation of the data collected, improvement methods were determined by focusing on waste elimination or reduction.

6.8. Lean manufacturing strategies for process improvement were determined and protocols for implementation developed.

6.9. Revised processes by application of lean were assessed, repeating steps above to determined process savings including cycle reductions.

6.10. Labor, supplies, and reagent costs were determined from the savings realized. Raw materials volume savings were used in evaluating raw material availability; cost savings were utilized in the specific product cost evaluations.

6.11. Table 2 that follows specifies the evaluation of product costs affected by lean waste elimination. The basic product cost was a summation of the cost of the reagents, supplies, and labor per unit. Application of labor cost used in the determination of product cost was based on the summation of labor required to produce a unit of product. Labor costs were the amounts of time required to perform an activity, defined in dollars per hour, summed over the

production length of a unit of product. Samplings of the production process were conducted before and after application of lean waste elimination. The cost of the product, using the basic cost summation noted above, was determined for each sample and compared. Based on the samples, if the cost of the product before application of lean waste elimination was greater than the cost of the product after application of lean waste elimination, it was determined that the application of lean reduced product costs. The table that follows clarifies the methodology used.

Table 2.

Determination of Product Costs

Item	Description
Research Question 1	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?
Product cost (P)	The direct cost of reagents (R), supplies (S), and labor (L), where: $P = R + S + L$
Sample	Measurements of production before and after.
Application	Increases in productivity from lean were applied to product cost assessments; time in hours quantified into labor costs (dollars/hrs). Additional savings.
Test	Measure of cost to manufacture the product before application of lean waste elimination and after.
Product cost before lean (P_0)	$P_0 = R_0+S_0+L_0$, where, R =Reagent cost; S_0= Cost of supplies; L_0=Labor cost, before lean.
Product cost after lean (P_L)	$P_L = R_L + S_L + L_L$, where, R_L=Reagent cost after lean; S_L=Cost of supplies after; L_L=Labor cost after.

If $\mathbf{P_0 > P_L}$ the application of lean waste elimination reduced product costs.

Unit of Analysis

The production process was evaluated, with a focus on waste. Information obtained was documented on data collection forms. Upon identification of waste, the current system was measured prior to intervention. Metrics included volume of waste produced, time measurements in hours and minutes, labor costs in dollar per hour and direct costs in dollars per unit. Methods to eliminate the waste were developed and implemented, and/or potential effects of waste elimination determined. For wastes that were eliminated, the resulting changed process was evaluated. For proposed plans for waste elimination, mathematical calculations and forecasts served evaluation methods.

Table 3 that follows presents a composite of the research variables and their unit(s) of measure for each defined question. The four variables identified were volume, time, records, and supplies. Volume was associated with both of the research questions. The volume of reagents used was a factor in determining product costs in the first research question. The primary metric for the second research question was the comparative volume of the raw material before and after application of lean waste elimination used in determining the influence on the amount of material. Time was used as a variable to evaluate product costs relative to the amount of labor required in the production of a unit of product, as labor costs. The records variable was also used to evaluate product costs in the first research question by determining the number reviewed as a part of labor costs. Supplies, the last variable noted in table 3 that follows, was used to evaluate product costs by determining the amount used per unit of product, adding the results to the additional measures on costs.

Table 3.

Research Unit of Analyses

Variable	Description/Use	Measurement
Volume	Raw material or other liquids. Research question 1 metric - liquid reagent volume is used to evaluate product costs - cost used in making the product. Research question 2 metric - Volume of raw material used; evaluates material before lean and after.	Milliliters (mL)
Time	Research question 1 metric – Time is used to evaluate product costs. The amount of time used in making the product is a measure of the cost of labor (man-hours); cost of the product.	Hours or minutes
Records	Research question 1 metric - The production process includes record reviews. The number of records reviewed is a measure of labor involved; product cost component; number/man-hour cost.	Number
Supplies	Research question 1 metric – Supplies used in production; cost of the product per number.	Number

Linking Data to Propositions and Interpreting the Findings

The summary of these assessments were used to determine the affect of waste elimination from lean manufacturing on product cost and raw material availability in the production of pharmaceuticals, evaluating the potential of applicability on approaches to reducing healthcare costs. The statistical analysis used to evaluate the data was determined by the data collected, aligned accordingly. The statistical software used to conduct the analyses and interpret the findings was SPSS. SPSS was selected as the tool for statistical analysis because of its 37 year history of continual improvement as established software, which is currently used in 90% of U.S. universities (Seiter, 2003; Studt, 1996; www.spss.com). The top ten pharmaceutical companies use SPSS for data analyses (www.spss.com). In addition, this author has first hand experience with the software academically and professionally.

An ANOVA was used to statistically evaluate the data when there were multiple variables and to test significant differences in hypotheses. The research also involved factors, with interaction of factors possible, requiring a factorial design such as ANOVA (Montgomery, 2001). An alpha level of 0.05 was selected to limit the probability of concluding that the null hypothesis of no differences is incorrect only 5% of the time. Since ANOVA was used, the following were assumptions and analyses limitations.

Statistical Assumptions and Limitations

1. The values of the independent variables are randomly selected.
2. The independent and dependent variables have a linear relationship.
3. The independent and dependent variables have been accurately measured.

4. The independent and dependent variables are normally distributed, continuous, and are interval or ratio data.
5. The independent variables are not correlated.
6. There is homoscedasticity - variance of prediction errors is constant for all values of independent variables (M. Hayden, class notes, Fall 2005).

Based on the data collected from the test population, additional analytical tools were used for describing, evaluating, and interpreting information for data-driven conclusions.

The research methodology described above resulted in the key components of the case study identified in figure 23 that follows. Represented are the five elements of a case study - study questions, the propositions, the unit of analysis, the linking of data to propositions, and the criteria for interpreting the findings. The case study questions are listed and highlighted in the table. The propositions are process examinations and evaluations that results in the identification of wastes, listed as findings. The unit of analysis for each question is a sample of the production system before and after waste elimination with testing of the samples described for each research question. The testing for the product cost research, before and after waste elimination, is the summation of parameters that results in the cost of the product: reagents, supplies, and labor. The testing or unit of analysis for the question associated with raw material availability, is raw material volume before and after waste elimination using statistical analysis to determine the comparative significance. The data obtained from the samples, linked to the propositions, were tested as noted, the results presented in the table. The last element, criteria for interpreting the findings, is represented in the table at the analyses heading.

Research Question 1	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial pharmaceutical stem cells reduce product costs?
Sample	Production system before and after waste elimination
Category	***Method***
Test	Product cost (P): $P = R + S + L$, where: R = cost of reagents; S = cost of supplies; L = cost of labor Cost before lean: $P_0 = R_0 + S_0 + L_0$ Cost after lean: $P_L = R_L + S_L + L_L$ If $P_0 > P_L$ then the application of waste elimination from lean manufacturing reduced product costs.
Findings	Identification of associated waste
Results	Measurements of the product cost parameters of the sum cost of reagents, supplies, and labor before wastes identified above were eliminated and after.
Analyses	Summation of product cost per unit before application of lean waste elimination and after. The difference in the before and after results determine the influence of lean waste elimination on the cost of the pharmaceutical.
Research Question 2	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?
Sample	Production system before and after waste elimination
Category	***Method***
Test	Statistical analysis to evaluate the significance of volume of raw materials before and after waste elimination. ANOVA at a significance level of 0.05 was used.
Findings	Identification of associated waste.
Results	Measurements of the volume before and after waste elimination for significance by statistical analyses.
Analyses	The results of the statistical analyses were evaluated to determine whether the change or difference in raw material volume before and after was significant.

Figure 11. Key components of the case study.

Chapter Summary

The aim of this study was to determine and evaluate the influence of applying lean manufacturing principles and strategies of waste elimination to the manufacturing processes used in the production of non-controversial stem cell pharmaceuticals. The foci of the research are on product costs and raw materials relative to availability, or amount, for manufacture into the stem cell pharmaceutical. The cost of pharmaceuticals is a leading factor in increasingly high healthcare costs. The results of this research on product cost reductions have implications for measures evaluated to reduce overall national healthcare costs.

This research investigated the influence of lean waste elimination on a single type of stem cell pharmaceutical manufacturer. A case study design was the methodology used for the research. The design was selected as the research strategy since the cumulative influence of eliminating waste by application of lean manufacturing on a single pharmaceutical supplier was evaluated. The five elements of a case study design were described consisting of the study questions, the propositions, the unit of analysis, the linking of data to propositions, and the criteria for interpreting the findings.

Chapter 4

RESULTS

Introduction

The findings and analyses of the research conducted to evaluate the influence of lean manufacturing waste elimination on the production processes of non-controversial stem cell pharmaceuticals are presented in this chapter. There were two questions of the study and a hypothesis answered from this research:

Research Question 1. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Research Question 2. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Research Findings and Analyses

The findings, results, and analyses of the research follow. The research was conducted by the methodology described in Chapter 3. The method employed is presented first, numbered, with the findings or results, and analyses thereafter.

General Data Collection

1. Manufacturing procedures were obtained and reviewed for the product under study. The procedures are listed below as well as on the associated data form. These procedures included set-up processes, manufacturing steps, quality control requirements and inspection points.

Findings

Data collection - procedures

- Aseptic processing – Defined techniques utilized to avoid contamination. Techniques included not allowing pipettes or syringes to touch the rim or outer surfaces of bottles or other containers when transferring materials; cleaning the outside of packages before opening; avoiding reaching across open bottles and containers; when liquids were poured to avoid splashing.
- Cleaning, maintenance, calibration and quality control of equipment - Outlined the schedule for cleaning, maintenance and quality control of all

laboratory equipment on a daily, weekly, biweekly, monthly, semiannual and annual basis. These procedures were to ensure that equipment would function as expected.

- Controlled rate freezer – A freezer that provided uniformed, programmed cooling of biological specimens. Control of the rate of freezing of biological specimens was important to optimize the viability of the cells. The controlled rate freezer was used with a program defining specific cooling rates.
- Processing with hespan - Defined and detailed the steps involved in the manufacture of the biological raw material using hydroxyl ethyl starch, known as hespan, for the isolation of hematopoietic stem cells for cryogenic storage.
- Cryopreservation - Detailed steps involved in preparing the final products of stem cell pharmaceuticals for storage at very low temperatures with minimal loss of cell viabilities.
- Daily quality control - Daily assessments to ensure reagents, equipment, and processes functioned as expected. Specific reagents were tested for reactivity and specificity whenever a new lot number was placed into use, and rechecked, thereafter, on each day of use. Reagents were observed visually for abnormal appearance, cloudiness or turbidity. Reagents were stored in original containers at recommended storage temperatures when not in use.
- Delivery of samples – Defined the process to document delivery and receipt of the biological raw material by using courier tracking numbers and respective manifests.

- Entering microbiology results in the information database - Detailed the computer entry steps for input of microbiological test results into the database and defined record retention.
- Environmental monitoring - Assessment of the controlled manufacturing facility to ensure the limits of air and surface quality were maintained. The process also evaluated the effectiveness of cleaning and sanitization practices by and of personnel that could have an impact on the bioburden of the controlled environment.
- Equipment management – This procedure documented receipts of equipment; defined critical equipment; documented service and corrective action to laboratory equipment; documented storage of equipment records.
- Liquid nitrogen dry shipper/filling and cryostorage condition verification – Maintenance of deep freezing process and equipment.
- Performing microbiology cultures - Outlined the process for microbiological detection in aerobic and anaerobic culture media inoculated with samples that determined bacterial and fungal contamination. Microorganisms were present in the test sample if CO_2 was produced as the microorganisms metabolized the substrates in the culture medium. Growth of the microorganisms produced CO_2 that caused the color of the sensor in the bottom of each culture bottle to change from blue-green to a lighter green color or a mustard yellow color. A light-emitting diode projected light onto the sensor and the reflected light was measured. The more CO_2 generated, the more light was reflected. This was

compared to the initial CO_2 level in the bottle and the sample was determined to be positive or negative.

- Preprocessing setup and work document generation – Specified what forms to generate for recordkeeping and what materials were to be assembled on the cart for use in manufacturing.
- Quality control and maintenance of the auto-volume expressors – Defined the upkeep, usage, and calibration of an automatic filling device referred to as an expressor.
- Sanitization - Outlined the procedure for the proper cleaning of manufacturing rooms and other processing areas to include biological safety cabinets (BSC).

2. A comprehensive review of the associated documented procedures was completed and the actual production processes were observed to ensure a thorough knowledge of the manufacturing system for the assessment of waste.

2.1. Observations of the production process were conducted several times to completely document elements noted. Individual processes were also viewed in stages to better capture and verify information.

Findings

Process description - current state

Manufacturing started at the receipt of incoming raw materials sent from the customer to be processed into biological pharmaceuticals as stem cells. The materials were delivered by courier, unpacked and checked at a staging area. The shipping boxes containing the biomaterials were checked for damage and compared to a preprinted manifest of incoming items. Damages were recorded and associated information sent to

the client contact department for follow-up. If there were discrepancies between the numbers of materials expected and received a notation was entered on the manifest for further resolution. Each boxed shipment should have contained paperwork, the biomaterial in its collection bag wrapped in absorbent towels and placed in a zip lock bag along with three separate, foamed protected, tubes of samples of the biomaterial for outside vendor testing. All of the separate materials were housed in a lidded plastic bin. During the incoming inspection process the boxes were unpacked, contents removed and verified. The bins were transferred to an environmentally controlled assembly area.

Assembly consisted of cleaning and preparation of the outside of the biomaterial bag. Isopropyl alcohol was lightly sprayed on the outside of the bag and removed with lint paper to clean the exterior. The paperwork was taken out of the bin and reviewed with associated data entered into the computer system. The information entered included the material identification number, collection date and time, for all materials from domestic (U.S.) customers. A noted finding was that international materials required additional data entry, changing the production flow.

Labels were generated from the information entered into the computer system and applied to the biomaterial bag as well as other supplies. Samples of the material that were collected separately in tubes were placed in a tube rack and refrigerated until they were shipped out to the testing vendor daily. The bag of biomaterial, final storage containers, other supplies and work documents were transferred to a new processing bin which was placed on a cart with other manufacturing materials. The cart of materials was passed-through a designed gateway, to reduce the potential of contamination, for further

manufacturing. Disposal of the original incoming plastic bins and lids completed the assembly process.

A finding noted during the assessment of the manufacturing area was the separation of production into cellular manufacturing stations of separate modules that used a biological safety cabinet as the working platform. The modules of biological safety cabinets were in a clean room designated as Class 10,000 per ISO 14644-1 (http://www.fda.gov/cder/guidance/5882fnl.htm). FDA (2004) describes the Class 10,000 environment as having a total air particle count of 10,000 particles per cubic foot or less of a particle size 0.5 micron and larger. These types of manufacturing environments, commonly referred to as clean rooms, are used to limit the microbes in the air and on surfaces to reduce the potential of product contamination from these particles.

Ten units of biomaterials could be processed per cabinet. Each cabinet was supplied by a separate cart of collected production materials. The carts were composed in the assembly area and consisted of reagents, instruments, gauze, disinfectants, and work documents.

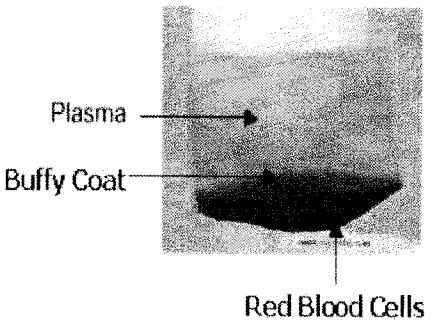
The next step in manufacturing of the biomaterial into the stem cell pharmaceutical was the aseptic processing of the raw material in the manufacturing process. Aseptic processing employs defined handling methods to reduce the risk of contamination. Methods included the prerequisite of cleaning outer containers before they were opened; spraying gloves with alcohol throughout the process; and ensuring materials did not touch each other. Processing steps, equipment, lot numbers of reagents with their expiration dates, and operator identification were all recorded on work documents. Materials were arranged, labeled, and prepared for processing. A finding

noted was the weighing of each material and that six milliliters (mL) of the biological material was removed from the bag for quality control (QC) testing prior to processing of the material into stem cells. The tests conducted were total nucleated cell count (TNC), ABO Rh or blood type, bacterial evaluation for sterility, stem cell count referred to as CD34+, and cell viability. It was also noted that all of these tests, with the exception of the bacterial evaluations, used 1-mL of the raw material. The bacterial evaluations used a total of 5-mL of the raw biomaterial aspirated from the bag – one mL for aerobic bacterial testing and 4-mL for anaerobic bacterial testing. It was identified that these series of quality control tests were performed on the material before and after final processing. The samples were placed into individual bottles for the inoculation procedure for bacterial evaluation. The inoculation bottles were designed supply items.

Processing of the material started with the addition of a liquid protein expander called hespan, supplied in 500 mL bags. The amount of hespan added was 20% of the volume of the raw material to be processed. Calculations were recorded on work documents as well as other documentation associated with the manufacturing process. These included equipment used, processing times, component weights, and the identification of the person performing the manufacturing step.

The reagent was added to the material by injection through a coupler port previously wiped with alcohol. A finding noted was that the remaining hespan reagent at the end of the production day was discarded. An average of 17.9 mL of hespan was used for processing per unit or bag. The bags of raw material were placed in a centrifuge, balancing the cups within by addition of gauze as needed. The material was spun in a centrifuge, which separated the components of the biomaterials by density gradient,

differentiating into its component parts. The bags of biomaterial were removed from the centrifuge and hung within the safety cabinet for 15 minutes. Settling of the heaviest component was at the bottom with the lighter on top; see figure 12 that follows.



(Source: Rotary Blood Bank Tughlakabad Institutional Area, 2007)

Figure 12. Density separation of raw material into component parts.

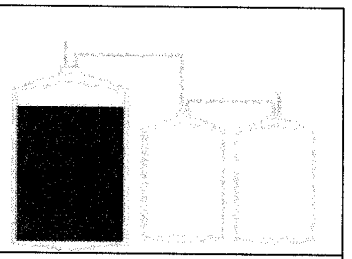
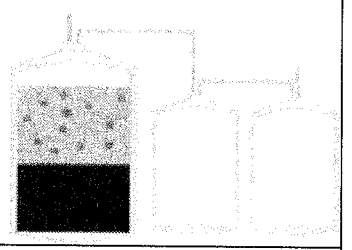
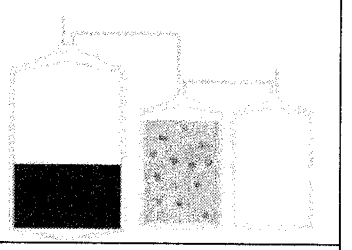
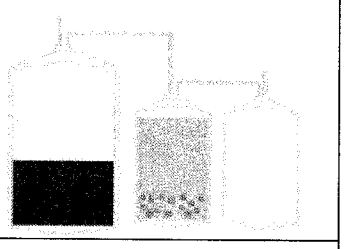
The lightest portion made up the more water based part or the plasma portion. Plasma consists of about 95% water and 5% proteins and salts. The proportion of plasma in the biomaterial was about 55% (O'Neil, 2007). The next layer was the buffy coat that consisted of white blood cells and the stem cells. Stem cells were that portion of the material that made up the final product. The bottom portion was the layer of red blood cells.

The manufacturing process removed those waste components of the biomaterial that would not be used and harvested the final product of stem cells for permanent storage. The plasma portion and the red blood cells were removed by selection and pressure transfer. The bag was placed on a manual expressor and the plasma portion, to include the buffy coat of white blood cells with stem cells, was pushed out of the

container bag into a connecting bag by applying pressure. What remained in the original bag were the expanded red cells and hespan that were discarded.

The next step was a second centrifugation of the biomaterial for further component separation. The plasma portion with the buffy coat of white blood cells and stem cells, referred to as leukocyte rich plasma, was centrifuged a second time to again differentiate the leukocyte rich plasma into its component parts. The bags of biomaterial were removed from the centrifuge and again hung in the cabinets to promote settling.

The last step in the component separation part of manufacturing was the removal of stem cells from the remaining components. An automatic expressor was used to transfer 21.5 mL of the leukocyte rich plasma of stem cells to a separate connected storage bag. Figure 13 that follows depicts the manufacturing process stem cells.

