2019

A Feasibility Study on Utilizing Data Science as an Advanced Lean Manufacturing Tool in the Biopharma Manufacturing Sector

Tanya Heerts
University of Northern Iowa

A Feasibility Study on Utilizing Data Science as an Advanced Lean Manufacturing Tool in the Biopharma Manufacturing Sector

Abstract

The critical understanding, on which all else hinges in the biopharmaceutical industry, is that value is only added when a drug or a biologic is produced as a safe, efficacious first-pass product, in an efficient and effective manner. Every other activity is an expense and a cost to the company. In a tightly regulated industry that is facing turbulent times, the need to reconcile rising costs while still maintaining quality within the processes and products is imperative within the biopharma manufacturing sector. Current literature suggests that data science will have major implications in the future of biopharmaceutical manufacturing, however this emerging field still faces a long road for development and refinement for systematic use within manufacturing. Nonetheless, the strategies behind lean and data science essentially embody the same purpose: reduce waste and inefficiencies within the production flow and processes. The purpose of this paper is to demonstrate the feasibility of using big data analytics as an advanced lean manufacturing tool, as well as propose a possible model for integration with respect to constraints and challenges faced with utilizing big data analytics within the biopharma manufacturing sector.

A FEASIBILITY STUDY ON UTILIZING DATA SCIENCE AS AN ADVANCED LEAN MANUFACTURING TOOL IN THE BIOPHARMA MANUFACTURING SECTOR

A Graduate Research/Project Paper
Presented to the Graduate Faculty
of the
Department of Technology
University of Northern Iowa

In Partial Fulfillment of Requirements
for the
Non-Thesis Master of Science in Technology Degree

By
Tanya Heerts
May 1st, 2019

Approved by:

Julie Zhang

Signature of Advisor — Date: 5/3/2019

Nilmani Pramanik

Signature of Second Reviewer — Date: 5/03/2019

ABSTRACT

The critical understanding, on which all else hinges in the biopharmaceutical industry, is that value is only added when a drug or a biologic is produced as a safe, efficacious first-pass product, in an efficient and effective manner. Every other activity is an expense and a cost to the company. In a tightly regulated industry that is facing turbulent times, the need to reconcile rising costs while still maintaining quality within the processes and products is imperative within the biopharma manufacturing sector. Current literature suggests that data science will have major implications in the future of biopharmaceutical manufacturing, however this emerging field still faces a long road for development and refinement for systematic use within manufacturing. Nonetheless, the strategies behind lean and data science essentially embody the same purpose: reduce waste and inefficiencies within the production flow and processes. The purpose of this paper is to demonstrate the feasibility of using big data analytics as an advanced lean manufacturing tool, as well as propose a possible model for integration with respect to constraints and challenges faced with utilizing big data analytics within the biopharma manufacturing sector.

TABLE OF CONTENTS

1. Introduction

The manufacturing of biologic materials and biopharmaceuticals can be a complex process due to the number of variables encountered during production and subsequently can be a very expensive process. To put the financial impact into perspective, a single batch of a viral biologic vaccine could cost upwards to $250,000 from upstream to downstream processing. Advanced lean manufacturing tools and Lean Six Sigma (LSS) can leverage a biopharmaceutical organization to compete at global scale by managing waste and variability and thus churn cost-savings. Subsequently, operating expenditures are decreased which begets lower prices for consumers and therefore increases buying power. However, these tools are not trade secrets to the industries. Lean and LSS are widely practiced methodologies in the biopharmaceutical industries (Melton, 2005). So, this begs the question… if the competing top biopharma companies are properly practicing similar Lean and LSS tools in accordance to their prescribed methodologies and tools (presumably), how can biopharma companies truly gain a competitive advantage against other competing companies using the same tools and methodologies? Biopharma manufacturers, especially with the inherent complexity and variability involved with the production processes within this industry, need a more granular approach to analyzing, identifying and correcting process flaws. The landscape of the biopharma manufacturing industry is changing; thus, this research will focus on what will most likely be the future of this sector – big data and application of predictive analytics via data science as a new advanced lean manufacturing tool. The scope of the research will include creating a feasibility study on integrating data science in a biopharma manufacturing organization by proposing a conceptual framework for managing constraints. The scope of the study will include the current practices, advantages, limitations and challenges that this sector must overcome for successful implementation and utilization of the data. In addition, wireless network optimization to for utilization of big data within a manufacturing environment has been explored.