The raw biomaterial was collected in the larger bag of a three part bag system. The system was shipped to the manufacturer for processing into stem cells. A finding noted was the removal of 6-mL of biomaterial from each unit for pre-testing during the processing method.	
The processing of the material started with light centrifugation that differentiated the material into its different components. The position of settling was based on the weight or density of the components. The component part that was heaviest settled to the bottom.	
The lighter plasma containing the buffy coat of white blood cells and stem cells were expressed off by squeezing pressure into a connecting bag. Red blood cells with hespan remained in the original bag for discard.	
The leukocyte rich plasma of stems was centrifuged heavily a second time to separate remaining components.	
The material was expressed into a third bag and the stem cells, which was the final product, were collected for storage. 9 mL of the unused plasma was removed for post process testing of each unit.	

(Source: Rotary Blood Bank Tughlakabad Institutional Area, 2007)

Figure 13. Process converts raw biomaterial into stem cells.

The bag of stem cells was pre-cooled along with a cryopreservative consisting of a mixture of 50% DMSO (dimethyl sulfoxide) with 5% dextran 40. Cryopreservatives protected the stem cells from trauma caused by the freezing process to follow. The stem cells were mixed with 5.2 mL of the cryopreservative and then transferred to a compartmentalized specialty freezing bag. A metal cassette was used to house the bag of stem bags, providing additional protection against damage during freezing and handling.

The final manufacturing processes of stem cell pharmaceuticals were freezing and storage. The freezing process started with a pre-freeze using a controlled rate freezer. A controlled rate freezer was used to provide uniformed, programmed cooling of the stem cells. Control of the rate of freezing of biological specimens was important to optimize the viability of the cells (CryoCell, 2006). The pre-freeze lowered the temperature of the biopharmaceutical product of stem cells to -90°C (-130°F). The product was carefully removed from the controlled rate freezer and transferred to the permanent storage freezer of liquid nitrogen. A dry shipper with internal temperature below -90°C was used to transport the product from the controlled rate freezer to the area of the permanent storage freezer to protect against open environmental room temperatures to prevent thawing. The product was placed in the vapor-phase of the liquid nitrogen freezer, completing the freezing process, lowering the product's temperature to -190°C (-310°F). Stem cells may be stored in this cryopreserved state for at least 15 years with some believing indefinitely (Mugishima, Harada, Chin, Suzuki, Takagi, Hayakawa, et al., 1999).

A current state value stream map of the process was created. Processes, materials, flow, cycle times, information, and staging areas are included; see figure 14 that follows.

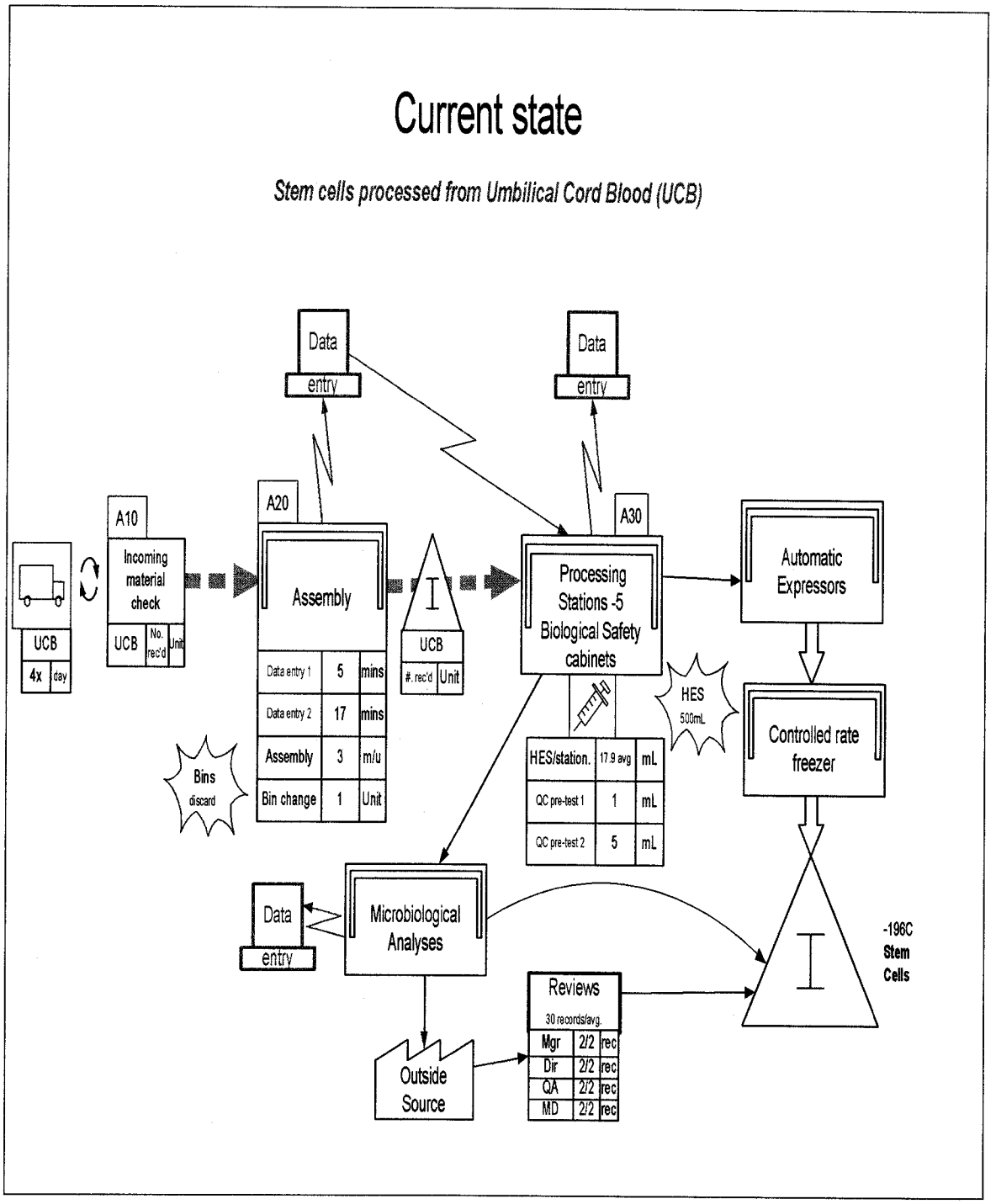


Figure 14. Current state value stream map with waste as spiked icons of Kaizen bursts.

The above current state value stream map depicts the manufacturing process from incoming material receipt through to final product storage by cryopreservation. Incoming materials of biological raw materials arrived by transport courier truck four times per day. This process is represented on the map by the truck icon that includes the table below the icon of four shipments per day denoted as 4x in the cell with day in the next cell of the table. Interaction between the courier and the receiving staff follows, determining what items were received compared to what were expected. This interaction is denoted on the map by the curved arrows between the truck icon and the incoming material check process block. At the checking process icon the number of units is identified on the map in the table at the bottom of the check block icon. A push arrow is between the incoming check process and the next process of the assembly of shipment items pushed forward.

The assembly process involves data entry, material assembly, and changing of bins. Each of these steps is identified in the table attached to and below the assembly process box icon. The table denotes the type of step and the time required for the step in minutes. Data 1 is the computer entry process for domestics and the associated entry time. Data 2 is the process for international shipments. The difference in processing of shipments was noted as a finding in the manufacturing system.

Above the assembly process on the map is a computer icon connected by an arrow denoting information flow from the assembly process into the computer database. A Kaizen burst spiked icon to the left of the assembly process table identifies a finding of a potential opportunity for waste elimination. Incoming holding lidded bins were discarded as trash at the end of the assembly process.

The next process on the current state value stream map is the staging of the materials for the next manufacturing step. This is represented on the map as an inventory stage denoted by the triangle icon with the I in the center. The table under the inventory icon identifies the number of units associated. Another push arrow follows as the processing materials are moved to the clean rooms for manufacturing using biological safety cabinets (BSC) as work platforms. This process is connected above to a computer icon to show information transfer into the database. Below the process block is a needle icon representing the entry of a medical item, the hespan reagent, into the product. Connected to this icon is the data table for the process that identifies the manufacturing steps associated with the research parameters. These are reagent use per milliliter (mL) and the identification of raw materials usage at this stage for pre-QC testing. A Kaizen burst spiked icon to the right of the process icon identifies the finding that there is a possible opportunity for waste elimination associated with reagent use.

Another separate connecting arrow on the map is from the BSC processing to microbiological analyses which is a separate stage that also includes the attached computer icon representing data entry. The results of the analyses feed back, connecting arrow, to the final inventoried product described below.

The ending manufacturing steps on the map are mixing of the stem cell material with a freezing protectant and dispensing of the product into a storage bag container using automatic expressors. This stage is followed by the initial freezing using a controlled rate process and then the end storage referred to as cryopreservation. The final product is stored frozen at about -190ºC as inventory, represented by the triangle icon, until there is a medical need for the product.

2.1.1. A general data collection form was completed to record process findings: employee, reagents, equipment, records, and set-up; see figure 15 below.

<table>
<tr><th colspan="2">GENERAL DATA COLLECTION</th></tr>
<tr><td colspan="2">Procedures: The following procedures were reviewed and evaluated
* Processing with hespan * Cryopreservation *Aseptic processing; sanitization
* Delivery of processing samples * Controlled rate freezer * Equipment management
* Environmental monitoring * Preprocessing setup and work document generation</td></tr>
<tr><td colspan="2">Process Description: Delivery, receipt, and processing of biological raw materials to be manufactured into stem cell pharmaceuticals. Delivery by courier. Receipt/evaluation of delivery, unpacking, data entry & creation of work documents. The raw material was processed using hydroxyl ethyl starch (hespan or HES) to enrich for the total nucleated cell population for hematopoietic stem cells, $CD34^{+}$. Cells subsequently cryopreserved in DMSO and dextran - cryoprotectant. Cells can be stored safely in liquid nitrogen vapor phase, ($\leq$ -135^{0}C) to preserve viability. The stem cell pharmaceutical product was stored in a 25 ml bag with 2 compartments (20 mL and 5 mL). Each bag had an integrally attached segment that allowed for additional quality control samples at transfusion or thawing. Storage of the finished frozen product was in the vapor-phase of a liquid nitrogen freezer tank - temperature of $\leq$-135° C; average temperate was -190° C.</td></tr>
<tr><td>Number of employees: Two in delivery; one per station-five stations; one employee each for freezing and storage. Total = 9</td><td>Reagents used:
Dimethyl sulfoxide (DMSO) with dextran Hydroxyl ethyl starch (Hespan)</td></tr>
<tr><td>Equipment: Centrifuge with oblong buckets and centrifuge inserts; biological safety cabinets; heat sealer; plasma expressor; digital balance; auto expressor.</td><td>Other supplies: Hemostats; scissors; tube rack; tube stripper; ice pan; ice; 70% ethanol; alcohol wipes; 70% isopropyl; red top specimen tubes; culture bottles; non-sterile and sterile disposable gloves; 4 x 4 gauze; transfer set; labels; scoupler.</td></tr>
<tr><td colspan="2">Records generated: Electronic data entry and manual work documents.</td></tr>
<tr><td colspan="2">Quality Control (QC) method: Sample testing</td></tr>
<tr><td colspan="2">Describe setup: Setup - supplying the processing cart with the following items:
1- Hespan, 500 mL bag 4 – small bags; transfer bags 4-5 sterile gloves
1 – package of non-sterile gauze 1- squirt bottle of ethanol 1 – bottle of alcohol
1 – box of alcohol prep pads 1- package of sterile gauze 1 – dish bin
2 – blue ice bins containing ice Non-sterile gloves; syringes; DMSO/Dextran</td></tr>
</table>

Figure 15. Data collection form identifies procedures, employees, supplies, equipment.

The completed data collection form, figure 15 above, contains the recorded findings of the general data collection process of this research. The process description defines the manufacturing process from receipt of incoming shipments, through manufacture to final product storage. Incoming biological material shipments were evaluated that included a data entry process and set-up of materials for the manufacturing. Manufacturing was the processing of the biological raw material using the expander reagent hespan. The process separated the raw material into its component parts by weight. The stem cells were separated out, collected, and processed for deep freezing or cryopreservation. The final product was a 25 mL bag of frozen stem cells that was stored using liquid nitrogen at an average temperature of -190° C or -320° F.

The data collected also included the number of employees per operational task, reagents, equipment, records, and supplies used to manufacture the non-controversial stem cell pharmaceutical. A comprehensive listing of set-up materials were included on the form to aid in quantification of product costs as well as identification of wastes.

2.2. Identification of waste, a key focus during observations and data collection, was recorded for further evaluation.

2.2.1. The eight types of wastes, listed below, that were described in the lean philosophy were used to guide the waste identification process:

- Overproduction
- Waiting
- Excess inventory or work-in-process (WIP)
- Defects
- Transportation

- Motion
- Processing
- Under utilizing people

Identification of waste

Table 4 below list the findings of waste elimination opportunities identified during the general data collection activity and process analyses. These findings are further assessed in the analyses section below as well as in the evaluation sections.

Table 4.

Waste Identified

Waste	Process	Location
Time – data entry	Assembly	Staging area I
Bins and bins discarded	Receiving	Staging area I
Duplicate testing	Bacterial testing	BacT lab
Duplicate testing	Lab analyses, cell counts	Chemistry lab
Multiple record reviews	Bacterial testing	Various
Reagent - hespan	Processing	Clean room

Analyses

A review of operating procedures, observations of work practices, data collection and assessment of the current state value steam map identified the elements of waste that follows. The production process where the waste was identified is also described.

Time waste - data entry. Data from the paperwork shipped with the biomaterial was entered into the computer system. A finding was the two different types of standard shipments received actually defined the data entry process. Domestic shipments were those sent within the U.S. and internationals were those from outside of the continental U.S. Standard input information that was common for all shipments was entered consisting of the material identifications and the collection dates and times.

A finding of process differences occurred with international shipments. Additional information was entered for internationals requiring added processing time or labor costs. The current state value stream map, figure 14, shows that for Data 1, domestics, the data entry process took five minutes. For Data 2, internationals, the data entry process took 17 minutes. The additional information for internationals was the same for domestic shipments; however, the point and source of entry were different. For domestic shipments, the additional information was entered into the computer system at the time the service was ordered by the customer. This portion of the data entry for domestics occurred well prior to biomaterial receipt. With international materials data were recorded manually on paper shipped with the biomaterial; data was entered at the time of receipt with the biomaterial to be processed. Table 5 below shows the differences between data entry of domestic products versus international data entry points and time.

Table 5.

Data Point Entries

Data points	Domestic	International
Billing/shipping information	0	20
Client/product name – first, middle, last	3	3
Collector's name	3	3
E-mail, birth date, due date and number of children.	0	4
Gender	1	1
Health history	0	38
Hospital/Doctor information	0	16
Owner	3	3
Owner's sample collection date & time	2	2
Paternal information	0	11
Scan client ID barcode	1	1
Signature box	0	3
Time and date of collection	2	2
Unique identification number	0	1
Total number of data entry points	15	108
Entry time (minutes)	5	17

There were 15 data entry points for domestic shipments and 108 for internationals, for a difference, 108-15, of 93 points. The time required to enter data for domestics was 5-minutes and for internationals 17-minutes, for a difference, 17-5, of 12 minutes. These data point entries and time task differences of 93 points and 12 minutes were process wastes or labor costs between international and domestic shipments. Another finding was impediment of production flow due to the process differences for data entry of shipments.

Bins and lids waste. At the end of the assembly process another finding of potential waste elimination was noted. The secured bag of biomaterial was shipped in a plastic, lidded bin. The biomaterial was secured by the leak proof collection bag that was also wrapped in absorbent towels and then placed in a plastic zip locked sealed bag. The secured three sample tubes of biomaterial were placed in individual protective foam sleeves and then placed in the zip locked bag, resulting in three layers of protection. The zip locked bag was then placed in the plastic bin and sealed with the lid. At the process assembly staging area these bins were unpacked and discarded along with the lids. New bins were used to hold the materials for the next stage in the manufacturing process. The discarded bins and lids were not recycled, adding to product cost due to supply waste.

Duplicate testing waste. Processing began with removal of six milliliters (mL) of the biological material from each unit for six different quality control tests. Five of the tests were referred to as pre-counts which were those conducted prior to processing. However, a finding of the manufacturing assessment was the test results were not used to change the current production process.

One mL of the material was used for four quality control tests assessing pre-total nucleated cell count (TNC), ABO Rh or blood type, pre-stem cell count referred to as pre-CD34+, and pre-cell viability determination. A finding within the process was that only one of the four tests, the test for blood type, added product value. The other three tests for determining the pre-total nucleated cell count, pre-stem cell count, and pre-cell viability were used to evaluate staff performance. These tests were conducted on every unit. A finding from the review of 712 production records revealed that none of the pre-test results were used for changing staff performance because all of the results were under action limits. An additional finding was that these tests were performed again, after production processing, on the final product for qualification.

The other 5-mL of the 6-mL sample was used for the pre-bacterial evaluation of sterility using 1-mL of the raw biomaterial for aerobic bacterial testing and 4-mL for anaerobic bacterial testing. As noted, a finding in the process assessment was that these series of quality control tests were performed on the material before and after final processing. The results of these pre-bacterial evaluations were intended to be used for staff evaluation to enhance the production process. As noted above, a review of numerous production records revealed that these test results were not used because no data identified a need for intervention since all results were well under action limits. A finding was the managerial review process to assess staff performance, based on pre-test results, only occurred 60-days after testing. A needed intervention would not affect immediate production with changes going into affect no earlier than 180 days later due to procedural process change requirements. There were no test results out of specification.

The bacterial pre-production test determined the bacterial load incoming. This incoming characteristic cannot be altered for the cellular product and no changes occurred as a result. The information was added to the data file on the product. Bacterial testing was performed again on the final product. This last test, along with other assessments, was used to qualify the final product. The qualifying information was added to the data file and product label. Test results did not alter the product or the process.

Over processing is one of the eight types of wastes described in lean manufacturing (Womack, Jones, & Roos, 1990; Daley, 2003). Processing waste occurs when unnecessary steps and activities are performed. Rechecks, testing that adds no value, inefficiencies from improper manufacturing designs, and even producing higher quality products than customers are willing to pay for or is needed are common types of processing wastes. Daley (2003) notes that redundant activities are a primary source of processing wastes. W. Edward Deming in *Out of the Crisis* (1988) declared that quality cannot be tested into the product, but is achieved by design. The FDA reiterates this principle in their publication *FDA Quality concerns* (2001), noting that the FDA is concerned that industry inappropriately uses testing to document quality. Quality assurance in these industries was by documentation and not by design. The FDA goes on to reinforce that quality cannot be tested into products; it needs to be built in, which is quality by design (Massa, 2004). The uses of pre-tests, in conjunction with post-tests conducted in the manufacturing processes of this case study were redundant activities, illustrative of attempts at quality by test and not design. Pre-tests are one example of the type of waste in testing that adds no value to the product, as described by the lean

manufacturing philosophy. Application of lean manufacturing would eliminate non-value adding pre-tests.

Multiple record reviews waste. The production process consisted of several outputs of data that required supervisory, managerial, and other staff's reviews and assessments to include the medical director who was a licensed physician. The documentation and review process for bacterial testing consisted of multiple records.

Documentation of all initial positives for bacteria was entered into the organization's deviation management process utilizing the form depicted below in figure 16. A separate form was completed for each positive test that consisted of manual entries of more than 700 data points per month. There were supervisory reviews and signatures twice; the department director's reviews and signatures twice; quality assurance's reviews and signatures twice and then the medical director's review and signature. This process involved six different staff members to complete the form. The process included several hand-offs of the form, to include back-and-forth motions. Designated spaces to fill out were provided on the form; see figure 16 that follows. This manual form was used for record keeping of this process. There were spaces for description entries, tracking numbers, system requirements, corrective actions, product disposition and reviews. There was also a section for selection and description of the investigation into the cause of the test results which may or may not have been internal. Due to the data input on the one document by several different persons, the process consisted of wait times as one area of the form was completed by a group and transferred to another, with waiting occurring until the source for completion did so.

UNPLANNED DEVIATION/NONCONFORMITY REPORT

SECTION 1 – INITIATION DEVIATION REPORT #: DV_____

Dept. Deviation Discovered: _____ Date Discovered: _____

Deviation/Nonconformity: (What was the deviation/nonconformity?):

_____

_____

Requirement: (What is the requirement?):

_____

_____

Initiator: _____ Date: _____

Remedial Action/Correction: (What immediate action was taken to correct the deviation/nonconformity?):

_____

_____

Recommended Disposition of Product/Material:

☐ Continue Further Processing ☐ Reject ☐ Quarantine ☐ N/A

Lead Investigator: _____

Dept. Manager: _____ Date: _____

Technical Lab Director: _____ Date: _____

SECTION 2 – QUALITY ASSESSMENT

Has Product been distributed? ☐ Yes ☐ No ☐ N/A Event Code: _____

Quality Review: _____ Date:

_____

SECTION 3 – INVESTIGATION SUMMARY (Attach Deviation/Nonconformity Investigation Summary Form)

SECTION 4 – QUALITY REVIEW

☐ No Deviation Occurred Per Investigation ☐ Environmental ☐ Personnel ☐ Equipment
☐ Component/Material ☐ Specification ☐ Procedure ☐ Process ☐ Supplier ☐
Undetermined ☐ Other: Describe: _____

Final Disposition of Product/Material: ☐ Accepted ☐ Rejected ☐ N/A

Corrective Action Required? ☐ No ☐ Yes - See CAR #: _____

FDA Reportable ☐ No ☐ Yes _____ NY State Reportable ☐ No ☐ Yes (Reported_____)

Quality Review: _____ Date: _____

Medical Director Review: _____ Date: _____

Figure 16. Deviation report for bacterial investigation; numerous areas of data entry.

The manufacturing process averaged 30 positives per month which produced 30 separate forms with 210 signatures for the one process. This documentation system consisted of the processing waste of rechecks and/or reviews, redundant documentation and over handling. Application of lean manufacturing focused on elimination of the duplicate and different elements of this processing waste that included motion, transportation of the documents, and handling by the multiple sources. Reengineering of the documentation system would consist of standardization and changing from strictly manual records to electronic by application of an excel spreadsheet that captured the data daily. The reviews and signatures of the departmental director, quality assurance, and the medical director would be performed from one document. Thirty documents would be reduced to one and the 210 signatures reduced to four. Wastes associated with motion, transportation of the documents, and the multiple hand-offs of the records would also be eliminated and/or reduced as a result of moving to an electronic data management system.

Reagent waste – hespan. Another processing step with a finding of waste was with the use of the reagent hespan. Hespan is a liquid protein expander that was added to each biomaterial during the manufacturing process at a ratio of 1:5. The hespan added was 20% of the volume of the raw material to be processed. At the end of the production day the remaining reagent in the bag was discarded. A data collection form was created to further evaluate the use of this reagent; see figure 17 that follows.

Hespan reagent
Data Collection

Type of raw material: Hydroxyethyl Starch (Brand name: Hespan or HES)

Process: The biological raw material was processed using hydroxyl ethyl starch known as hespan to enrich for the total nucleated cell population to include the hematopoietic stem cells; $CD34^{+}$.

Volume	*Sample 1*	*Sample 2*	*Sample 3*
Volume (mL) of raw material	89	103	77
Volume of hespan used	17.8	20.6	15.4

Identify *waste, to include from defects, scrape, and rework*: At the end of the addition of HES, the remaining volume was discarded. HES was supplied in bags, 500mL per bag. If a tech used, for example, only 20mL out of the bag and it was the end of the day, meaning it was the end of processing for that day, the remaining hespan was discarded. Direct observation revealed that this practice was the standard work method.

Opportunities: Eliminate waste of the reagent HES

Identify which lean manufacturing strategies should be utilized for process improvement:

Kaizen	**X**	TPM	JIT
5S		1-piece flow	Control of variation

Justify strategy(s) selected: The rate of use of the reagent HES was not proportional to the amount purchased. HES was purchased and dispensed in 500mL bag. One bag per work station was dispensed. After production, at a rate of 10 units per station maximum, the remaining HES was discarded. Therefore, at an average of about 17.9 mL per unit, with 10 units, approximately 179 mL were used with 321 mL discarded. This work practice was also identified during direct observation of the process. Upon questioning why this was being done, answers were to avoid possibly of contamination. However, there was no evidence provided to support the conclusion.

Figure 17. Hespan data collection defines reagent usage and discard.

The hespan data collection, figure 17 that follows, describes the process for which the reagent was used. The form consists of data for three different shipments of biological raw material evaluated relative to the use of the reagent. The volume of the raw material was recorded as well as the volume of the hespan used which was added at a rate of 20% of the volume of the material. Hespan was supplied in 500 mL bags. An average of 17.9 mL of hespan was used per unit. Each work station was supplied with a separate bag of the hespan. The maximum processing capability of each work station was ten units of biomaterial per production day with an average usage of hespan per unit of 17.9 mL. The total amount of hespan used from the 500 mL bag was 179 mL. This resulted in the discard rate of 321 mL of hespan per station as recorded on the form.

These findings were also supported by direct observation of this work practice. Explanations for this type of waste was based on an unsupported assumption that if more than one work station used the same bag there would be cross contamination. There were no studies conducted to support this claim as well as no supportive literature provided. In addition, as previously described, the manufacturing process occurred in a clean room that includes consistent air filtration every 20 seconds and employed aseptic processing.

The maximum production rate for the facility was 50 units per processing day. Production consisted of the distribution of the 50 units among the five manufacturing cellular platforms, each processing ten units. The procedure was to use separate carts of manufacturing materials, each supplied with a 500 mL bag of the reagent. Each unit averaged 17.9 mL of reagent, for a total of 179 mL used out of the bag for the ten production units. The remainder of reagent, 500 mL - 179 mL or 321 mL was discarded at each of the five processors. This resulted in the daily discard of 1,605 mL of the

reagent hespan. However, the discard rate could be higher based on how production was distributed per workstation. For example, if there were 40 units to process and the work was distributed evenly among the five work stations, each 8 units, the rate of hespan used would be different. Each of the work stations would use about 143.2 mL, discarding 356 mL. Multiplied by 5, the discard would be 1784 mL per day. Variations in production volumes were constant, making the increasing waste of the reagent a part of the process. A change in the design of the process was required for improvement.

As noted in the last section of the data collection form, the lean strategy used as the basis for eliminating the waste of the reagent hespan, optimizing usage, was the continual process improvement of Kaizen. The process was redesigned, to include using smaller aliquots of the reagent, with distribution among the work stations. Elimination of this waste resulted in the proportional savings in reagent costs, quantified in the product cost analysis section. The elimination of the other wastes previously identified were also added to the assessment on product cost to evaluate accumulative cost reductions.

Raw Material Availability Evaluation

The relative research question is: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

A review of the completed general data collection form started the evaluation to determine the availability and usage of raw materials. Findings were recorded on the raw material collection form, figure 18 that follows.

Raw Material
Data Collection

Type of raw material: Biological raw material, umbilical cord blood (UCB)

Process: Manufacturing - The raw material was sampled prior to manufacturing into stem cells for pre-quality control (QC) tests that were repeated for final product quality control testing. Six milliliters (mL) of the raw materials were removed from each specimen.

Volume	*Sample 1*	*Sample 2*	*Sample 3*
Volume incoming (A)	205 ml	152	167
Volume removed for pre-QC testing (B)	6	6	6
Volume for manufacturing (C) = A – B	199	146	161

Identify waste, to include from defects, scrape, and rework: The production process removed 6-mL of the raw material from each unit for six different pre-QC tests. Five of the six tests were reworked at the end of the production process to qualify the final product. The pretest results did not alter the production process.

Opportunities: Reduce or eliminate use of incoming raw material for QC pretests.

Identify which lean manufacturing strategies should be utilized for process improvement:

Kaizen	X	TPM	JIT
5S		1-piece flow	Control of variation

Justify strategy(s) selected: Kaizen is the continual small incremental improvements made, adding value and eliminating waste, resulting in a synergy of significance. Application in evaluating the use of incoming material relative to availability for production was associated with an opportunity for incremental improvements.

Figure 18. Raw material data describes volumes before and after manufacturing.

Procedures were reassessed and work activities observed again, concentrating on those tasks where the stem cell raw materials were used to identify waste elimination opportunities. The completed raw material data collection form above, figure 18, describes the processes where the material was used to determine potentials to reduce or eliminate usage for a direct increase in availability. The finding was that the raw material was sampled prior to manufacturing for pre-quality control tests. A consistent 6-mL of the raw materials was removed from every unit or shipment prior to manufacturing. This is shown on the form in the volume table. The volume assessments for three different shipments, denoted as samples, were recorded on the form. Incoming volume, denoted as A, amount of raw material removed for QC pretests denoted as B, and the volume remaining for manufacturing into stem cells is denoted as C resulting from A minus B. Each sample was reduced by 6-mL for QC testing. An additional 712 records were reviewed showing that 6-mL was removed from each of the 712 shipments for QC pretests, reducing the amount of available raw material for stem cell production consistently.

The findings noted that 6-mL of the biological raw material removed was used for six different pre-quality control tests. Five of the six tests were duplicated at the end of the production process to qualify the final product. The use of the raw material for duplicate testing was identified as a potential waste elimination opportunity.

The end of the form lists common lean manufacturing strategies to select for process improvement. These are Kaizen, TPM, JIT, 5S, 1-piece flow and control of variation. The lean manufacturing strategy recorded on the form for evaluation of

reduction or elimination of waste of the raw material was Kaizen. Kaizen is the continual small incremental improvements made, adding value and eliminating waste, resulting in a synergy of significance.

1. The completed data collection forms which list processes and process steps were reviewed to identify the activities where the raw materials, from which the non-controversial stem cells were obtained, was used. Also, procedures were reassessed and work activities observed again, concentrating on those tasks where the stem cell raw materials were used to identify waste elimination opportunities.

Findings

Duplicate testing - quality control (QC)

A finding from the assessments was that the biological raw material was used in only one other aspect than manufacturing, in quality control testing. The production process removed 6-mL of the biological material from each shipment for quality control pretests. Another finding from the assessments was that the results of the tests were not used to affect processes or the product. The manufacturing process was not altered as a result of the tests and the test results were not used for direct product qualification. The QC tests were repeated at the end of production to qualify the product.

The 6-mL of raw biological material removed for QC pretests reduced the amount of raw material for producing stem cells proportionately. The findings included the determination that the pre-testing added no value; this was also supported by the fact that the tests were performed again, or reworked, after the stem cell product was made.

Analyses

The findings show that the biological raw material was used in only two processes which were manufacturing to produce the final stem cell pharmaceutical and quality control for pretests. Potential of increasing the amount of raw material available for manufacturing was with quality control pretests.

Six milliliters (mL) of the raw material were removed from the shipped unit, prior to manufacturing, for quality control pretests. These tests were referred to as pretests because they were performed a second time after the product was made for qualification. Six tests were performed from the 6-mL sample. The findings show that the tests were for pre-TNC, blood type, pre-stem cell count, pre-aerobic bacteria, pre-anaerobic bacteria, and pre-cell viability determination. Five of the six pretests were duplicated at the end of the production process as part of end stage testing to qualify the final product.

Four quality control pretests were conducted from 1-mL of the 6-mL sample. These tests were the pre-TNC, blood type, pre-stem cell count, and pre-viability determination. The one test for blood type was the only one of the four tests directly associated with the product, adding value. A finding was that the one test for blood type would require only a nominal, drop-wise amount of the raw material. The other three pretests for determining pre-TNC, pre-stem cell count and pre-cell viability were not directly associated with product evaluation.

The largest portion of the 6-mL sample, 85%, removed from the biological raw material was the 5-mL sample used for the pre-bacterial evaluation of sterility. Bacterial pretests required 1-mL of the raw biomaterial for aerobic bacterial testing and 4-mL for

anaerobic bacterial testing. These series of quality control tests were performed again as a part of the qualification of the final product. The findings show that the results of bacterial testing did not alter the production process. In addition, there could be no direct invention in the processing of the stem cell product to alter bacterial load incoming or outgoing due to risk to the cells and subsequent growth potential (CryoCell, 2006).

Records of the results of 712 quality control pretests were assessed to determine what was done with the test results. A finding from the evaluation of the data was that there were no manufacturing actions taken as a result of the test results. Interviews revealed that the pretests were intended to be used for staff evaluation to monitor and enhance their production techniques. As noted above, findings from a review of numerous production records revealed that these test results were not used. There was no data that identified a need for intervention since all results were well under action limits. It should also be noted that the managerial review to assess staff performance based on pre-test results occurred 60-days after testing. An intervention would not affect immediate production with changes going into affect no earlier than 180 days later due to procedural process change requirements. The findings were that there were no test results out of specification that required intervention.

The other utility of the pretest for bacterial evaluation was stated to determine the incoming bacterial load of the raw material to support the findings of the final tests. A finding noted that the incoming characteristics such as bacteria could not be altered for the cellular product and no changes occurred as a result (CryoCell, 2006). The findings were that the pretest results were only added to the data files on the products. The second

testing for bacteria that was performed again on the final product was the one that was used. Along with the other second set of quality control tests, these test results were used to qualify the final product. The qualifying information was added to both the data file and product label. However, a finding was none of the pretests results altered the product, the production process, or were used for labeling.

2. Manufacturing records were evaluated to determine starting volume and processed volume of the cells. These findings were recorded on the raw material data collection form. The differences were calculated to determine the volume of raw materials/stem cells used.

Findings

The findings from a review of 712 manufacturing records, representing 712 units of raw material, identified that 6-mL of the biological raw material were removed from each of the 712 shipments or units for pre-quality control testing. None of the pretests results were used; not for product qualification, or process adjustments, or staff interventions

Potential waste of raw materials/stem cells, identified from the above assessments, were recorded and described including possible opportunities to reduce the amount of stem cell raw material used.

Findings

The pre-QC testing consisted of six tests with five repeated after manufacturing to qualify the final product. A finding from assessments noted that none of the five repeated test results altered the manufacturing process, justifying elimination opportunities.

Therefore, the five pre-QC tests were identified as waste of the biological raw material needed for medical treatment.

3. Lean manufacturing strategies for process improvement were identified and protocols for implementation developed.

Analyses

The lean strategy to increase the amount and availability of the biological raw material for production of therapeutic stem cells was the elimination of duplicate QC testing. There were two sets of QC testing performed. The first was pre-QC testing before the manufacturing process, utilizing 6-mL of the raw material for six tests. The second testing set was after processing, repeating five of the six tests. Application of lean waste elimination proposed to eliminate the five pretests since the test results did not alter the manufacturing process. However, a finding from the literary review of the research was pharmaceutical testing included those required by regulatory agencies such as the FDA as well as accreditation organizations. An impact analysis was conducted to evaluate the affect of eliminating the waste of pretests relative to regulating, accrediting and certifying requirements.

Impact analyses of regulating requirements

Elimination of duplicate QC testing was identified as waste for elimination as an application of lean manufacturing in the production of non-controversial stem cell pharmaceuticals. The pharmaceutical industry is heavily regulated with major restraint viewed as impediments to change. A finding from the research was that changes proposed by lean waste elimination warranted the evaluation of regulatory requirements to be included in the research to determine the affect of waste elimination strategies.

A finding from the research was most federal regulatory oversight of the pharmaceutical industry was from FDA that specifies quality system requisites. Other governmental requirements included those from both state and local agencies. Governmental oversight and requirements were based on the type of organization and its product as classified by the regulating body. If an organization produced different products, the requirements were based on the more stringent, for tighter control and assurance. The organization that was the subject of this research produced one product.

An additional finding was that biopharmaceutical manufacturers may also be voluntarily accredited, registered, and/or certified by other quality system standards such as ISO, the International Organization for Standardization, by which they must comply. The organization of this case study was ISO certified, accredited by an industry standard from the American Association of Blood Banks (AABB) and was in the process of being accredited by an international industry standard from the Foundation for the Accreditation of Cellular Therapy (FACT). Proposed process changes must be in compliance with these regulating and accreditation bodies.

There were five different pre-manufacturing quality control tests identified as waste as a result of applying lean manufacturing waste elimination. Evaluation of the influence of implementing lean manufacturing and assessment of the affect proposed changes would have on regulating and accreditation standards required each standard to be comprehensively examined. Table 6 below summarizes regulatory compliance requirements relative to the proposed lean manufacturing waste elimination of the pre-tests. Table 7 summaries accrediting compliance requirements relative to proposed lean manufacturing waste elimination of the pretests.

Table 6.

Regulatory Requirements and Application of Lean

Test	FDA	State	Local	Current	Lean
Pre-TNC	No	No	No	Yes	No
Pre-CD34+	No	No	No	Yes	No
Pre-Viability	No	No	No	Yes	No
Pre-BacT Aerobic	No	No	No	Yes	No
Pre-BacT Anaerobic	No	No	No	Yes	No

The first column in the above table lists the pretests proposed for waste elimination. The next three columns denote whether the specific regulatory governmental agency, listed above the associated column, required the test to be performed. The last two columns identify the current process and the proposed process by application of lean waste elimination. The columns are labeled current and lean respectively. Results are denoted as *Yes* when there was a requirement by that agency/source or *No* when there was not.

Regulatory requirements were dependent upon the classification of the company or organization by its product types. The organization of this case study was classified as a manufacturer of cord hematopoietic stem/progenitor cells for autologous (self) use, or use in a first- or second-degree blood relative per FDA. State and local classifications were aligned with federal, FDA. The findings from the regulatory assessment were that

all of the pretests slated for waste elimination by application of lean manufacturing because they did not add value to the product were also not required by governmental regulating agencies.

Requirements by accrediting organizations and industry standards are listed in Table 7 that follows. There are three such agencies consisting of requirements by ISO, the AABB, and FACT. The first column of the table below lists the pretests proposed for waste elimination from lean manufacturing. The other five columns denote whether the specific agency or source, listed above the associated column, required the test to be performed. Results are denoted as *Yes* when there was a requirement or *No* when there was not. The highlighted cells in the table above identify those elements that conflict between proposed waste elimination strategies and accreditation requirements. There were five pre-tests identified as non-value adding waste for elimination by the application of lean manufacturing. The findings show that one of those tests, the pre-TNC, was required by one of the three accreditation bodies, that of the AABB. All of the other pretests slated for elimination were also not required by accrediting organizations. See Table 7 that follows.

Table 7.

Accreditation Requirements and Application of Lean

Test	FDA	State	Local	Current	Lean
Pre-TNC	No	**Yes**	No	Yes	**No**
Pre-CD34+	No	No	No	Yes	No
Pre-Viability	No	No	No	Yes	No
Pre-BacT Aerobic	No	No	No	Yes	No
Pre-BacT Anaerobic	No	No	No	Yes	No

There were two options for the organization in addressing the one conflict between the proposed lean manufacturing waste elimination strategies and the AABB. The organization could request from the accrediting body a variance to eliminate the pretest citing specific validated reasons in justification. The other option was to sustain the accrediting standard, continuing to perform the one conflicting pretest and eliminating the others.

4. The difference between the volumes of stem cells/raw materials used before proposed process changes and after were quantified. The significance of the difference was determined by statistically evaluating the two population means using ANOVA to answer the following null and alternative hypotheses.

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of

available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Findings

A statistical analysis of factorial design using a one-way ANOVA was used to assess the significance of the differences of the mean volume of raw materials before and after process interventions by application of lean manufacturing principles of waste elimination to answer the null and alternative hypotheses. ANOVA tests the differences of the means of test data to determine significance. If the differences are significant, the null hypothesis can be rejected. The data output of that analysis is presented in Appendix B. The results show that the significance of the change in the amount of available raw biomaterial for processing after application of lean manufacturing was determined to be 0.000. Since this value is less than the set significance level of 0.05, the null hypothesis of no significant difference was rejected. The findings show the amount of available biological raw material after application of waste elimination from lean manufacturing was significantly greater than the amount of raw materials before application of lean.