The research will leverage theory-based knowledge obtained from classes taken in the Master of Science (M.S.) of Technology program at the University of Northern Iowa (UNI) to real-world context by examining a large-size biologics company to empirically verify proposed models. In addition, the research will be supported with guidance and consideration from the Manufacturing Technology curriculum subject matter. Specifically, classes such as TECH 6275 *Advanced Lean Manufacturing*, TECH 6250 *Technology of Productivity Improvement*, TECH 5165 *Wireless Communication Networks,* and TECH 6258 *Total Quality Management,* have been most beneficial to the research of this topic and will be used in consideration for productivity improvement in the biopharma manufacturing sector. In summary, the culmination of the research will build upon what has been learned from the Manufacturing Technology curriculum coursework.

2. Rationale

Beyond traditional advanced manufacturing practices and LSS methodologies, utilizing big data can be a critical tool for realizing improvements in yield, especially in any manufacturing environment in which capacity restraints, process complexity and/or process variability are present and often at considerable costs. As alluded to above, over 200 variables may be encountered while manufacturing biologics, in which these variables can experience a variation in yield that ultimately affect capacity and outcome of the final product (Auschitzky, Hammer & Rajagopaul, 2014). To accommodate to the market needs, the biopharma industry has shifted their focus from a research-based mentality to a boardroom mindset with intent on cost cutting in order to meet the challenges faced within this sector to provide affordable medicines. Therefore, any means to reduce cost of goods in the manufacturing processes without compromising quality, while still maintaining stability and efficacy of the biologic, is an imperative need in the biopharma industry. Current literature suggests that big data is a feasible solution to give the biopharma industries the competitive edge needed to improve operations and thus provide economically justified prices on drugs and biologics to those who need it most (Rantanen & Khinast, 2015).

Nonetheless, a preliminary literature review of big data utilization within the biopharma industry reveals fragmented insights from various studies; however, no comprehensive feasibility study of similar nature to the proposed research topic could be found. In summary, there is a need for a better understanding of the constraints in big data with a structured approach in identifying and modeling constraints to ensure a constraint-free integration to the biopharma industry. More specifically, the following research questions and objectives need to be addressed:

1. What are the current industry practices in Biopharma in relation to data science and advanced lean manufacturing practices?

2. What are the typical constraints found in application and integration of big data within a complex organization, such as the biopharma sector?

3. Identify and suggest optimization in strategy and design of wireless communication networks to utilize big data in real time within a large manufacturing organization.

4. Identify and suggest a conceptual framework for integration and overcoming constraints in the Big Data within the biopharma industry.

3. Literature Review

Biopharmaceutical Industry Overview

Vaccines are a crucial factor to maintaining a healthy population across the world. According to Proano, Jacobson, and Zhang (2008), vaccines are the second most useful resource in fighting lower infant mortality rates in developing countries (clean water is number one in fighting infant mortality rates). In line