5. A statistical analysis of factorial design using a one-way ANOVA was used to assess the significant differences in the means of materials before and after process interventions by application of lean manufacturing principles of waste

elimination to answer the null and alternative hypotheses. A paired t-test was used to further evaluate statistical significance.

Findings

The results of the ANOVA were significant as noted above. A paired t-test statistical analysis was conducted to further assess the significance of the increase in the amount of raw material after the application of lean waste elimination. A paired t-test was used to evaluate the relationship of the amount of raw material before and after lean waste elimination. The output of the analyses is presented in figure 19 that follows.

The result of the significance is located in the last column, identified by the notation of Sig. under which is the result of zero (.000). This value is less than the set significance level of 0.05, denoting that the difference in samples before application of lean waste elimination and the samples after is significant. This finding shows that the increase in the amount of available biological raw material after application of lean waste elimination is statistically significant. The results of the paired t-test supports the results of the ANOVA finding, both determining that the increase was significant.

Paired Samples T Test

		Paired Differences					T	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair	Control & Test	6.15385	1.46039	.20252	6.56042	5.74727	30.386	51	.000

Figure 19. Paired t-test show that lean waste elimination was significant (Sig.).

Product Cost Evaluation

The relative research question: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Determination of the product cost

Basic product cost is a combination of the cost of goods used to manufacture the product, labor utilized, equipment, utilities, facilities, and expected minimum profit margin (Brierley, Cowton, & Drury, 2001). Jones (1991) defines primary product costs as fixed and direct costs. Fixed costs are those with limited variability such as the cost of the facility, utilities, and equipment. Direct costs are the costs of goods or materials used to produce the final product and the labor required to change those materials into the final product. Holding fixed costs constant, to include profit margin or return on investment, product cost can be evaluated based on its variable direct costs of labor and material used to product of unit of product.

The first research question of this study addressed the influence of waste elimination from lean manufacturing on product costs. Product costs have been defined as the cost of labor and materials or supplies used to manufacture the product. These costs were evaluated separately, and subsequently combined, presented as a cumulative affect of lean manufacturing on product cost as described below, starting with assessment of labor costs influenced by lean.

Labor costs were those applicable to the human resources necessary to produce a unit of product. This study limited the assessment of labor costs to those expenditures directly associated with product manufacture and does not include non-related administrative or support labor costs such as accounting, marketing, and unrelated management functions. Labor costs assessed were relative to productivity, per product.

Productivity is a relationship between outputs and inputs which is increased by generating higher outputs to inputs (iSixSigma, 2007). Enhancing productivity results in, for example, less rework, less time, elimination of duplicity, and optimal use of resources (Lewis, 2002). Optimization of productivity occurs with the better possible measured outputs and measured inputs, for a ratio of the two measures. Improvement in this productivity ratio is achieved by decreasing the input to output ratio (iSixSigma, 2007). Either input or output change would also cause a change in the resulting ratio, affecting productivity and therefore labor costs associated with product costs. An increase in input, with output unchanged, would decrease productivity. An increase in output, with input unchanged, would increase productivity.

Direct inputs associated with product costs in this research were supplies and labor used to produce the output or unit of stem cell product pharmaceutical.

Productivity was increased when the direct costs of supplies and labor decreased. These product costs are delineated further below. Presented first is the numbered methodology, as defined in chapter 3 of this research, used in the evaluation of product costs.

1. The cost of the stem cell pharmaceutical product was evaluated by delineating costs of reagents, supplies, and labor per unit, documented on the product cost data collection form in figure 20. Process steps were characterized, recording the operation, the materials used to include volume or amount, as well as the type of equipment utilized for the process operation. The information was recorded on the product cost data collection form, figure 20 that follows.

Findings

Review of the product cost collection form

The product cost data collection form, figure 20, identifies the findings of four costs that makeup the cost of the product: reagents, supplies, labor, and miscellaneous. The latter was defined as negligible costs from miscellaneous items with the other three costs as the primary costs of the product. Reagents listed are hespan and the DMSO/Dextran mixture. Plastic bins, lids, sample storage bags, bacterial (BacT) testing bottles, and metal cassettes were listed as supplies. Labor cost differentiates the pay for the levels of labor consisting of technologists (Tech), production management, and a physician. These labor costs were standardized to a single rate of $56 per hour based on the accounting practices of the organization that was the subject of this case study.

Product cost

Data Collection

Unit description: Production process of non-controversial stem cell pharmaceuticals-incoming assessment, manufacturing, storage bins/lids, reagents, labor, supplies, cryopreservation freeze.

Costs

Reagents	Supplies	Labor	Miscellaneous
Hespan – Average 17.9 mL/unit at 20% of product volume; 1:5 ratio; DMSO /Dextran	Plastic bins, lids, BacT bottles, gauze; sample storage bags; metal cassettes.	$26/hr Tech; $60/Mgmt; $180/hr physician; $56/hr total equivalent	Negligible use of alcohol spray, pipette tips, etc.

Determine *value*: unique product identification, separation of biological raw material into pharmaceutical stem cells, final product qualification testing, and cryopreservation freeze storage.

What is the *value stream*? Incoming inspection and assembly, data entry and product labeling, manufacturing by density gradient centrifugation and separation, microbiological final qualification testing, cryopreservation deep freeze final storage.

Determine and record material *flow*: receiving of shipment, assembly, processing which included sampling for pre-QC tests and manufacturing by centrifugation, prep for final storage, cryopreservation deep freeze final storage.

Evaluate *pull*: Manufacturing was a *pull* process-production started only at incoming of the raw material shipment from customer to manufacturer; no customer *pull,* no manufacturing.

	Operation 1	*Operation 2*	*Operation 3*
Man hours (hr)	Domestic=5 m =.083hr Int. = 17 m = .283 hr	2 hours BacT	BacT record review: MTech 0.5; Mgmt 1; Physician .2
Cost per hour	Domestic = $2.17 Int. = $7.36	$56	$60/Mgmt; $180/hr Physician; $56/hr equivalent

Identify *waste*: variation-data entry; discarded bins & lids; duplicate testing; reagent waste-hespan; multiplicity-record reviews, signatures by techs, supervisors, directors, and physician.

From the above examination, define system *perfection*: reduction in record reviews; standardization data entry; optimization-hespan reagent; elimination of duplicate testing; recycle bins & lids.

Identify which lean manufacturing strategies should be utilized for process improvement:

Kaizen	X	TPM		JIT	
5S	X	1-piece flow		Control of variation	X

Justify strategy(s) selected: Kaizen–improvement in BacT testing, record reviews, data entry, hespan optimization, bins & lids. 5S–put in order and standardized record reviews that included improvement from record generation, reviews, and signatures of 30 different records by the expensive management group. Control of variation-differences in data entry requirements, domestic vs international shipments caused wait times, additional data entry points and labor costs; standardize process to control variation. Note: operation 1-data entry; operation 2- testing; operation 3- reviews.

Figure 20. Product cost data details costs of reagents, supplies, labor.

The product cost data collection form continues by defining the stem cell product's manufacturing process value and value stream relative to the lean philosophy. The findings show that these values for the product consisted of unique product identification, separation of the biological raw material into pharmaceutical stem cells, final product qualification and cryopreservation deep freeze storage. The value stream of the production process was the incoming inspection and assembly, data entry and product labeling, manufacturing by density gradient centrifugation and separation, microbiological and analytical qualification testing, and cryopreservation deep freeze final storage at -190º C.

The next element in the lean manufacturing process to perfection was to understand the flow of the product. The production process of these non-controversial stem cell pharmaceuticals flowed from receiving of the shipment of the biological raw material to assembly and data entry. Processing, which included sampling for pre-QC tests and manufacturing by centrifugation followed. The end stages of production flow were the preparations for storage, cryopreservation deep freeze, and storage of the final stem cell product.

The pull element of lean manufacturing waste elimination described initiation of manufacturing when the customer shipped the raw material. There was no pushing of the product on the customer from an inventory of waiting products. The production process of these types of stem cell pharmaceuticals was inherently by a pull process. Production started only at receipt of the biological raw material shipment from the customer to the manufacturer. If there was no customer *pull* by shipping of the raw material to the manufacturer, production did not and could not occur.

The completed product cost data collection form, figure 20, further delineates the findings of labor costs into man hours and associated costs per hour for three operations where wastes were identified. The findings are listed below.

Waste identified

- Variations in data entry caused increased processing time.
- Duplicate QC testing to include BacT, TNC, CD34+, viability.
- Discards of bins and lids; hespan reagent waste
- Multiplicity in record reviews within the BacT process.

The lean manufacturing strategies for the elimination of the wastes found were Kaizen, 5S, and control of variation. Variances in the data entry requirements for domestic versus international shipments caused wait time delays, additional data entry and labor costs. Control of variation by process standardization was the strategy employed for elimination of this type of waste. The elimination of duplicate testing, optimization of the use of hespan, and ending the discard of the supplies of bins and lids apply directly to the strategy of continuous, incremental improvements from Kaizen. The strategy of 5S would sort, set in order, and standardize record reviews in the BacT process. Improvements would consist of reducing the number of records, reviews, and signatures of 30 different records by the expensive management group.

The data collection form denotes the waste of supplies separately and the manufacturing processes by operation where wastes were found:

Operation 1 = Data entry

Operation 2 = Testing

Operation 3 = Reviews

Operation 1, data entry of domestic versus international (Int.) shipments, on figure 20, show the finding of the differences in data entry times and labor costs at the $56 equivalent for the two different shipments:

Time/Cost Domestic = 5 m (minutes) = 0.083 hr = $2.17

International = 17 m (minutes) = 0.283 hr = $7.36

Operation 2 for BacT testing required 2-hours of labor at $56 per hour. Operation 3 for record reviews consisted of the findings of the labor costs of the medical technologist (MTech) at 0.5 hours, management (Mgmt) review of 1-hour (hr) at $60/hr and the physician's review of 0.2-hour at $180/hr. The equivalent cost was established by accounting for all activities as $56 per hour.

Analyses

The manufacturing process of this case study began with the receipt of raw biomaterial for processing at the assembly area. Materials were sorted, bags cleaned and trimmed of excess hanging tubing, and data entered into the computer system. Findings from the assessment of the assembly process to identify waste in applying lean manufacturing determined that the data entry steps varied between domestic and international shipments.

Data inputs common to both shipments were material identifications and the collection dates and times. These input elements completed the data entry process at the assembly stage for domestic shipments. Internationals required additional inputs at the assembly stage negatively increasing the assembly process time and associated labor costs applicable to the product cost. As noted, the additional information was the same for domestics; the point and source of data entry were different.

The additional information of data entry for domestic shipments was entered into the computer system at the time the service was ordered by the customer. These data entry processes for domestic shipments occurred well prior to material receipt, as early as six months prior with an average of two months before shipment. International data for entry was recorded manually on paper that was shipped with the biomaterial for processing. The data was entered into the computer system by production staff at the time of receipt with the biomaterial to be processed. This portion of the data entry process for domestic shipments was not performed by production staff but was conducted by order takers from the sales service staff that performed this function routinely. Table 4, above in the general data collection section, shows the differences between data entry of domestic shipments compared with international data entry points. Domestic data entry required 15 data points whereas internationals consisted of 108. The difference, 108-15, was that 93 additional data points were entered into the computer system at production for internationals.

The average production time required to enter data for domestics was 5-minutes whereas for internationals it was 17-minutes. The difference, 17-5, was that 12 additional minutes were needed to enter data into the computer system for each international unit compared to domestic. The findings of production differences between data entry for internationals compared to domestics were an additional 93 points and 12 minutes of process wastes for each unit impeding production flow between domestic and international shipments.

Application of lean manufacturing waste elimination removed the processing waste caused by the differences in data entry of international and domestic shipments.

The extra data entry for internationals was moved out of production to the area where this data entry was routinely performed. Productivity was increased by removing 12-minutes of input processing time, or labor costs, due to the 93 points of additional data entry. The removal also resulted in enhanced production flow.

The findings show that the influence of lean manufacturing waste elimination was an improvement in productivity that translated to a decrease in labor costs. A manufacturing process is improved when the productivity ratio of input to output is increased by decreasing the input. Productivity is the cost of the labor utilized (iSixSigma, 2007). The productivity ratio of the data entry process is a relationship between the times required, as labor costs, for data entry as the input, with the output the number of units processed per the time interval.

Before application of lean manufacturing waste elimination, the productivity ratio of domestic shipments compared to internationals was determined as follows. Different productivity ratios denoted for domestic and international shipments are due to the variation of the processes before application of lean. Times are labor costs per unit of product for the data entry processes.

Productivity before application of lean manufacturing

Domestic = Input / output = 5 minutes (m) / unit

International = Input / output = 17 minutes (m) / unit

The overall production capacity for the facility was 50 units per day with an international shipment average of 10% or 5 of the 50 units; 45 units domestic, 5 international. Daily labor costs for the assembly processing time for the shipment mixture, before application of lean, were determined as noted in the following.

Domestic = 45 units times 5 minutes/unit = 225 minutes

International = 5 units times 17 minutes/unit = 85 minutes

Total = 310 minutes of labor costs

Productivity after application of lean manufacturing:

Domestic = Input / output = 5 minutes (m) / unit

International = Input / output = 5 minutes (m) / unit

As a result of lean manufacturing waste elimination the data entry process for domestic and international shipments were standardized. The results for an overall production capacity of 50 units per day, with 10% internationals, follow.

Domestic = 45 units times 5 minutes/unit = 225 minutes

International = 5 units times 5 minutes/unit = 25 minutes

Total = 250 minutes of labor costs

In order to improve productivity the ratio of input to output should be improved by a decrease in input to output. The findings show that the process before application of lean required 310 minutes of labor costs for data input for a maximum output of 50 units per day. After application of lean waste elimination the input was decreased from 310 minutes of labor costs to 250 minutes. The input to output ratio before lean was 310: 50 or 6.2:1; after, the ratio was 250:50 or 5:1. Application of lean manufacturing waste elimination decreased the labor costs for the data entry process by 20%.

Product costs were also affected by a decrease in materials used in the production process (iSixSigma, 2007). The pre-bacterial testing was identified as a waste for elimination due to it being non-value adding testing duplicity because of additional bacterial testing at end processing that qualified the product and since there was no

actions taken as a result of the pre-bacterial test results. Elimination of the pre-tests cut the materials used by 50%. The application of lean manufacturing reduced the pre-testing that utilized two specially designed bacterial detection bottles, categorized as goods or supplies used in the manufacturing process. Each designer bottle carried a cost of $4.37. The findings show that a daily savings, at maximum production of 50 units per day resulted in $437; weekly savings would be $2,185; monthly $8,740 and a savings of $104,880 each year for this one waste elimination.

This productivity model from elimination of pre-bacterial testing can also be expressed as a decrease in input to output. The input of four bacterial tests, 2-pre and 2-post decreased to the two different post tests. Application of lean manufacturing waste elimination increased the productivity of bacterial testing by 50%. In addition, findings show that the associated bacterial identification determination or confirmation process, whereby bacterial positives were shipped out to a contracted laboratory, proportionately decreased by 50%. The time involved as labor cost in bacterial testing, and for other eliminated pre-tests as well as additional tasks to include sampling, handling, incubation, microbial identification, and record reviews also decreased labor costs. These labor cost inputs were reduced by 50% as a result of the application of lean waste elimination.

Bacterial testing results required additional supervisory review and assessment that included the medical director, a licensed physician. Documentation of all initial positives were entered into the organization's deviation management system. An individual record was generated for each positive. The records consisted of manual entries of more than 700 data points per month. Supervisory review and signatures occurred twice per record, as well as the department director's reviews and signatures

twice, and the quality assurance review and double sign-off. The medical director also reviewed each separate record and signed off. The process averaged 30 individual forms each month that resulted in the generation of 210 signatures for the one process. Findings from the assessment for application of lean manufacturing waste elimination determined that this documentation system consisted of processing wastes of rechecks and reviews, redundant documentation, and over handling. Implementation of lean manufacturing eliminated these different elements of processing waste. The system of documentation would be reengineered from a strictly manual paper system to electronic by application of an excel spreadsheet capturing the data daily. Review by the supervisor continued to occur daily as this is a standard work process of the supervisor to assess test results. However, reviews and signatures by the departmental director, quality assurance, and the medical director would be performed from one document. Application of lean manufacturing waste elimination resulted in a process enhancement from 30 separate documents to one and from 210 signatures to four for a resulting labor cost reduction.

Improvement in the documentation system was due to a decrease in inputs from 210 signatures to 4. The 30 records were reduced to the one. Increases in productivity can be qualified as a reduction in the ratio of inputs to outputs from 210:30 to 4:1 as a result of the application of lean manufacturing waste elimination. Reducing the number of records from 30 to one realized a 97% increase in productivity. A 98% increase in productivity was obtained by reducing the number of signatures from 210 to 4 through the application of lean waste elimination providing the associated decrease in labor costs.

Application of lean manufacturing also optimized the use of the reagent hespan. Hespan was added to each biomaterial at a ratio of 1:5 or 20% with an average of 17.9

mL of hespan used per unit/biomaterial. Each work station was being supplied with a separate bag of the hespan aliquot in 500 mL bags. Maximum production capacity per workstation was ten units, therefore using 179 mL of hespan out of the 500 mL bag. The rest of the reagent in the bag was discarded after use. The discarded or wasted amount per work station was 321 mL per day. As previously noted, this finding of waste was also supported by direct observation of the work practice. Reasoning for this waste was based on an unsupported hypothesis that if more than one work station used the same bag there would be cross contamination. No studies were conducted to support the claim of risk as well as no supportive literature was provided. In addition, the manufacturing process was performed using aseptic techniques in a Class 10,000 clean room that included consistent air filtration every 20 seconds. Findings from benchmarking efforts also revealed that other manufacturers did not follow this practice of discarding the remaining reagent and their production practice did not result in cross contamination.

The application of lean manufacturing eliminated the waste of the hespan resulting in optimization of reagent usage. The discard rate of the reagent hespan for a maximum production rate of 50 units per processing day was 1,605 mL. Elimination of this waste resulted in the proportional savings in reagent costs, noted below, and to the reduction in product cost from the reduced usage of the reagent.

Increased utilization of the reagent hespan realized the following cost reduction findings. Hespan was purchased in 500 mL bags at a cost of $0.41 mL. The production process before application of lean used a maximum of 179 mL from the 500 mL bag, discarding the rest of the reagent for a reagent/hespan cost of $1.15 mL. Application of lean manufacturing waste elimination optimized reagent usage to the direct cost of $0.41

mL. The cost of the reagent was thereby reduced from $1.15/mL to $0.41/mL for an enhancement of 280%. Saving per day equals $658, per week $3290; $13,161 a month and an annually savings of $157,932. Of note, the annual savings in costs from the elimination of waste of the reagent and bacterial testing bottles alone is over $262,812.

2. Waste identified from the above assessments of product cost, raw materials, and from the general data collection activity were factors used in evaluating product cost reductions with the following findings.

Findings – wastes identified

- Time – data entry
- Discard of bins and lids
- Duplicate QC testing
- Hespan reagent
- Biological raw material as a result of duplicate testing
- Associated labor costs

3. Lean manufacturing strategies for process improvement were identified and protocols for application developed.

Results

Kaizen, 5S, and control of variation were the lean manufacturing strategies used for the elimination of the wastes identified. The Kaizen strategy of continuous, incremental improvements was the foundation for waste elimination that included optimization of the reagent hespan. Data entry requirements for domestic versus international shipments were standardized from the strategy of control of variation. The elimination of duplicate testing and discarding the supplies of bins and lids were

strategies of continual improvement. The 5S strategy standardized record reviews. Control of variation by process standardization was the common strategy employed for waste elimination and development of application protocols.

Research methods 4 & 5

Research methods four and five are presented below with the findings at the end. The results were combined to present details of the product cost reductions and the summation following.

4. Wastes eliminated were tallied and associated costs applied. The sum of the cost savings generated from elimination of waste was subtracted from the cost per unit before process changes occurred to eliminate the waste. The results were defined as reductions in cost per unit due to application of lean waste elimination.
5. The costs of production, after improvements, were evaluated by delineating costs of reagents, supplies, and labor per unit produced; see Table 8 below.

Table 8.

Product Cost Reductions

Item	Cost before lean	Cost after lean
BacT bottles used	$17.48	$8.74
Hespan reagent	20.59	7.34
BacT confirmation testing	30.00 (per unit= negligible, 0.60)	15.00
Total	$516.07	$366.08
Per unit/product	$486.07	$351.08

Findings

$486.07 - $351.08 = $134.99 was reduced per unit as a result of lean waste elimination. The findings show that the cost of the product was reduced by 28%.

6. Research methods 6, 6.1-6.12

The research methods denoted as 6, 6.1-6.12 in chapter 3 involved assessments of productivity evaluating the associated labor costs applicable to evaluation of the affect of waste elimination from lean manufacturing on product costs. Parameters included process evaluation, cycle times and WIP to delineate associated labor costs.

Findings from the research determined that takt time which is a measure of the rate at which a product needs to be finished to meet customer demand, was not applicable

to this type of product. Customers submitted the biological raw material for manufacture into stem cell pharmaceuticals for a repository of stem cells for potential use in the future. The demand for the product was based on a possible prospective future medical need and not at the end of production as prescribed by the assessment for takt. The defining and limiting factor that specifies the end of production of the product, ready for distribution to the customer based on their need for usage, for application of takt time in the production process renders this measure not applicable to this product type.

Relative to the assessment of distance traveled by employees in the performance of process steps, these were eliminated from the assessment. Equipment locations were based on power needs of the specialty systems and also the finding that the cellular manufacturing layout used was already the most conducive for lean manufacturing. The lean manufacturing principles and strategies, described in detail in chapter 2, identifies the production layout of the cellular design as the more advantageous for application of lean manufacturing. As a result, the research methods for 6, 6.1-6.12 were combined to present details of productivity evaluated as labor costs relative to product cost reductions as follows.

Figure 21 that follows contains the productivity data collected to evaluate labor costs relative to producing a unit of product. The information starts at the beginning of the process, at incoming of the raw material to be produced into pharmaceutical stem cells. The collected information ends at the record review process. A comprehensive discussion of the data collected follows figure 21.

Productivity
Data Collection

Processes: Incoming data entry was denoted as "1)"; bacterial testing review "2)."
1) Data entry-incoming 2). Generation, review, resolution bacterial testing documents.

Materials used: 1) Collection records 2) ID records, testing results, reports.

Determine process *value*: 1). ID & tracking 2). ID & reporting of potentially contaminating microorganisms.

What is the *value stream*? 1). Data review; data entry 2).Sampling, testing, evaluation, reporting.

Determine and record material *flow*: 1). Customer collection & shipping; manufacturer's receipt, inspection, data entry. 2). Each specimen was sampled twice for bacterial testing – prior to the beginning of manufacturing and after prior to freeze at final storage. Two sets of test results for each specimen obtained. Additional confirmatory testing when the initial positive. The confirmatory testing-verification of the specimen as positive; if so ID of positive microbe. Affect of antibiotics on the identified contaminating microbe finalized confirmatory testing. Testing results were reviewed and evaluated at four levels: supervisor, lab director, QA director, MD.

Process/Operation	*Sample 1*		*Sample 2*		*Sample 3*	
	Cycle Time	WIP	Cycle Time	WIP	Cycle Time	WIP
1. Data entry	19.2 m	2.2m	24.4	7.4m	17.9m	9.9m
2a. Record reviews - supervisors, QA	185m	36m	290m	72m	211m	66m
2b. Record reviews-MD	35m	1080m	17m	600m	25m	120m

Evaluate *pull*: 1) Pulled by customer. 2). Test results pulled; record reviews pushed.

Identify *waste, to include from defects, scrape, rework*:
1) Variations in the data entry processes for domestic and international shipments. Data entry for domestic took 5 minutes (m) and 17 m for internationals.
2) The record review of test results for BacT included large amounts of WIP whereby results lay in wait to be worked on. There were five types of staff that reviewed the records, in between which were extensive waiting times. Last review-medical director who came once per week; records waited.

Opportunities: 1) Standardization- data entry. 2) Re-engineering of record reviews.

Identify which lean manufacturing strategies for process improvement:

Kaizen	X	TPM		JIT	
5S	X	1-piece flow		Control of variation	X

Justify strategy(s) selected: Kaizen-improvement in the data entry & each step of review process. 5S for data entry & streamlining, set-in-place, sorting, & standardizing the review process. Control of variation for standardization of both processes.

Figure 21. Productivity data for data entry and record review processes show variations.

Productivity

Cycle times and WIP were evaluated for those primary processes where time wastes were identified affecting productivity as labor costs. These are denoted in figure 21 above..

Findings

The two work processes of data entry at the incoming assembly process and record reviews of BacT test results were assessed. A productivity data collection form was used to document the evaluation; see figure 21.

Review of the productivity data collection form

The form includes the description of materials used and consist of findings relative to process value. Item number 1) was used to denote information data regarding the data entry process and item number 2) denoted the record review process. The process value for the data entry was defined as the purpose of the data that was entered which was to identify and track the raw material or incoming shipment. The process value for record review was the identification and reporting of any contaminating microorganisms.

The next sections of the information on the productivity data collection form defines the value stream and internal *pull* for each process. Data entry started with the review of data and correct entry into the database. Pull was directly by the customer as a result of them shipping the raw material to be manufactured. For record reviews the value stream was sampling of the raw material for analyses, testing, reviewing and then

reporting the findings. The record review process was more of a push activity than pull in that test results were pushed to the reviewer. This caused wait times resulting in WIP.

The table in the middle of the data collection form is the statistics of cycle time and WIP evaluated for three different samples of the two operations. The review process was separated into two parts resulting in a total of three operations recorded. Time was measured in minutes (m).

Analyses

The statistics, table in figure 21, show that the cycle and WIP times varied for all operations. There was more consistency in the cycle times than WIP. The WIP times for the record review by the M.D. were the greatest, with the largest 1080 minutes or 18 hours. Findings from the investigation of the process determined that the records for review by the M.D. waited until there was time by the reviewer to do so. This was true for all of the WIP and cycle time variability in the record review process. As noted, a separate individual record was generated for each test result requiring each reviewer to evaluate each separately with 30 records or more, including attachments, per month.

The variations in data entry times were due to the differences in requirements of domestic and international shipments. The larger data entry times were those for international shipments resulting in a type of change over WIP and increased cycle times.

The findings for both the activities of data entry and record reviews show variations from one sample to the other throughout the processes. The lean manufacturing strategy for improvement were control of variation and 5S organization with Kaizen as the foundation for these incremental, continuous improvement elements.

Control of variation was used to standardize the data entry process. Prior to the application of lean manufacturing waste elimination by variation control, the average data entry time for domestic shipments was 5-minutes and for internationals the time was 17-minutes. The differences were due to the type of information that was entered into the database at the incoming material assembly process at production. This portion of data entry was moved out of production to the routine data entry staff standardizing this activity as illustrated below.

Productivity before application of lean manufacturing

Domestic = Input / output = 5 minutes (m) / unit

International = Input / output = 17 minutes (m) / unit

Productivity after application of lean manufacturing:

Domestic = Input / output = 5 minutes (m) / unit

International = Input / output = 5 minutes (m) / unit

These enhancements resulted in standardized cycle times of 5-minutes for both types of shipments. WIP was removed, eliminating the change over requirements from domestic to international shipments.

The record review process would be improved by reducing the number of records to review by the 5S lean strategy and standardization to control variation and reduce WIP. An average of 30 manual records were generated with 210 signatures for the one process. A redesign of the documentation system consisted of changing from manual paper records to electronic by application of an excel spreadsheet that captured the data daily. Reviews and signatures of the departmental director, QA, and the medical director

would be performed from one document. Thirty documents would be reduced to one and the 210 signatures reduced to four, reducing cycle times.

The record review process would change from more of a push activity to a pull process. Instead of the records being manually forwarded to each reviewer, the reviewers would pull the electronic records from the database when they were ready to review them, reducing waiting WIP. Product cost evaluations relative to productivity associated with labor costs were determined as follows.

Findings

Organizational estimates for labor production costs were calculated at a standard of $56.00 per hour. Each shipment or customer order is quantified at eight hours per day to process. Application of lean manufacturing waste elimination results in the following specific labor cost reduction findings.

- Reengineering of the documentation system for bacterial assessment - Improvement in productivity as labor costs in the documentation system was due to a decrease in inputs from 210 signatures to 4. Thirty records were reduced to one. Labor costs associated with this activity was based on the time required to generate, compile and assess each record by each staff person to include managers, directors, quality assurance, and medical director. The time required for the activity before and after application of lean manufacturing was determined. Before lean the activity was calculated as requiring 0.225 hrs; after lean 0.133 hours. The process was reduced by approximately 41% in labor costs. In addition, a 50% reduction in work for

this activity was also realized by the influence of lean manufacturing waste elimination. The pretests were eliminated, cutting that work activity in half.

- Elimination of pre-sampling - Obtaining samples for the six pretests and associated handling were eliminated. Labor required for the sampling activity was determined to require 0.83 hours for maximum production.
- Data entries specific to internationals eliminated - Lean manufacturing application eliminated the processing waste caused by the differences in data entry of international and domestic shipments. The extra data entry for internationals was moved out of production to the area where the data entry was routinely performed. Labor required for data entry and handling of domestic and internationals shipments per day for maximum capacity, before application of lean manufacturing, was determined to require 5.167 hrs. After implementation of lean manufacturing waste elimination labor requirements as costs were reduced to 4.167 hrs. The influence of lean resulted in a decrease in labor by one hour for this process. Labor costs for production and all association activities were standardized by the organization at $56.00 per hour. Qualified, the influence of lean reduced the cost of this activity by 21%.
- Costs of external confirmation results – When a sample was positive for the bacterial test, it was externally shipped out to another vendor or supplier laboratory for confirmation testing. The confirmation test consisted of identification of the type of microbe and determination of its sensitivity to applied antibiotics. The cost of each test averaged $30.00; with 30 positives

per month the cost for this supplier was $900.00 per month. Daily costs were estimated at $30.00. The influence of lean manufacturing reduced the confirmation testing by 50%, quantified as a reduction from $30 per day to $15. This activity included labor costs that were also reduced 50% as well as the supplier costs.

Product costs

Table 9 that follows contains the details of the findings on product costs affected by waste elimination from application of lean. Process findings have been added as well. The methodology by which costs were determined are specified in the table. Product cost (P) for this research was defined as the sum total of the direct cost of reagents (R), supplies (S), and labor (L): $P = R + S + L$. Samples of the manufacturing process were taken to make this determination. Measurements of production processes before and after application of waste elimination from lean manufacturing were conducted. Increases in productivity, reducing labor costs, realized from lean were applied to product cost assessments, with time in hours quantified into labor costs (dollars/hrs).

Additional cost measures were savings in the cost of reagents used in a unit of product, categorized as supplies. The number of records for review and duplicate testing were cost measures in the categories of both labor costs and supplies. These measurements of the cost to manufacture the product before the application of waste elimination from lean manufacturing and after the application of waste elimination from lean manufacturing were used to test or evaluate results. The findings are clarified in the table that follows.

Table 9.

Product costs

Item	Description
Product cost (P)	$P = R + S + L$ The direct cost of reagents (R), supplies (S), and labor (L).
Cost before lean (P_0)	$P_0 = R_0 + S_0 + L_0$ Where: P_0 = Product cost before lean R_0 = Reagent cost before lean = \$20.59 S_0 = Cost of supplies before = \$17.48 L_0 = Labor cost before lean = \$448.00 $P_0 = \$20.59 + \$17.48 + \$448.00$ $P_0 = \$486.07$
Cost after lean (P_L):	$P_L = R_L + S_L + L_L$ Where: P_L = Product cost after lean R_L = Reagent cost after lean = \$7.34 S_L = Cost of supplies after lean = \$8.74 L_L = Labor cost after lean = \$335.00 $P_L = \$7.34 + \$8.74 + \$335.00$ $P_L = \$351.08$

If the product cost before lean, P_0, is greater than the product cost after lean, P_L, or $\mathbf{P_0 > P_L}$ then the application of waste elimination from lean manufacturing reduced product costs. Since $P_0 > P_L$, or \$486.07 > \$351.08, the application of lean manufacturing waste elimination reduced the cost of the non-controversial stem cell pharmaceutical.

The product cost before application of lean, P_0, was \$486.07 and after, P_L, the cost was \$351.08, for a reduction of \$134.99 per unit of pharmaceutical. The findings show that a 28% decrease in product cost was realized as a result of lean waste elimination.

Future State Value Stream Map

A future state value stream map was created that defined the manufacturing system after waste elimination. Figure 22, that follow, is the future state value stream map that identifies process changes. Standardization of the data entry process at the assembly stage and recycling of the bins and lids were captured in the table below the assembly icon on the map. The next stage of manufacturing was processing using BSCs as the work platform, represented on the map by the labeled icon. Waste elimination optimized hespan reagent use and eliminated the pre-QC testing, denoted on the map as QC 1 >0.1 mL instead of the prior 6-mL of raw material used. Production continues on the map to the next phase of microbiological analyses that resulted in the multiplicity of record reviews from bacterial testing. Lean waste elimination improved the process to one record from 30. The table below the icon identifies numerical differences.

Additional improvements were realized from the elimination of waste application. The future state value stream map includes an icon identified as outside source. Positive microbiological results were sent to an outside source, or testing vendor, for confirmation of the test findings. This process of confirmation occurred for both pretests results and the finals test results. Elimination of the pretests, as a result of the application of lean waste elimination, also eliminated the associated outsourced testing. The elimination of the pretests reduced this type of non-value added testing by 50% as well as the outside source vendor confirmation testing by 50% proportionately.

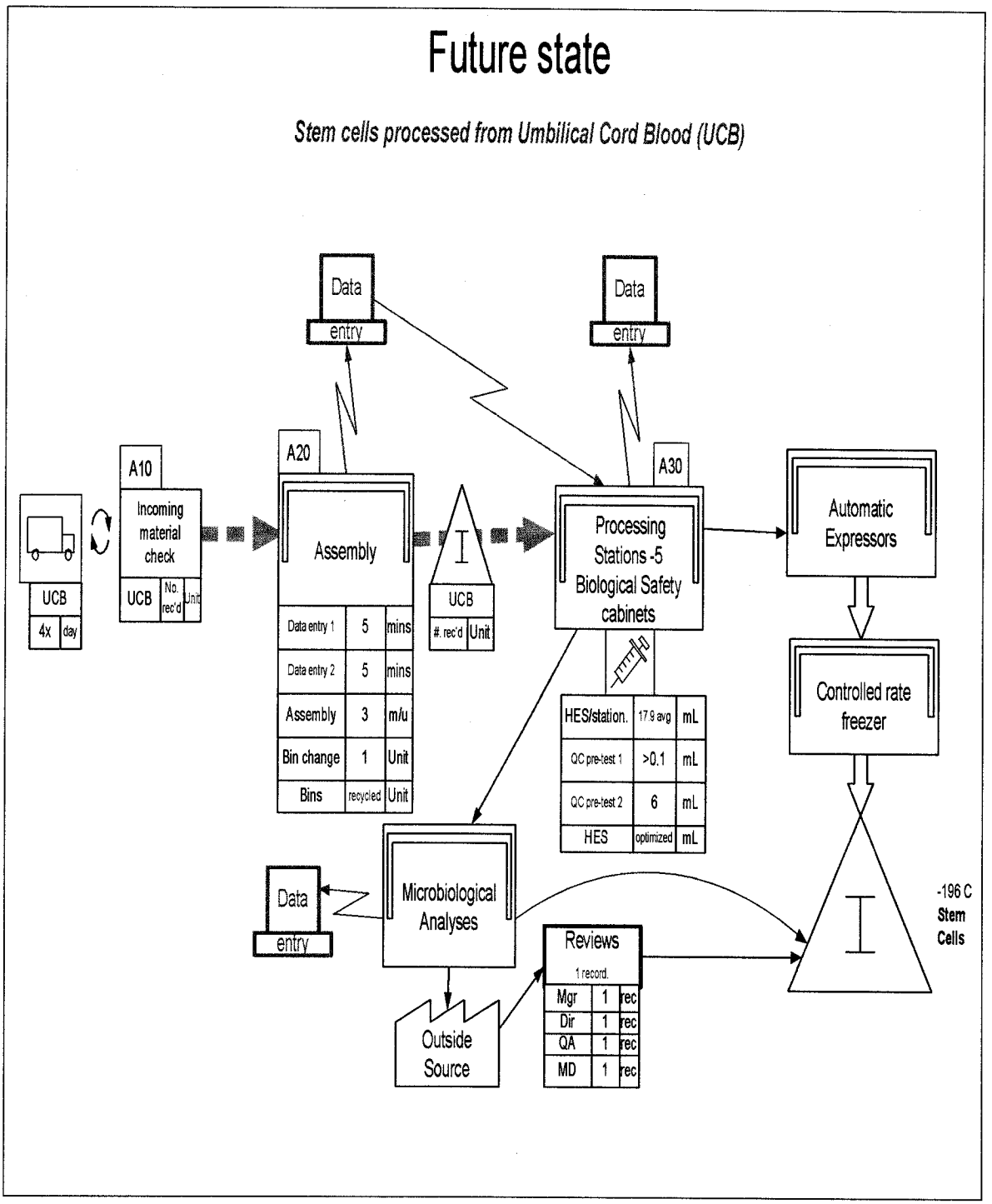


Figure 22. Future state value stream map of manufacturing after waste elimination.

Current State Versus Future State

A comparative analysis of the current state value stream versus the future state value stream map was conducted. The maps are shown together in figure 23 that follows. The differences between the current state value stream map and the future state value stream map show that the Kaizen bursts on the current state map are not on the future state map. The Kaizen bursts were opportunities to be realized, denoted on the current state map as bins and hespan. The bins used in the assembly process were being discarded. Application of lean realized this opportunity of using the discarded bins by recycling them into reusable components. The reagent hespan at the processing station of the current state value stream map used an average of 179 mL out of the 500 mL bag. The remaining 321 mL were thrown away. Application of lean waste elimination optimized the use of the reagent through discontinuation of this practice. The Kaizen bursts on the current state map were realized on the future map no longer appearing.

The current state map of the assembly process show two different processing times for data entries of domestic and international shipments. Lean manufacturing standardized the data entry processes resulting in the future state map consisting of the same data entry time for both domestic and international shipments. The processing stations on the current and future state value stream maps are also different in the amount of raw material used for pre-tests in the two states as noted in the tables below the icons.

Managerial review of analytical bacterial test outcomes on the value stream maps identifies the cycles of activities. The amount of documentation was also included. Differences in current state and future state maps denote the change in the process by reduction of both cycle activities and associated documentation listed in the tables.