with this, the biologics industry has demonstrated growing popularity as evident by the rising projected demand from 22% in 2013 to 32% by 2023 (The Economist, 2014). This is only expected to increase as currently around a third of all the projects in late-stage pharma research & development are biologics, in which this stage can take five to seven years to come to fruition to the market (Evans, 2010). To begin with, the term biopharmaceutical (biopharma) is used to describe the segment of the pharmaceutical industry that creates drug products that are extracted from biological sources (biologics), such as blood or blood products, gene therapies, vaccines, and cell therapies. They may be safer and more effective, or better targeted, than small molecule pharmaceuticals (e.g. aspirin), but unfortunately, they are generally higher cost and more complex to develop and manufacture (Schuhmacher, Gassmann & Hinder, 2016). Additionally, manufacturing biologics may encounter over 200 variables within the production flow in which these variables can experience a variation in yield that ultimately affect capacity and outcome of the final product (Auschitzky et al. 2014). Based on the complexity of the production and characterization of large molecule biologics, the current price of the average biologic is more than 22 times that of a traditional, chemically synthesized small-molecule drug (Price & Rai, 2016).

Another challenge faced by biopharma companies include the fact that this particular industry is heavily regulated by governmental agencies since biopharma companies are legally bound entities; therefore, any changes made to equipment, reagents, or processes must fall within the scope of the agreed upon specifications. Otherwise, the company would need to refile the biologic's manufacturing process with regulatory agencies, which could take months for approval and often comes with high costs and burden to revalidating process changes (Pavlovic & Bozanic, 2010). Thus, biologics may be viewed as a highly valued and promising field amongst an industry wholly encompassed by innovation, however this medicine must still be economically viable for healthcare providers and their patients. In addition, changes to processes and procedures must work within the approved manufacturing outlines and regulations. To accommodate to the market needs, the biopharma industry has shifted their focus from a research-based

mentality to a boardroom mindset with intent on cost saving and improved efficiencies in order to meet the challenges faced within this sector. Therefore, any means to reduce cost of goods in the manufacturing processes, without compromising quality, is an imperative need in the biopharma industry.

Advanced Lean Manufacturing Background

Traditionally, biopharmaceutical companies have utilized methodologies such as Lean and Six Sigma (6σ) as the incumbent approach to reduce waste and variability and improve yield in the manufacturing processes. These methods have resulted in major improvements to the biopharmaceutical industry and therefore has helped this sector maintain a competitive edge. An overview of the methods will be defined and illustrated by case studies below.

Lean manufacturing was first conceptualized by the highly successful philosophy behind the Toyota Production Systems (TPS) as described within the book, "The Machine That Changed the World" (Womack, Jones & Roos, 1990). The ideas and philosophy within this book had introduced and popularized the lean manufacturing concept across the world when it was published in 1990. The driving force and ultimate goal of lean manufacturing practices has essentially remained the same; to create and maximize value for their customers through eliminating muda (waste) from their products or services by strategically creating optimized flow systems and pull manufacturing demand (Holweg, 2007). Thus, a lean manufacturing operation continuously works toward adding value to processes and products that customers desire by removing wastes and increasing productivity. Nonetheless, lean manufacturing is not a means to the end, but rather a continuous improvement program with a pursuit for perfection. There is not a defined end point to Lean; it's a progressive methodology and success is measured by increasing manufacturing performance achieved through lean practice tools such as 5S, Kanbans, Value Stream Mapping, 7S, Theory of Constraints, Kaizens, Just-In-Time (JIT) and Pull Manufacturing (Melton, 2005). In relation to biopharma and advanced lean manufacturing, identification and elimination of waste is especially important

to this sector. According to Ismail, Ghani, Rahman, Deros and Haron (2013), the top sixteen drug companies spent over $90 billion in manufacturing 2001, which roughly half that amount was wasted. Therefore, the concepts and tools of lean manufacturing have been applied and practiced across the biopharma industry to increase the efficiency of their operational and manufacturing processes by optimizing resources, reducing waste and controlling inventory with great effect (Melton, 2005). For example, Astra Zeneca had trialed Pull Manufacturing, a popular concept of Lean manufacturing, which had shifted the focus of manufacturing efforts from quantity output to customer demand. The outcome of this trial resulted in reducing lead time on a multibillionaire dollar product by 25% during a period when demand was increasing by 30% for said product (Shanley, 2005).