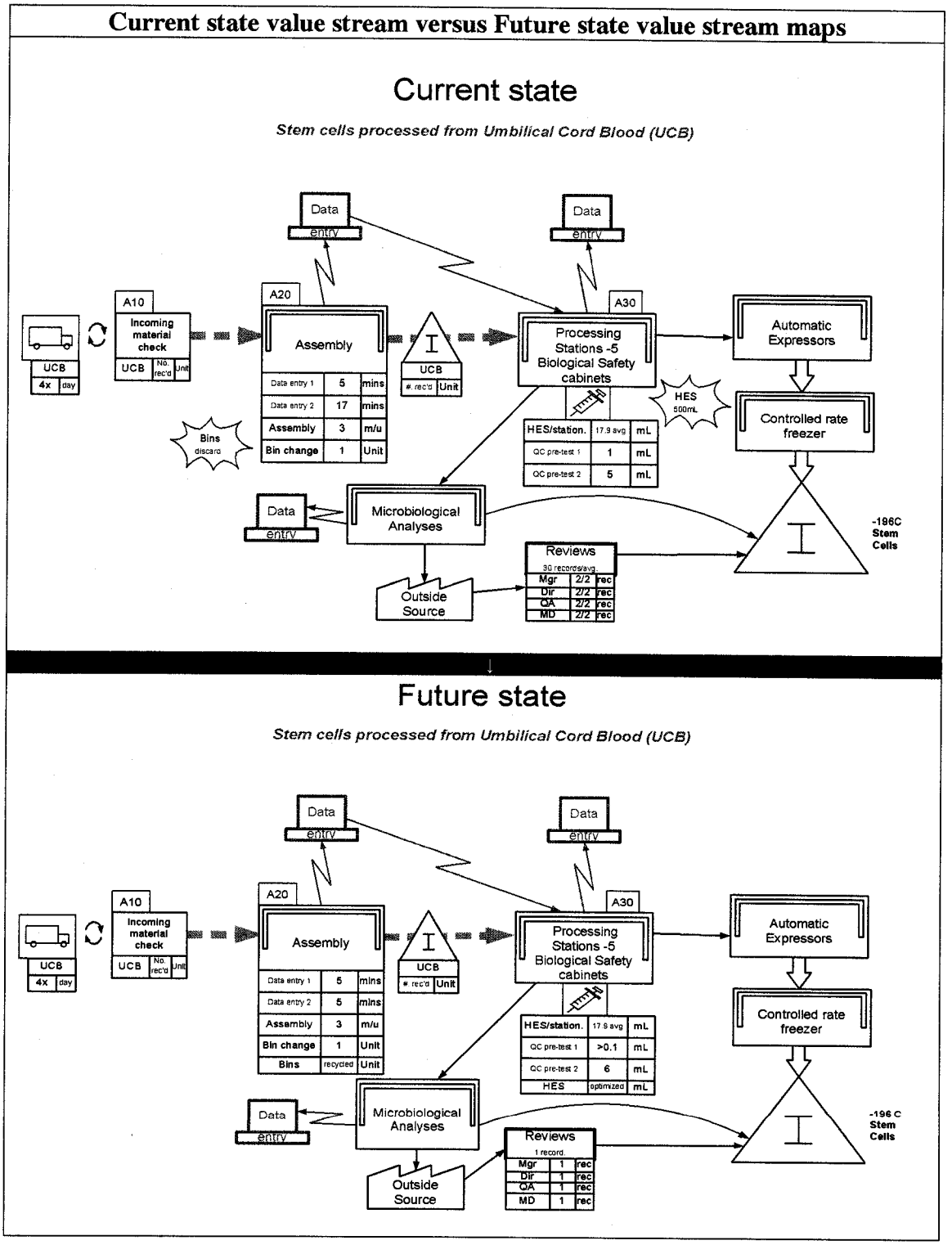


Figure 23. Current, top, and future, bottom, states value stream maps.

The gaps between current and future states defined on the value stream maps were closed by the application of lean manufacturing waste elimination. The Kaizen bursts on the current state value stream map were utilized through lean, not appearing on the future map. Processing and assembly cycles were standardized, closing that gap. Raw materials used in pretests were saved as a result of implementing lean manufacturing's waste elimination principle, increasing the amount of raw material for production of these therapeutic non-controversial stem cell pharmaceuticals.

Influence of Lean

The foundation of lean manufacturing is the identification of waste and its elimination or reduction. The wastes identified from this study were the foci of the research for applying lean manufacturing waste elimination and evaluating influence relative to the study questions and hypotheses. There were two study questions and associated hypotheses of the research relative to two parameters: product cost and raw material availability. Table 10 that follow delineates and well as summaries the wastes findings aligned with the affected research question parameter.

The left column of the table lists the wastes identified from the research. The right column lists the associated research parameter for each waste identified. There were six wastes identified, with five of the wastes associated with the research question as to whether lean waste elimination influenced product costs. Product cost was defined as a summation of the cost associated with reagents, supplies, and labor costs. Evaluation of the production process identified only one area where the raw material was used other than manufacturing which was in QC testing; see table 10 that follows.

Table 10.

Wastes Identified Aligned with Research Parameters

Waste	Research parameter
Data entry process time difference	Labor cost – product cost
Reagent, hespan usage, volume	Reagent – product cost
Record review process time	Labor cost – product cost
Duplicate QC sampling of raw material, volume	Raw material availability
Duplicate QC testing	Labor and supplies – product cost
Discarding bins and lids	Supplies – product cost

This research was based on the defined questions and associated hypotheses to be answered from the study. The following summarizes and aligns the findings.

Research Question 1 - Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product cost?

Overall product cost per unit for the pharmaceutical was reduced by 28% as a result of eliminating waste in supplies and labor with the latter due to reduced processing time within the manufacturing system. Direct labor costs were reduced by 25% and the total reduction in the cost of goods or supplies was 42.2%. Specifically, labor costs were reduced by decreasing processing times for data entry, record reviews, and elimination of

duplicate tests. The cost of supplies for BacT bottles and vendor testing services were reduced by 50%. Reagent cost for the supply of hespan was reduced by 35.6% as a result of applying lean waste elimination. The cost of the product prior to lean manufacturing waste elimination was $486.07; after waste was eliminated the cost of the product was reduced to $351.08. In summary, the cost of the stem cell product was reduced by $134.99 or 28% as a result of the application of lean manufacturing waste elimination to pharmaceutical production processes.

Research Question 2. Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Null Hypothesis. H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis. H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material of non-controversial stem cell pharmaceuticals after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

There were two processes in the production of non-controversial stem cell pharmaceuticals where the raw materials, from which the stem cells were obtained, were used. These were the manufacturing process itself and quality control testing. The production process removed 6-mL of the biological raw material from each shipment for

six different quality control tests prior to manufacturing. These tests were referred to as pretests since they occurred prior to production. Five of the six pretests were repeated at the end of the production process as part of end stage testing to qualify the final product. There was one test of the six that was not repeated and was the only test of the six pretests directly associated with the product, adding value. The volume of raw material required to conduct the one test was nominal, drop-wise. The other tests were being performed to primarily evaluate the production performance of staff. Findings from the assessment of the data determined that there were no actions taken as a result of the pretest findings. In addition, the quality control pretests were repeated as part of product qualification. As a result, the pretests which used 6-mL of the crucial raw material were identified as a potential waste elimination opportunity.

The pharmaceutical industry is regulated by the FDA, state, and local governmental agencies. In addition, pharmaceutical companies may also be accredited by standards such as ISO as well as industry standards. These regulating and accrediting organizations have requirements that include specified quality control testing. In order to consider eliminating a test, regulating requirements must be ensured. A review of regulatory requirements revealed that none of the pretests were required by the governmental agencies. Three accrediting agencies also did not require all pretests, with one agency requiring one of the pretests that could be waved or sustained. As a result, the pretests were slated for waste elimination. The volume of crucial raw material saved for stem cell production was directly proportional, 6-mL.

The application of lean manufacturing due to the elimination of pretests to the production processes of this biological pharmaceutical supplier resulted in a product

savings per unit of 6-mL. Averaging forty specimens or shipments per production day increases the availability of raw biomaterial by 240-mL. Maximum capacity of 50 shipments per production day increases the amount of raw biomaterial to 300-mL.

The statistical significant of the increase in the raw material as a result of waste elimination was evaluated using ANOVA. ANOVA tests the differences of the means of test data to determine significance. If the differences are significant, the null hypothesis can be rejected. The mean of the raw material volumes before application of lean waste elimination and the mean after were evaluated by ANOVA. The results determined that the increase was significant. A paired t-test statistical analysis was also conducted which supported the conclusion that the 6-mL increase was significant. The application of lean to the production of stem cell pharmaceuticals increased the availability of raw materials.

Tabular Summations

The following are tabular summations of the findings and analyses to restate the findings associated with results presented in this chapter. Figure 24 is the tabular summation of product cost findings that includes the methods used aligned with the results. Figure 25 is the tabular summation of raw material availability findings that also includes the methods used aligned with the results. Each table includes the associated research question. The aim of this summation was to align the results in relationship to the research test methods.

Research Question 1	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial pharmaceutical stem cells reduce product costs?	
Sample	Production system before and after waste elimination.	
Category	***Method***	***Results***
Findings	Identification of waste	• Reagent – hespan • Supplies – bacT bottles, outsourced confirmation tests, bins & lids. • Labor – data entry, record reviews, duplicate testing.
Test	Product cost (P): $P = R + S + L$, where: R = cost of reagents; S = cost of supplies; L = cost of labor Cost before lean: $P_0 = R_0 + S_0 + L_0$ Cost after lean: $P_L = R_L + S_L + L_L$ If $P_0 > P_L$ the application of waste elimination reduced product costs.	Before / After • Reagent $20.59 / 7.34 • Supplies 17.48 / 8.74 • Labor 448.00 / 335.00 Product cost: $486.07 / $351.08
Results	Measurements of the product cost parameters of the sum cost of reagents, supplies, and labor before wastes identified above were eliminated and after.	Product cost before: $486.07 After: $351.08
Analyses	Summation of product cost per unit before application of lean waste elimination and after. The difference in the before and after results determine the influence of lean waste elimination on the cost of the pharmaceutical.	$P_0 > P_L$ or $486.07 > $351.08; the application of lean manufacturing waste elimination reduced the product cost of the pharmaceutical.

Figure 24. Research Question 1 - product cost summation.

Research Question 2	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial pharmaceutical stem cells increase the availability of crucial raw materials?	
Sample	Production system before and after waste elimination.	
Category	***Method***	***Results***
Findings	Identification of wastes	Duplicate testing utilizing, as waste, 6-mL of biological raw material
Test	Statistical analysis to evaluate the significance of volume of raw materials before and after waste elimination.	ANOVA and paired t-test at a significance level of 0.05 was used.
Results	Measurements of the volume before and after waste elimination for significance by statistical analyses.	Below significance level of 0.05: ANOVA = 0.000 Paired t-test = 0.000
Analyses	The results of the statistical analyses were evaluated to determine whether the change or difference in raw material volume before and after is significant.	Application of lean manufacturing waste elimination removed the non-value adding pretests resulting in a direct increase of raw materials by 6-mL. This increase is applicable to each unit of product manufactured. Daily production increased by an additional 300-mL at full capacity production.

Figure 25. Research Question 2 - raw material availability summation.

Chapter Summary

The research commenced with a comprehensive data collection process from reviews of procedures, records, quality control methods, and direct observations of the manufacturing processes with a focus on waste identification. Production began with the pulling, or initiation of manufacturing, by the customer by sending material to be processed. Production ended with final storage of the manufactured customer-specific stem cell pharmaceutical. A current state value stream map was created that included information exchange and process flow.

Based on the research, several opportunities for waste elimination within the manufacturing system were found. Findings consisted of variations in the data entry process, duplicity in testing, reagent discards, lack of recycling or re-use opportunities, multiple record reviews and generation. Each finding could be categorized as processing waste with associated labor costs. An evaluation was conducted to determine the impact of waste elimination on regulatory and accreditation requirements, specifically relative to duplicity in five different quality control tests. There were no conflicts with regulatory requirements associated with waste elimination opportunities. However, there was one conflict relative to one of the five tests by an accreditation standard. Options for resolution of the conflict were presented which consisted of sustaining the one test in question or requesting variance to eliminate. All other waste elimination opportunities posed no conflicts with regulatory requirements or accreditation standards. A future state value stream map was created that included opportunities found based on waste elimination.

It was further found that the influence of the application of lean waste elimination on the production processes of non-controversial stem cell pharmaceuticals resulted in a labor cost reduction of 25%, goods or supplies were reduced by 42.2%, and a 35.6% reduction in reagent use. Product costs were defined as the cost of reagents, supplies, and labor. As a result of lean waste elimination it was found that product costs were reduced from $486.07 per unit to $351.08, a 28% reduction. Raw material volume, defined as availability, was influenced by application of lean waste elimination from the elimination of duplicity in testing that used 6-mL per unit. It was found that the volume increased per maximum production day to an additional 300-mL. Statistical analysis by ANOVA and a paired t-test resulted in the finding that the volume increase was statistically significant. A key finding was that application of lean waste elimination increased the availability of crucial raw material for the production of stem cell pharmaceuticals. As a result, it was found that both research parameters of product cost and available raw materials were positively influenced by lean waste elimination

Chapter 5

CONCLUSIONS

Introduction

Presented in chapter 5 are conclusions of the research, all based on findings and methodology previously presented in chapters 3 and 4 respectively. The aim of this research was to determine the influence of the application of lean manufacturing waste elimination on the production processes of biopharmaceutical suppliers. A case study design was the methodology employed for the research assessing a specific biopharmaceutical manufacturer of non-controversial stem cells. The manufacturer processes stem cell pharmaceuticals from raw biological materials supplied by individual customers.

There were two specific aspects of the production process that were the foci of the investigation: product cost and raw material availability. The problem statement below specifies the intent and purpose of this research.

Statement of the Problem

The problem for this research was to determine the influence of applying the principle of waste elimination from lean manufacturing on product cost and raw material availability in the production of non-controversial stem cell pharmaceuticals.

The research was conducted on production processes by comprehensive evaluation, mapping, and documentation using customized data collection forms, to identify and analyze potential waste within the manufacturing system. The foci of the investigation were on reducing the cost of the product and usage of the supplied biological raw material through the elimination of waste. Decreasing the cost of a product provides increased market opportunity, higher returns on investments, and economical stem cell pharmaceuticals to more patients. A decrease in pharmaceutical costs potentially reduces associated healthcare costs. Reducing usage of the biological raw material in the production of stem cells provides an increase in the availability of the raw materials that are in short supply for these life-saving pharmaceuticals.

There were two research questions and hypotheses developed from the problem statement that were answered from the study. The following discusses those answers and conclusions from the research.

Influence on Product Costs

Research Question 1: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals reduce product costs?

Application of lean manufacturing was initiated with the identification of waste in the manufacturing system. The elimination and/or reduction of waste are core concepts of the lean manufacturing technology. The assessment for waste resulted in four findings in the production process adversely affecting product cost: variations in the data entry process of incoming shipments at initial assembly; duplicity in quality control testing; multiple reviews and assessments; and the practice of discarding reagents and supplies.

Variations in data entry

Variations in the data entry process of incoming shipments occurred based on shipment type and the type of staff performing the data entries. Assessment of the assembly process to identify waste in applying lean manufacturing determined that data entry steps varied between domestic and international shipments. Internationals required 93 additional inputs, or 85% more inputs than domestics, at the assembly stage increasing the processing time by production staff for these types of shipments. As noted, the additional data entry of information for international shipments were the same for domestics; the point and source of data entry were different. The information for data entry of domestic shipments was entered into the computer system by sales service staff at the time the service was ordered by the customer, weeks before the shipment was received for manufacture.

All data entry for internationals occurred at receipt of the shipment, keyed in by production staff, at the start of the manufacturing process. This difference in who performed this data entry also added to the increase in the process at production. Production staff only performed this part of data entry for international shipments whereas service staff performed the task routinely for all domestic shipments which represents the larger proportion of shipments. The production staff only performed this data entry 10% of the time whereas service staff performed the task 90% of the time. As a result, the time required for production staff to perform the activity was much longer than for the sales service staff, increasing processing time and therefore labor costs.

Application of lean manufacturing to eliminate the waste from variations in data entry standardized the process for all shipment types, thereby controlling the variation.

Control of variation is a standard component of lean manufacturing. The change resulted in an increase in productivity due to the reduced time for performing the activity. Time was that part of product cost that translated into the cost of labor required in performing a function. The conclusion and influence of waste elimination from lean manufacturing was the time reduction required to perform data entry during production by variation control and reduction. The resulting conclusion was the associated proportional decrease in labor costs applicable to product costs.

Testing

Two sets of quality control tests were being performed on every unit. A pretest was performed on the raw material sampled prior to production and another after for final product qualification. Pretest results did not alter a process; findings were not used, only filed and the tests were duplicated, performed again at the end of processing for qualification of the product. The pretests were determined to be waste for elimination since the tests were duplicated for final product qualification.

Labor costs were also reduced in the testing process by the elimination of the non-value adding pretests for an associated decrease in labor utilized. Costs were decreased due to elimination of these testing activities. Elimination of the pretests increased production and enhanced processing flow adding value by refining of the value stream from waste elimination. The concluding influence of lean waste elimination was the reduction in labor costs by eliminating the labor expended for duplicate testing which is a form of processing waste.

Another conclusion was a decrease in the cost of goods of testing supplies. The quality control pretests were eliminated since the results did not alter the manufacturing

processes and the tests were performed again at the end of production of the biomaterial into stem cell pharmaceuticals. Elimination of this testing duplicity resulted in a 50% reduction in the cost of associated testing supplies reducing the cost of goods and product costs. The conclusion of the application of lean waste elimination to testing waste was a reduction in both supplies and labor costs, with a proportional decreased in product costs.

Record reviews and assessments

The review and assessment of records by managers, directors, and a physician were decreased by the application of lean waste elimination resulting in a decrease in the associated labor costs. The multiple reviews of a plethora of individual documents by the very expensive review group was reduced to a nominal amount, eliminating in excess of 200 duplicate records, 700 data points, reviews and signatures. The reengineering of the system from primarily manual to electronic reduced processing wastes from rechecks, redundant documentation, reviews, and over handling. The result was a streamlined assessment process that adds value, reduces errors, enhances track ability, and simplifies usage. The concluding synergy of these process changes reduced the amount of labor cost required associated with a reduction in product costs, which is the influence of lean waste elimination.

Reagent usage

Application of lean manufacturing waste elimination optimized the usage of the reagent hespan, ending the practice of discarding the reagent without cause. The reagent was being discarded at a rate of up to 64% per day due to an unconfirmed practice. Comprehensive evaluation of the validity of the practice determined there was no support to confirm the practice yet there was evidence to negate the practice. The conclusion was

the elimination of reagent waste optimizing the use of this reagent for cost effective supply utilization affecting product costs.

Recycling of bins

The incoming shipments of materials were housed in plastic lidded bins. The materials inside the lidded bins were encased biomaterial contained in a polyethylene leak proof bag that was wrapped in absorbent towels and then placed in a zip locked bag. Paperwork was also in the bins of materials. The purpose of the bins was to contain the separate items in one holder. After the items were removed from the bins, the bins, along with the lids were discarded. Application of lean manufacturing waste elimination identified this waste of the bins, along with the lids, and both were recycled. The conclusion was cost savings, as well as the associated environmental savings and usage, which resulted in improved production by optimization of the use of supplies and materials that were associated with product costs. In addition, lean waste elimination influenced the practice of intentional recycling.

In conclusion, lean waste elimination reduced product costs by decreasing labor costs in four different aspects of the manufacturing process where there were findings of waste. Also from the findings, reagent usage was optimized and the costs of goods or supplies were reduced in testing and packaging. The following summarizes the concluding influence of waste elimination from the technology of lean manufacturing on product costs. The equation used for determining product cost is specified below.

Product cost = Reagents + Supplies + Labor costs, defined as follows.

Reagents

- Hespan discard waste

Supplies

- Testing supplies
- Bins and lids

Labor

- Incoming data entry
- Duplicate testing
- Record reviews

Measures of the cost to manufacture the product before application of waste elimination from lean manufacturing and after were taken with the following results.

Before lean: $P_0 = R_0 + S_0 + L_0 = \$20.59 + \$17.48 + \$448.00 = \$486.07$

After lean: $P_L = R_L + S_L + L_L = \$7.34 + \$8.74 + \$335.00 = \$351.08$

Increases in productivity translating to decreases in labor costs realized from lean were applied to product cost assessments, with time in minutes quantified into labor costs (dollars/hrs). Additional measures that reduced product costs were savings in the cost of reagents, number of records for review (also labor costs) and supplies. A savings in product costs of $134.99 or 28% per product was the concluding realization as a result of applying lean waste elimination to the production of stem cell pharmaceuticals.

Additional conclusions from the application of waste elimination from lean manufacturing were the affect of process changes that noticeably decreased cycle times. Table 11 that follows delineates the process reductions, identified by a decrease in the metric or measurement and improvements, before and after lean.

Table 11.

Process Changes from Lean

Measurement	Before	After
Data entry-time	17 minutes	5 minutes
Points	108	15
BacT bottles	4	2
Hespan reagent	321 mL discarded	0
Recycle bins & lids	0	100%
Record Reviews	30	1
Signatures	210	4
Testing	12	7

In conclusion, data entry times were reduced by 71% and the associated number of data entry points decreased by 85%. The number of testing supply bottles decreased by 50%; the 321 mL of the reagent wasted per process was eliminated; records to review were reduced by 97% with the associated number of signatures decreased by 98%; and recycling of bins & lids. This concluding synergic affect of significant enhancements from process changes was a result of the application of lean waste elimination on the findings of waste in production of non-controversial stem cell pharmaceuticals.

Tabular Summation

The following is a tabular summation, figure 26, of the findings, analyses, and conclusions for the first research question associated, which involved products costs assessments, to restate the findings associated with conclusions presented in this chapter. This table adds to the previous table presented in chapter 4 by the addition of the conclusions column at the end of the table in the last column. The table is an accumulation of the data and findings from the start of the research through to conclusions.

The table consists of the specific associated research question listed first, followed by the sampling plan, the categories, methods, results and conclusions. Under the category heading are the specific categories of findings, test, results, and analyses. The corresponding methods, results and conclusions are listed to the right. Of note, each finding is presented under the results column to the right side in the table, with the conclusion in the ending column.

The aim of this summation was to align the results in relationship to the specific research question, methods, tests, findings, results, analyses and the culminating focused conclusions of the research. This visual presentation defines and specifies the influence of waste elimination from application of lean manufacturing on the product cost of the pharmaceutical.

Research Question 1	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial pharmaceutical stem cells reduce product costs?		
Sample	Production system before and after waste elimination		
Category	***Method***	***Results***	***Conclusions***
Findings	Identification of waste	• Reagent-hespan • Supplies–bacT bottles, outsourced confirmation tests, bins & lids. • Labor–data entries, record reviews, duplicate testing.	Optimization of reagents and supplies, with a reduction in labor.
Test	Product cost (P): $P = R + S + L$, where: R = cost of reagents; S = cost of supplies; L = cost of labor Cost before lean: $P_0 = R_0+S_0+ L_0$; Cost after lean: $P_L = R_L+S_L+ L_L$. If $P_0 > P_L$ the application of waste elimination reduced product costs.	Before / After • Reagent $20.59 / 7.34 • Supplies 17.48 / 8.74 • Labor 448.00 / 335.00 • Product cost: $486.07 / 351.08	Manufacturing costs were reduced.
Results	Measurements of the product cost parameters of the sum cost of reagents, supplies, and labor before wastes identified above were eliminated and after.	Product cost before: $486.07 after: $351.08	Product cost was reduced, for each unit, by $134.99.
Analyses	Summation of product cost per unit before application of lean waste elimination and after. The difference in the before and after results determine the influence of lean waste elimination on the cost of the pharmaceutical.	$P_0 > P_L$ or $486.07 > $351.08; the application of lean manufacturing waste elimination reduced the product cost of the pharmaceutical.	The cost of the pharmaceutical decreased by 28%.

Figure 26. Research Question 1 – product cost conclusions summation.

Influence on Raw Materials

Research Question 2: Does the application of waste elimination from lean manufacturing to the production processes of non-controversial stem cell pharmaceuticals increase the availability of crucial raw materials?

Null Hypothesis.

H_0: $\mu \geq \mu_1$. There is no significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Alternate Hypothesis.

H_0: $\mu < \mu_1$. There is a significant increase in the amount of available raw material after application of waste elimination from lean manufacturing to production processes and the amount of available raw materials before application.

Conclusion

Raw material usage for every shipment within the production process consisted of removal of 6-mL of the incoming biological material for six different quality control pretests. One mL of the biomaterial was used for four of the pretests. The other 5-mL of the 6-mL sample was used for the pre-bacterial testing, with 1-mL of the raw biomaterial for aerobic bacterial pretest and 4-mL for anaerobic bacterial pretest. The remaining raw material was processed into the final product of stem cells. The final product was again quality control tested as part of the qualification process of the end product. Application of lean manufacturing waste elimination determined that no actions were taken as a result of the pretest results and that five of the six pretests tests were non-value adding. The one test for blood type was directly associated with the product, adding value. Determination

of blood type required a nominal amount, drop-wise, of the raw material. Application of lean manufacturing waste elimination removed the non-value adding pretests resulting in a direct increase of raw materials by 6-mL for every unit for an additional 300-mL at full capacity production. The ANOVA and paired t-test statistical evaluations determined that the increase in the raw material from the influence of lean waste elimination was significant.

Tabular Summation

The following is a tabular summation, figure 27, of the findings, analyses, and conclusions for the second research question to restate the findings associated with conclusions presented in this chapter. This table adds to the table presented in chapter 4 by addition of the conclusions column at the end of the table The table consists of the specific associated research question listed first, followed by the sampling plan and the categories, methods, results and conclusions. Under the category heading are the findings, test, results, and analyses. The corresponding methods and additional headings are listed to the right. The findings are presented under the results column to the right side of the table, with the conclusions in the final listing.

The aim of this summation was to align the results in relationship to the specific research question, findings, results, and the focused conclusions. This visual presentation specifies the influence of waste elimination from lean manufacturing on the amount and availability of the raw material for production of the pharmaceutical.

Research Question 2	Does the application of waste elimination from lean manufacturing to the production processes of non-controversial pharmaceutical stem cells increase the availability of crucial raw materials?		
Sample	Production system before and after waste elimination		
Category	*Method*	*Results*	*Conclusions*
Findings	Identification of wastes	Duplicate testing utilizing, as waste, 6-mL of biological raw material	Non-value adding testing were part of the production process.
Test	Statistical analysis to evaluate the significance of volume of raw materials before and after waste elimination.	ANOVA and paired t-test at a significance level of 0.05 was used.	An alpha level of 0.05 limits the probability of concluding the null hypothesis of no differences is incorrect only 5% of the time.
Results	Measurements of the volume before and after waste elimination for significance by statistical analyses.	Below significance level of 0.05: ANOVA = 0.000 Paired t-test = 0.000	ANOVA and paired t-test determined that the increase in raw material from lean waste elimination was significant.
Analyses	The results of the statistical analyses were evaluated to determine whether the change or difference in raw material volume before and after is significant.	Application of lean manufacturing waste elimination removed the non-value adding pretests resulting in a direct significant increase of raw materials by 6-mL for every unit for an additional 300-mL at full capacity production.	The results of both statistical analyses were significant. The application of waste elimination from lean manufacturing significantly increased the volume of the biological raw material for production of the non-controversial stem cell pharmaceutical.

Figure 27. Research Question 2 – raw material availability conclusions summation.

Recommendations

The research and application of lean waste elimination to the production processes of stem cell pharmaceuticals reduced product costs and increased the available biological raw materials for manufacture. These significant results warrant sustained application throughout the manufacturing system as well as evaluation extending to support processes based on these findings. In addition, the methods used to obtain the reduction in product costs and further assessment of the increase in the biological raw material should be expanded.

Several of the methods used resulting in the reduced product costs, relative to the first research question, were established quality improvement tools of standardization, simplification, and organization. The different methods by which incoming shipments were processed for data entry resulted in increased processing and work stoppages. The process was simplified by standardizing to one method, reducing variation. Standardization produced the reduction in labor costs from decreased processing time that also resulted in the enhancement of production flow. Redundant quality control tests were simplified to one set of tests. The review process of results initially consisted of numerous records, reviews, and sign-offs. The process was improved by organization, combining records, standardizing reviews and reducing the number of required signatures, which simplified the process. Opportunity for standardization exists where there is variation. Simplification and organization are opportunities for processes wherever there are redundancies. These positive findings from the research should be further utilized in future studies focusing on standardization, simplification, and

organization in the processing of stem cells should be pursued to potentially realize additional benefits.

The problem from research question two of this study was to determine whether the application of lean waste elimination increased the available raw materials. The findings show that the amount of the biological raw material for manufacturing into stem cell pharmaceuticals was significantly increased as a result of the application of lean waste elimination to production processes. An increase in raw material should correlate with an increase in the number of therapeutic cells in the materials. As a result there should also be an increase in the quality of the final product which applies to an increase in the amount of the therapeutic CD34+ cells. Additional studies to evaluate this type of potential increase in quality due to increased raw material are opportunities for further research.

Cumulative outcomes from both research questions were the production of two value stream maps of the production system used in the manufacturer of stem cell pharmaceuticals. Opportunities for further studies could include an extension of the findings by evaluation of areas established as waste elimination potentials such as staging and inventory. In addition, process flow and redefining of the value stream are other opportunities for further studies.

Researcher Observations - Additional Studies

The purpose of this research was to investigate the influence of lean waste elimination on product cost and the availability of the biological raw material in the production of non-controversial stem cell pharmaceuticals. The production process was

the focal point of the research. Researcher observations suggest that additional studies in lean waste elimination to build upon the findings of this research would include broadening the scope based on the following focal points in evaluating product cost, raw material availability, and standards.

- Expansion of the study to support processes.
- Focused assessment of waste based on each of the eight categories of waste.
- Purposeful design of waste elimination strategies at product development phases and technology transfer.
- Inclusion of waste elimination as a standard element of a quality management system.
- Harmonization of lean waste elimination with other quality standards.

Expansion to support processes

This research was focused on the investigation of the influence of lean waste elimination on product cost and raw material availability with concentration on the production process. The results identified significant positive influence on both parameters. Additional studies would expand the scope of investigation to supporting manufacturing areas such as inventory, purchasing, research and development processes, and storage, maintaining specificity of the research to product cost and raw material availability.

Broadening of the scope could also include external operations such as the initial collection process of the biomaterial that occurs prior to shipment for manufacture into stem cells. This focus would be directly relative to the volume of raw material available for production, evaluating waste elimination opportunities at the onset of obtaining the

raw material. Another applicable external process that could impact product costs would be vendor services such as the testing that is outsourced. Conclusions from this study were the 50% decreases in the outsourced testing service needs and supplies. Further research would investigate waste elimination strategies in supplied services.

Focused assessment of waste

The technology of lean manufacturing identifies eight different common types of waste in organizations which are listed below. Processing waste was identified in this study from duplicate testing, multiple record reviews, and discard of reusable supplies. WIP, waiting, and motion waste were noted in the data entry and record review processes. The wastes identified involved 50% of the common types of wastes described in the lean manufacturing philosophy. Further studies on the influence of lean waste elimination on product cost and raw material availability in the production of non-controversial stem cell pharmaceuticals would investigate the other 50% of the types of wastes in the manufacturing process. The eight categories of waste are listed below:

1. Overproduction
2. Waiting
3. Excess inventory or WIP
4. Making defective product
5. Transportation
6. Motion
7. Processing waste
8. Under-utilizing people

Design of waste elimination

Quality by design is the foundation of robust quality management systems. The inclusion of lean waste elimination as a standard aspect of product and process development at the design phases supports this foundation, warranting additional study on a broader level. The determination of product cost and raw material usage would be references for continued research.

As the biotech industry focuses on emerging technical applications of stem cells, an appropriate, updated quality system applicable to the needs of the biotechnology industry could prove beneficial. Further studies for quality system development are needed, aimed at reducing product cost and increasing the short supply of biological raw material for production of stem cell pharmaceuticals.

Lean waste elimination standard

A modernized quality management system inclusive of lean waste elimination as a standard element would be another broader aspect for further research studies. Systems for consideration are ISO 9000, regulatory requirements of the Quality System Regulations (QSR) and current Good Manufacturing Practices (cGMPs) that are mandates for the pharmaceutical industry.

In addition, focused studies could be conducted to include lean waste elimination in the established quality system by inclusion as a metric standard in evaluation activities. Assessment of lean waste elimination would be part of the performance review of the quality system to include an established element on management review agendas.

Harmonization of lean

Harmonization of quality standards is a need throughout industry because of the necessity of organizations to comply with different requirements. The findings and associated conclusions from this research identified a need to ensure requirements would be sustained with process enhancements from the application of lean waste elimination. Requirements include the quality standards noted from the research such as ISO and cGMPs, but may also include international regulatory requirements and industry standards. Further studies of lean waste elimination would explore issues of harmonization, evaluating each of the common categories of quality systems listed below:

- Management Responsibilities
- Resources
- Operations
- Evaluation

Chapter Summary

Application of lean manufacturing waste elimination reduced the costs of both goods and labor which were the primary measures of product cost. The costs of goods were reduced by elimination of pretests reducing the cost of the associated materials by half. Optimization of reagent usage reduced the cost of this good over 60%. Recycling of bins and lids also contributed to reduced cost of goods.

Labor costs were reduced by reengineering of the documentation and review systems decreasing the amount of labor required for the accomplishment of both assessments and reviews. Elimination of pretests reduced associated labor requirements

as well. Process improvements in the data entry activity between domestic and international shipments as a result of the application of lean waste elimination standardized the process through harmonization, the outcome of which resulted in labor reductions.

The amount of raw material available for manufacturing was significantly increased as a result of the elimination of biomaterial waste from duplicate testing. This processing waste was a result of quality control pretests, conducted a second time for product qualification, with elimination of the testing duplicity by application of lean waste elimination.

Implementation and application of lean manufacturing waste elimination to the processes of biopharmaceutical production both decreased product cost and significantly increased the availability of raw materials for production of stem cells. The elimination of wastes in the manufacture of non-controversial stem cell pharmaceuticals reduced the cost of this medical product. These results posed indications of the potential of lean waste elimination in reducing the cost of other pharmaceuticals with implication of reducing healthcare costs, described below, as well as providing opportunities for further studies.

Implications in Reducing Healthcare Costs

The results of this research evaluating the influence of lean waste elimination on the production processes of stem cell pharmaceuticals have implications in reducing healthcare costs associated with the cost of pharmaceuticals. In chapter one of this study it was identified that pharmaceuticals are one of the leading contributors to continuously rising healthcare costs. Pharmaceutical use has increased consistently over the last decade and is expected to continue this trend. The larger aging population, maintenance

drugs, preventative pharmaceuticals and especially advances in medical treatments such as with stem cells are all reasons that pharmaceutical usage will continue to rise as well as their costs. Efforts to reduce healthcare costs would need to address the cost of pharmaceuticals.

This research also determined that the current primary efforts in reducing healthcare costs were focused on limiting serve, increasing deductibles, and other cost-sharing strategies. These efforts have only shifted the cost to other sources with no real reduction in healthcare costs. It is of no surprise that these efforts have failed in reducing healthcare costs since they were not aimed at the major cost centers of healthcare such as the cost of pharmaceuticals.

The production processes used in the manufacturer of pharmaceuticals were previously identified as wasteful and inefficient. This research supports the findings that there are opportunities for waste elimination in the production processes of biological stem cell pharmaceutical manufacturers. The use of the raw material that is the substance of the functionality of the pharmaceutical was optimized in the production process as a result of lean waste elimination. In addition, the application of lean waste elimination to production processes realized quantifiable results for product cost reductions of pharmaceuticals. Applying similar efforts of lean waste elimination to other types of pharmaceutical production processes could have transferable results decreasing product costs. Systemically applied, reducing the costs of pharmaceuticals, which is one of the leading contributors to high healthcare coosts, by lean waste elimination holds potential.

The high cost of healthcare in the U.S. is a large complex, multifaceted issue with intricate factors involved. An established method for solving large complex problem

is by dissection into manageable parts that are solved individually until the entirety is resolved. The technology of lean waste elimination could prove to be a solution to manage one of those parts.

Conclusion

Cellular therapy continues to be an emerging, evolving technology conducive to quality system development and design with stem cells at its core. The current limitations on advances in cellular therapy, especially stem cell technology, are due to inadequate resources. Optimization of these limited resources could be obtained by application of lean waste elimination.

Advances in technology, such as stem cell utilization, are the future directions of medicine, promising advances in healthcare not realized before. As with all technology, the processing of the development of stem cells in the treatment of the human condition cannot go undirected. Progress also requires ethical responsibility, both of which can be better assured through technology management.

REFERENCES

Alukal, G. (2003). Create a Lean, mean machine. *Quality Progress*, 36(4), 29-34.

American Association of Blood Banks. (2005a). *Facts about blood and blood banking.* Retrieved April 18, 2005, from http://www.aabb.org/All_About_Blood/FAQs/aabb_faqs.htm#5

American Associated of Blood Banks. (2005b). *Blood.* Retrieved November 10, 2005, from http://ww.aabb.org

America's Blood Centers. (2005). *Blood facts.* Retrieved November 10, 2005, from http://ww.abc.org

American Red Cross. (2005a). *Donating blood.* Retrieved November 13, 2005, from http://ww.abc.org

American Red Cross. (2005b). *American Red Cross asks for help with blood shortage.* Retrieved February 24, 2007, from http://redcrossgulfcoast.org

Appleby, J. (2001). Hospital costs drive health care spending up. *USA Today*, Retrieved November 11, 2005, from http://www.usatoday.com

Ashley, E. D. (2005). *Antimicrobial drug shortages.* Retrieved March 17, 2007, from http://www.infectiousdiseasenews.com/200501/frameset.asp?article=pharmconsult.asp

Bansal, A. K., & Koradia, V. (2005). The role of reverse engineering in the development of generic formulations. Pharmaceutical Technology, 29(8), 50-53.

Blood Centers of the Pacific. (2005). *About Blood Centers of the Pacific.* Retrieved March 20, 2007 at http://www.bloodcenters.org/aboutus/default.htm

British Broadcasting Company. (2000). Japan the most healthy country. Retrieved March 26, 2007, from http://news.bbc.co.uk/1/hi/health/774434.stm

Brierley, J., Cowton, C., & Drury, C. (2001). How product costs are calculated and used in decision making: A pilot study. *Managerial Auditing Journal,* 16(4), 202-206.

Borror, K., O'Rourke, P., & Skirboll, L. (2000). A stem cell primer. *Forum for Applied Research and Public Policy, 15*(1), 54-58. Retrieved October 28, 2007, from Research Library database.

Borger, C., Smith, S., Truffer, C., Keehan, S., et al. (2006). Health spending projections through 2015: Changes on The Horizon. *Health Affairs,* W61-W74.

Chapman, C. D. (2005). Clean house with Lean 5S. *Quality Progress*, 38(9), 27-32.

Chiarello-Ebner, K. (2006). Gottlieb challenges manufacturers to make processes more efficient. *Pharmaceutical Technology*, 30(5), 22.

Cord Blood Transplant Study. (2005). Retrieved October 15, 2007 from https://web.emmes.com/study/cord/default.htm

CMS. (2005). Department of Health and Human Services, Centers for Medicare and Medicaid Services (CMS), Office of the Actuary. Retrieved November 14, 2005 from http://www.cms.hhs.gov

Coates, J. (2004). The Radical Solution to Rising Healthcare Costs. *Employment Relations Today*, 31(2), 2-6.

Commonwealth Fund. (2003). *American Health Care: Why So Costly? Testimony for the Senate Appropriations Subcommittee, Karen Davis, Ph.D., and Barbara S. Cooper.* Retrieved November 11, 2005 from http://www.cmwf.org

Cowman, C. A., & Hartman, M. B. (2005). Financing Health Care: Businesses, Households, and Governments, 1987-2003. *Health Care Financing Review*, 1(2), 1-26.

Crabtree, R. (2006). *Value stream mapping – the what, the why, and the how.* Retrieved November 10, 2007 from http://www.metaops.com

Crosby, P. (1988). *Quality is Free.* New York: McGraw-Hill.

Crowley, B. L. (2006). The cost of cheaper drugs. *The New York Post.* Retrieved November 25, 2006 from http://www.nypost.com

CryoCell. (2006). *Research and Stem Cell News.* Retrieved December 12, 2006 from http://www.cryo-cell.com/resource_center/stemcell_news.asp

Daley, K. W. (2003). *The Lean manufacturing Pocket Handbook.* Tampa Bay, Florida: DW Publishing Company.

Davey, W. (2006). Applying Lean manufacturing in the Component Lab. *AABB News.* Retrieved January 3, 2007 from http://www.aabb.org

Davis, K. & Cooper, B. S. (2003). American Health Care: Why So Costly? Testimony for the Senate Appropriations Subcommittee. *The Commonwealth fund.* Retrieved November 11, 2005 from http://www.cmwf.org

Deming, W. E. (1982). *Out of the Crisis.* Cambridge, MA: Massachusetts Institute of Technology.

Elliott, M. (2006). Strong Medicine. *Industrial Engineer*, 38(2), 39-46.

Environmental Protection Agency. (2005). *Lean manufacturing.* Retrieved February 15, 2005 from http://www.epa.gov/epaoswer/hazwaste/minimize/lean.htm

Evans, J. (2005). *Total Quality: Management, Organization, and Strategy* (4th ed.). Cincinnati, OH: South-Western Publishing Company.