The Lean methodology is oftentimes combined with another similar methodology, Six Sigma, as a collaborated effort known as Lean Six Sigma (LSS) to achieve the best results in the biopharma industry. Briefly summarized, Six Sigma is a data-driven, business improvement strategy that seeks to find and eliminate causes of defects and errors and other non-value added processes (Brue, 2002). Six Sigma establishes a clear and concise method to find root cause of an issue, such as wide process variation in production, followed by a systematic approach broken down into five phases: Define, Measure, Analyze, Improve and Control, also known as the DMAIC process (Pokharkar, Jadhav, Gholve & Kadam, 2010). Measurement of productivity is of paramount importance during the application of the DMAIC process because measurement from quantifiable data acts as a starting point that makes performance measurements at a later stage far more significant and provides an indication of whether the initial issue has been improved upon. Root causes and improvements are generated through hypotheses during brainstorming in the Analyze phase, which may then be tested through Design of Experiments (DOE), regression and/or hypotheses testing to confirm the hypotheses. The DMAIC process provides structure and direction to accomplish the goals set forth by the Six Sigma philosophy that a company should aim to manufacture at the highest quality level (≤ 3.4 DPMO) as well as the most efficient by eliminating unproductive steps and

streamlining processes. Because Six Sigma and Lean is augmented by a highly-structured framework for implementation, it is well suited to be used in tangent in the biopharma industry. For example, in a case study described by Ismail et al. (2013), Lean Six Sigma was applied to a biopharmaceutical industry with the intent to identify wastage and reduce cycle time in manufacturing. The company was able to reduce process cycle time by 54% in a selected production area by identifying and eliminating non-value added activities through value stream mapping and process flow mapping, which resulted in an overall cost savings of $141,480 at mid-year review.

As it can be seen, Lean and Six Sigma (or a combination thereof) can undoubtedly bring a company to a more efficient and thus competitive state if properly executed. Advanced lean manufacturing tools and LSS can leverage a biopharmaceutical the ability to compete at global scale by managing waste and variability and thus churn cost-savings. Subsequently, operating expenditures are decreased which begets lower prices for consumers and increases buying power. However, it must be noted that these methodologies are not tailored for the biopharmaceutical company and therefore there may be gaps in the methodologies in which the biopharma company could be missing signals and valuable insights from. These gaps could be the difference between the global leader in biopharma versus the second, third, fourth, etc. leading performer in the industry. As mentioned above, a biologic's manufacturing process can hold over 200 variables throughout the process that could result in an exponential number of yield functions due to interactions between raw material inputs, measurement equipment settings, intrinsic variability in in-vivo and in-vitro biologic assays, etc. Consequently, brainstorming during the analyze phase could theoretically result in significant number of hypotheses. Thus, inherent human bias is necessary during the analyze phase of the DMAIC process to make the investigation manageable and mitigate "paralysis by analysis". In addition, lean and LSS are now widely practiced methodologies in the biopharmaceutical industries (Melton, 2005). So, this begs the question... if the competing top biopharma companies are properly practicing similar Lean and LSS tools in accordance to their prescribed methodologies and tools

(presumably), how can biopharma companies truly gain a competitive advantage against other competing companies using the same tools and methodologies? Biopharma manufacturers, especially with the inherent complexity and variability involved with the production processes within this industry, need a more granular approach to analyzing, identifying and correcting process flaws and prevent reoccurring issues. To overcome these challenges, biopharmaceutical companies should consider facilitating a new and emerging practice to supplement the gaps in their LSS programs – big data analytics and data science.