FDA. (2004a). *Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice.* Retrieved June 7, 2007 from http://www.fda.gov/cder/guidance/5882fnl.htm

FDA. (2004b). Innovation and continuous improvement in pharmaceutical manufacturing. Pharmaceutical CGMPS for the 21st Century. *Process Analytical Technology (PAT) Subcommittee.* Retrieved January 11, 2007 from http://www.fda.gov

FDA. (2005). *Subpart C—Biologics Licensing § 601.12 Changes to an approved application.* Retrieved May 11, 2007 from http://edocket.access.gpo.gov/cfr_2005/aprqtr/pdf/21cfr601.12.pdf

FDA. (2006). *Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies – Draft Guidance.* Retrieved May 11, 2007 from http://www.fda.gov/cber/gdlns/cordbld.pdf

FDA. (2007). *Overview of the Drug & Biologics.* Retrieved January 11, 2007 from http://www.fda.gov

Finchbaugh, J. (2005). Problem Solving Through the Lean Len. *Quality*, 44(2), 36-37.

Ford, H. (1926). *Today and tomorrow.* Garden City, NY: Doubleday, Page Company.

George, M. L. (2003). *Lean Six Sigma for Service.* New York, NY: McGraw-Hill.

Gifford, C. (2007). Today's production management systems enable Lean, demand-driven supply chains. *Pharmaceutical Progressing.* Retrieved March 1, 2007 from http://www.pharmpro.com

Harrington, L. (1999). Focus on pharmaceuticals: Put good ideas to work. *Transportation & Distribution*, 40(9), 41-44.

Health Insurance Cost. (2008). *The National Coalition on Health Care.* Retrieved April 18, 2008 from http://www.nchc.org/facts/cost.shtml

Hewitt Associates LLC. (2004). *Health Care Expectations: Future Strategy and Directions* 2005.

HHS - Department of Health and Human Services. (2005). *Effects of Health Care Spending on the U.S. Economy.* Retrieved December 12, 2006 from http://aspe.hhs.gov/health/costgrowth

Holstein, W. M. (2006, December 31). For better care, work across lines. *The New York Times,* 3.9.

Institute - Institute for Humane Studies at George Mason University. (2006). Prescription Drug Regulation. Retrieved December 12, 2006 from http://www.iliberty.org/debates/id.3288/debates_detail.asp

International Organization for Standardization. (2008). About ISO. Retrieved March 10, 2008 at http://www.iso.org/iso/about.htm

International Society for Stem Cell Research. (2007). Stem cell primer. Retrieved September 12, 2007 from http://www.isscr.org

Introduction to Lean manufacturing. (2005). *Mid-America Manufacturing Technology Center.* Retrieved March 30, 2005 from http://www.mamtc.com/lean/intro_intro.asp

iSixSigma. (2007). Quality Glossary and Dictionary. Retrieved February 15, 2007 at http://www.isixsigma.com/dictionary/glossary.asp

Ishikawa, K. (1985). What *is Total Quality Control?* Englewood Cliffs, NJ: Prentice - Hall.

Jacoby, D. (2005). Mitigating high raw materials prices. Retrieved October 30, 2007 from http://www.purchasing.com/article/CA508491.html

Jensen, V., Kimzey, L., & Goldberg, M. (2002). FDA's role in responding to drug shortages. *American Journal of Health-System Pharmacists*, 59, 1423-1425.

Jones, L. (1991). Product costing at Caterpillar. *Management Accounting*, 72, 8.

Kadereit, S. & Hines, P. J. (2005). An overview of stem cell research. *New England Law Review*, 30, 607-622.

Kardian, J. (2006). Traditional Lean manufacturing may not be Rx for pharmaceutical companies. *Invistics.* Retrieved September 1, 2007 from http://www.invistics.com/documents/Lean_Manufacturing_in_Pharma_Final_072506.pdf

Kates, S. (1997). On the true meaning of Say's Law. *Eastern Economic Journal, 23(2),* 191-202.

Klawitter, K. (2006, October). Building a Leaner Lab. *AABB Annual Meeting & Txpo,* Miami Beach, Fl.

Knoppers, B., Saginur, M., & Kharaboyan, L. (2004). Umbilical Cord Blood Stem Cells: Issues with Private and Public Banks. *Health Law Journal, 12,* 17-34.

Kochar, P. (2004). What are stem cells? Retrieved September 15, 2007 from http://www.csa.com/discoveryguides/stemcell/overview.php

Lee, Q. (2003). *Implementing Lean manufacturing.* Retrieved March 25, 2005 from http://www.strategosinc.com

Leslie, M., Hagood, C., Royer, A., Reece, C. P., & Maloney, S. (2006). Using lean methods to improve OR turnover times. *Association of Perioperative Registered Nurses*, 84(5), 849-855.

Lewis, J. A. (2006). A tracking toll for lean solid-dose manufacturing. *Pharmaceutical Technology*, 30 (10), 94-112.

Lewis, R. (2002). *Definition of Lean manufacturing.* Retrieved March 12, 2005 from http://www.isixsigma.com

LifeBank. (2007). *Freezing Your Baby's Stored Cells.* Retrieved March 2, 2007 from http://www.lifebankusa.com/facilities_tour.php

Liker, J. K. (2004). *The Toyota Way*. New York, NY: McGraw-Hill.

Mancinelli, F., Tamburini, A., Spagnoli, A., Malerba, C., Suppo, G., Lasorella, R., de Fabritiis, P., & Calugi, A. (2006). Optimizing Umbilical Cord Blood Collection: Impact of Obstetric Factors versus Quality of Cord Blood Units. *Transplantation Proceedings*, 38(4), 1174-1176.

Mand, C. (2006). Lean: A cultural transformation. *AABB Annual Meeting & Txpo*, Miami Beach, Fl.

Manos, A., Sattler, M., & Alukal, G. (2006). Make Healthcare Lean. *Quality Progress*, 39(7), 24-30.

Marshall, J. (2006). Private company forum airs range of topical issues. *Financial Executive*, 22(6), 68-70.

Massa, T. (2004). *Life Cycle Management for Process and System Control An Industry Proposal.* Retrieved January 12, 2006 at http://www.fda.gov/ohrms/dockets/AC/04/slides/2004-4052S1_04_Massa.ppt#290,1,Life Cycle Management for Process and System

May, M. (2005). Lean thinking for knowledge work. *Quality Progress*, 38(9), 33-39.

McAdam, R., & Barron, N. (2002). The role of quality management in pharmaceutical development: Clinical trails analysis. *International Journal of Health Care Quality Assurance, 15 (2/3),* 106-124.

McNichols, T. & Hassinger, R. (1999). Quick and continuous improvement through kaizen blitz. *Hospital Material Management Quarterly*, 20(4), 1-7.

McVay, G. J., & Cooke, D. J. (2006). Beyond budgeting in an IDS the Park Nicollet experience. *Healthcare Financial Management,* 60(10), 100–106.

Merriam-Webster's medical desk dictionary. (1986). Springfield, MA: Merriam-Webster.

Monroe, C. D., Potter, L., Millares, M., Barrueta, A., &Wagner, R. (2006). Kaiser Permanente's evaluation and management of biotech drugs: Assessing, measuring, and affecting use. *Health Affairs*, 25 (5), 1340-1346.

Montgomery, D. C. (2001). *Design and analysis of experiments.* New York, NY: John Wiley & Sons, Inc.

Mugishima, H., Harada, K., Chin, M., Suzuki, T., Takagi, K., Hayakawa, S., et al. (1999). Effects of long-term cryopreservation on hematopoietic progenitor cells in umbilical cord blood. *Bone Marrow Transplant, 23 (4),* 395-396.

Myers, L. (2006, October). Going Lean. *AABB Annual Meeting & Txpo*, Miami Beach, Fl.

National Institute of Health. (2007). *Stem cell information.* Retrieved May 5, 2007 from http://stemcells.nih.gov/info/scireport/chapter1.asp

NETCORD-FACT. (2006). *International Standards for Cord Blood Collection, Processing, Testing, Banking, Selection and Release* (3rd ed.). Omaha, NE: University of Nebraska.

New York Times, The. (2007). *Blood shortage in New York region.* New York, NY: Associated Press.

Nolan, T., & Bisognano, M. (2006). Finding the balance between quality and cost. *Healthcare Financial Management*, 60(4), 66-72.

Norvis, D., Renner, S., Friedberg, R., Walsh, M., & Saladino, A. (2002). Quality Indicators of Blood Utilization. *Pathology and Laboratory Medicine*, 126(2), 150.

Ohno, T. (1988). *Toyota production system: Beyond large scale production.* Cambridge, MA: Productivity Press.

O'Neil, D. (2007). *Human Blood: An Introduction to Its Components and Types.* Retrieved March 21, 2007 from http://anthro.palomar.edu/blood/default.htm

Pauly, M. (1995). When does curbing health costs really help the economy? *Health Affairs*, 14(2), 68-82.

Perkowski, C. (1989). Designing Biopharmaceutical Facilities. *Mechanical Engineering, 111(9),* 54-55.

PlasmaCare. (2007). *About our company.* Retrieved March 1, 2007 from http://www.plasmacare.com

Policastro, E. (2006). Chemicals to cell cultures. *InTech, 56(3),* 46-50.

Powell, K. (2002). US labs bemoan lack of stem cells. *Nature,* 418(6896), 358.

PricewaterhourCoopers Health Research Institute; Survey shows rising healthcare costs cut into profits of large U. S. businesses. (2005, August 19). *Biotech Law Weekly,* 185.

Prindull, G., Prindull, B., & Meulen, N. (1978). Haematopoietic stem cells (CFUc) in human cord blood. *Acta Paediatr Scandinavia*, 67(4).

Radishofski, A. (2006). *Lean initiatives come up short for Sharma Manufacturers.* Retrieved January 10, 2007 from http://.www.manufacturing.net/article

Rooney, S., & Rooney, J. (2005). Lean Glossary. *Quality Process*, 38(6), 41-47.

Rotary Blood Bank, Tughlakabad Institutional Area. Retrieved from the internet March 1, 2007 from http://www.rotarybloodbank.org/rotary/donors.htm

Rother, M., & Shook, J. (1999). *Learning to see.* Cambridge, MA: Lean Enterprise Institute.

Seiter, C. (2003). SPSS 11. *Macworld*, 20(6), 37.

Shanley, A. (2004). *Merck's lean mission.* Retrieved January 10, 2007, from http://www.pharmamanufacturing.com

Siegel, J. (2006). Blood processors wrestle with an unfriendly supply chain. *Supply Chain/Logistics.* Retrieved December 18, 2006 from http://www.pharmaceuticalcommerce.com/frontEnd/main.php?idSeccion=379

Simmons, H. E. (2002). *Hearing on the rising costs of health care: How are employers and employees responding?* Employer-Employee Relations subcommittee of the House Education and the Workforce Committee. Retrieved September 18, 2007 from http://www.nchc.org/materials/speeches/Rising%20Cost.pdf

Stanley, J. (2004). *Applying Lean manufacturing in the Blood Center.* Retrieved December 11, 2006 from http://www.aabb.org

Strategos. (2005). Retrieved March 25, 2005 from http://www.strategosinc.com.

Studt, T. (1996). Why researchers need stat software now more than ever. *Research & Development,* 38(8), 34F-36F.

Thomas, H. (2005). Transforming the Pharma Industry: Lean Thinking applied to pharmaceutical manufacturing. Retrieved November 10, 2006 from http://www.fwc.com

University of Dayton. (2006). *An Implementation Road Map to Lean.* Retrieved December 11, 2006 from http://www.competitivechange.com

United States Patent and Trademark Office. (2007). *Information.* Retrieved April 15, 2007 from http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm

Value Based-Management. (2004). *Kaizen Philosophy and Kaizen Method.* Retrieved March 25, 2005 from http://www.valuebasedmanagement.net/methods_kaizen.html

Venables, M. (2005). Event management. *Works Management*, 58 (4), 44-46.

VerDuft, J. L. (1999). The Lean manufacturing Enterprise. *ASQ Annual Quality Congress*, Anaheim, CA.

Weber, D. O. (2006). Toyota-style Management Drives Virginia Mason. *Physician Executive*, 32(1).

Winslow, T., & Duckwall, C. (2001). Differentiation of Human Tissues image. Retrieved November 15, 2006 from http://stemcells.nih.gov/

Womack, J.P., Jones, D.T., & Roos, D. (1990). The *Machine that changed the world - The story of Lean Production*. New York: Rawson Associates.

Womack, J.P., & Jones, D.T. (1996). *Lean Thinking*. New York: Free Press.

Yin, R. K. (1994). *Case study research design and methods.* Thousand Oaks, CA: Sage Publications.

Yin, R. K. (2003) *Case Study Research: Design and Methods Third Edition.* Thousand Oaks, CA: Sage Publications.

Young, D. (2003). *FDA tells mail-order pharmacy to stop supplying drugs to Mass City.* Retrieved November 15, 2006 from http://www.ihg.gov

APPENDIX A

Current Drug Shortages as listed by the FDA *American Society of Health-System Pharmacists* (http://www.ashp.org/s_ashp/subindex2.asp?CID=480&DID=522); (http://www.fda.gov)		
Drug Name	**Use**	**Reason for shortage**
Albumin	Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate	No raw materials / blood plasma usage.
Albuterol Metered-Dose Inhalers	Treatment or prevention of bronchospasm	Environmental / ozone
Calcium Chloride Injection	Indicated for the treatment of hypocalcemia in those conditions requiring a prompt increase in plasma	Regulatory issues, No raw materials / blood plasma usage, and resulting increased demand.
Carmustine Injection	Used to treat various cancers, Hodgkin's disease or tumors	Supplier issues
Cefazolin Injection	Used to treat skin and skin structure, respiratory and other infections	Manufacturing problems
Cefotetan Injection (Cefotan)	Prevent infections	Manufacturing problems
Cefoxitin Injection	Treats infections	Manufacturing problems

Note. From "Drug Shortages," by the FDA. Retrieved from the internet March 1, 2008 from http://www.fda.gov/cder/drug/shortages/

Drug Name	Use	Reason for shortage
CytoGam (Cytomegalovirus Immune Globulin Intravenous (Human))	Against CMV disease associated with transplantation of kidney, lung, liver, heart, and pancreas.	Supply
Echothiophate Powder for Ophthalmic Solution	Cleaning contact lenses	Manufacturing problems
Ezetimibe/Simvastatin Tablets (Vytorin)	Control of cholesterol	Manufacturing problems
Fluorouracil Injection	Cancer treatment	Manufacturing problems
Fluphenazine Injection	Antipsychotic drug	None given.
Fluvirin Influenza Virus Vaccine	Warn off the flu	No raw materials & manufacturing problems.
Haemophilus B Conjugate Vaccine (HibTITER)	Measles, mumps, rubella vaccine	Manufacturing problems
Hydrocortisone Sodium Succinate	Use for a variety of conditions including endocrine, rheumatic disorders; collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, neoplastic diseases, edematous states, sclerosis, tuberculosis meningitis, and trichinosis with myocardial or neurologic involvement.	Suspended production of its hydrocortisone sodium succinate products in order to ensure adequate production of other medications.
Immune Globulin Intravenous	Use in the treatment of Primary Immune Deficiency, Kawasaki's disease, Chronic Lymphocytic Leukemia, bone marrow transplantation, AIDS, and Immune Thrombocytopenic Purpura.	Impurity; presence of unexpected white precipitate. Recalled due to suspicion of tampering.
Indocyanine Green	Diagnostic tool used for recording dye dilution curves.	Recall due to toxic effects; fundus after use.
Indomethacin Capsules	Used to treat acute gouty arthritis; attacks of severe joint pain.	Recall due to risk of hypotension and cardiac arrest.
Lansoprazole (Prevaid)	Acid reflux	Manufacturing problems
Liotrix Tablets (Thyrolar)	Treatment of hypothyroidism	Manufacturing problems

Drug Name	Use	Reason for shortage
Lymphazurin 1% injection (isosulfan blue)	Diagnostic product used to help visualize the lymphatic system	Shortage of raw materials.
Measles, Mumps, Rubella and Varicella Virus Vaccine Live Injection (ProQuad)	Vaccine used for the prevention of Measles, Mumps, Rubella and Varicella Virus.	Shortage of raw materials - lower than expected yields of bulk varicella-zoster virus used to manufacture vaccines.
Mechlorethamine Hydrochloride Injection	Used in cancer chemotherapy	Manufacturing issues
Melphalan Injection	Used to treat cancer	Raw materials
Meningococcal Polysaccharide Vaccine	An active immunizing agent used to prevent infection by certain groups of meningococcal bacteria.	Increased demand for product.
Methadone Hydrochloride Injection	For the relief of severe pain, for detoxification treatment of narcotic addiction, and for temporary maintenance treatment of narcotic addiction.	Product sold to another company.
Methotrexate Injection	A type of chemotherapy that is used to treat certain kinds of cancer and other diseases.	Unstated
Methylene Blue Injection	Used for the treatment of intractable idiopathic pruritus ani and is used for diagnostic tracing or identification.	Manufacturing delays
Methylprednisolone Sodium Succinate	A variety of conditions including endocrine, rheumatic disorders, dermatologic diseases, allergic states. Also used to prevent adverse reactions in patients receiving blood.	Increased demand for product and manufacturing delays.
Mivacurium Injection	Used to facilitate intubation and relax skeletal muscles as an adjunct to general anesthesia.	Discontinued - Competitive environment.

Drug Name	Use	Reason for shortage
Morphine Sulfate	Used preoperatively to facilitate anesthesia and sedate patients and to relieve moderate to severe pain.	Increased demand for product and manufacturing delays.
Nafcillin Injection	Used to treat infections caused by susceptible strains of penicillinase-producing staphylococci species.	Production delays
Oxacillin Injection	Also used to treat infections caused by susceptible strains of penicillinase-producing staphylococci species.	Production delays
Paroxetine (Paxil, Paxil CR)	Use to treat depression	Unstated
Penicillin G Benzathine Injection	Use for the treatment of severe infections caused by penicillin-susceptible microorganisms when rapid and high penicillin levels are required.	Manufacturing difficulties
Penicillin G Procaine Suspension for Injection	Used for the treatment of syphilis, treatment of moderate to severe infections caused by organisms susceptible to low concentrations of penicillin, prophylaxis against infection after exposure to Bacillus anthracis (anthrax).	Increased demand
Pneumovax 23 Pneumococcal Vaccine, Polyvalent	Prevention of invasive pneumococcal.	Increased demands
Prevnar Pneumococcal 7-valent Conjugate Vaccine (Diphtheria protein)	Prevention of invasive pneumococcal disease in infants, children.	Production problems
Pyridoxine Injection	Also known as vitamin B_6 and is used to treat isoniazid overdose, metabolic disorders, mushroom toxicity (monomethylhydrazine), pyridoxine deficiency, seizures, anemia.	Increased demand

Drug Name	Use	Reason for shortage
Scopolamine Injection	Used to prevent nausea and vomiting associated with motion sickness	Manufacturing delays
Scopolamine Transdermal	Used to prevent nausea, vomiting and dizziness	Manufacturing delays
Thiamine Injection	Treats thiamine deficiency	Unstated
Ticarcillin and Clavulanate Injection (Timentin)	Effective against ß-lactamase-producing, ticarcillin/clavulanate-susceptible organisms and is labeled for a variety of indications, including bone and joint infections, gynecologic infections, and other infections; septicemia, skin and skin structure infections, and urinary tract infections.	Increased demand
Trimethoprim Tablets	Treat infections urinary	Increased demand
Varicella-Zoster Immune Globulin	Prevention of chickenpox	No raw materials / blood plasma usage
Venlafaxine Tablets and Capsules (Effexor)	Used to treat depression, panic disorder, anxiety disorder; other uses.	Production delays
Zaleplon Capsules (Sonata)	Treat difficulty falling asleep (insomnia)	Increased demand

APPENDIX B

Data Analysis

Below is the analysis of the significance of the increase in the volume of raw material available after application of lean manufacturing.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	53417.308	41	1302.861	2605.722	.000
Within Groups	5.000	10	.500		
Total	53422.308	51			