Data Science Overview

Data science, also commonly known as data-driven science, is an emerging interdisciplinary field about scientific methods, processes, and systems to extrapolate knowledge or insights from data in various forms, either structured or unstructured, similar to data mining (Harding, Shahbaz & Kusiak, 2006). Likewise, big data includes high-volume, high-velocity and high-variety volume of informational data derived from an organization (Tormay, 2015). Another common term in data science is predicative analytics, which encompasses the set of data tools for future predicative events (Hazen, Boone, Ezell & Jones-Farmer, 2014). Hazen et. al aptly compares data science that of the epic poem by Samuel Taylor Coleridge, "Water, water, everywhere, nor any drop to drink," (pg. 72). Biologic manufacturing processes yield large amounts of data; however, this data is typically just used for monitoring processes, rather than process improvements (Fahey & Carroll, 2016). Critical information has been digitalized for several decades now and so companies could potentially have massive data sets to tap into, yet if one does not know how to look at the data for inferences or have the tools to utilize the data, it embodies the same degree of uselessness as described by the poem. Therefore, the primary reason companies such as the biopharma sector is investing in big data is to improve analytic capabilities and make smarter business decisions by having well-informed decisions that was driven by transformed, meaningful data (New Vantage Partners, 2012). According to Goodwin (2014), the top three area that data science can benefit most are better forecasts of product demand and production, understanding plant performance across multiple metrics and

providing service and support to customers faster. Undoubtedly, data science will be a part of the future for pharmaceutical manufacturing, especially in multivariate data analysis (Rantanen & Khinast, 2015).

It must be noted that data science is not an entirely new concept to companies to utilize for process improvement. Although, current use and development of this field has just hit the tip of the iceberg (and still has much more work to do in terms of developing technology to integrate and analyze big data), it has been trialed within top-tier biopharmaceutical companies with great success. In a case study highlighted by Henschen (2017), Merck has trialed the use of data analytics to drive manufacturing decisions. In 2012, Merck was observing above average scrap rates with a particular fermentation product, which subsequently resulted in low vaccine yield for this product line. The normal investigation procedures encompassed time-consuming activities and resources, with no real guidance on where to even hone into. However, with software (Hadoop®) developed to conglomerate the massive datasets, they could integrate data from 16 disparate sources (i.e. process historians, building management systems, temperature readings, etc.) in which they had isolated the confounding factors within the fermentation process that led to the production variance yield for the particular product. Nonetheless, it took three months to find root cause – the first month required data set aggregation from all disparate sources; the second month utilized R-based analytics to chart every batch made for that particular product onto a heat map for analysis; finally, the team developed models and DOEs to test hypotheses based on the analysis from the troves of data to find root cause. In another similar top-five biopharma company case study, data science was used to significantly increase its yield in vaccine production while incurring no additional capital expenditures (Auschitzky et. al, 2014). This was accomplished by taking seemingly obscure data from process segments, clustering closely related production processes, then applied statistical analysis to assess for the variables' impact on yield. This advanced analytics assessment resulted in target process changes in nine key parameters which ultimately resulted in increasing the vaccine yield by 50% or $5 to $10 million in yearly savings.

In another case study performed by Fahey and Carroll (2016) at an unnamed biopharmaceutical (vaccine) manufacturing facility, predictive analytics was utilized on a trial basis, in conjunction with a Six Sigma DMAIC investigation, to provide further insights into opportunities for improvements. The authors had determined multiple confounding factors by using a neural network approach to identify a combination of parameters to optimize the process in unison. The results of the case study had demonstrated high precision accuracy in yields of up to 94.12% based on the data analysis performed by the predictive analytics tool, RapidMiner®. Auschitzky et. al (2014) also conclude that neural networks are key in utilizing big data to model complex processes to quantify the impact of optimal ranges for the identified parameters. This was achieved by evaluating a case study of a European manufacturer of chemicals. The company had employed neural networks techniques to assess large and complex data sets for product yield optimization. The insights gathered from the results of the neural network led the chemical company to reset parameters; ultimately the chemical company was able to reduce its waste of raw materials by 20 percent and its energy costs by around 15 percent, thereby improving overall yield due to improving the parameters (pg. 3). As demonstrated by the results of the various case studies, this emerging new field of data science can be developed within the manufacturing sector to increase the quality, accuracy and yield of biopharmaceutical production output.

Overall, it can be concluded that big data analytics has already demonstrated its use and applicability for increasing the quality, accuracy and yield of biopharmaceutical production, albeit with challenges to be considered. However, a major challenge with incorporating data science as a lean manufacturing tool within the biopharma industry would require the need to make production process flows more transactional in nature. Currently, most processes are executed via transcription through paper batch records and/or disparate entities recording information, such as historians, building management systems, the bioreactor controller, etc. However, this data needs to be integrated into a linked, central database using electronic batch records and interfacing technologies so that it can be readily retrievable when needed (i.e.

investigations into scrap, suspected inefficiencies, unfavorable trends, etc.). As Fahey and Caroll had acknowledged from their case study (2016), "it is true to say that there is a wealth of data accumulated from modern day manufacturing, but it is also true to say that it is not stored with ease of access or extraction of value in mind (pp. 52)." Moreover, a central database that provides access to critical process parameters, resulting outputs and other related information can promote a better understanding of the precursors to biologic product success and enable supervisors to focus on refining the production processes to optimize outputs and process performance. As production processes become more electronically streamlined, complex, and available in real-time, wireless network infrastructures will need to adjust accordingly with no risk of loss, disruption or corruption to the data transfers, formation of data lakes, and information processing.

Wireless Technology Application in Biopharma Industry

In regards to adapting big data to fit wireless communication networks within the biopharma manufacturing industry, three modes of wireless technology to enable big data were presented as reoccurring themes during the course of the literature review: radio frequency identification (RFID), wireless sensor networks (WSN), and cloud computing. These three modes have been evaluated below.

Radio frequency identification (RFID). To begin with, RFID tags allow for real-time tracking by having the capability to emit a wireless data signal containing an identification number and information related to the tagged material such as lot number, expiry dating, current locations, inventory volumes, etc. (Ciampa, 2013). This is achieved by using radio waves, a tag, and a reader (Lee & Lee, 2015). In the biopharma industry, RFID is a useful wireless tool for electronic warehouse management, as well as real-time tracking of physical production flows. In a case study performed by Wang, Dai, Zhang, Luo, and Zhong (2010), RDIF-enabled manufacturing execution systems (MES) were implemented via the authors' proposed MES model at a pharmaceutical enterprise. According to the case study, key steps in the

production line were equipped with RFID-enabled Intelligent Data Terminal (IDTs) to operators and raw materials. Therefore, critical process parameters and steps, such as environment parameters, material components, technical parameters, quality parameters, etc. were measured and monitored in real-time. By monitoring, collecting and evaluating this data over an 11-month period, the pharmaceutical company was able to reduce the average production cycle by 23%, automate the work in progress (WIP) review, and had resulted in zero errors in distribution of the RFID-tagged materials. Of importance to note were the IDTs, which served as hardware platforms for RFID readers, in which selection and debugging of the IDTs were a significant factor to the success of the case study (Wang, et al., 2010). In another motivating example, passive RFID sensors were placed on gas sensors to monitor gas flows/exchanges in real-time; if fluctuations in the temperature and gas flows were detected via multivariate analysis, the gas sensors would self-correct against fluctuations of ambient temperature of individual passive RFID gas sensors (Potyrailo & Surman, 2013). This is important because uncontrolled fluctuations of ambient temperature can greatly reduce accuracy of gas sensors and potentially impact the product of the manufactured biologic product (Zellers & Han, 1996). As you can see, this example uniquely demonstrates that the RFID's capability extends beyond just a tool for warehouse management and inventory tracking only.

In Wang et al.'s optimized RFID-enabled MES model for pharmaceutical manufacturing, two critical elements were discussed – the base station (BS) and IDT (2010). The BS essentially acted as the liaison between the wireless sensor and IDTs and had communicated to the IDTs through 433MHz wireless networks. To mitigate the risk of interference, each BS occupied one frequency with 50 KHz as bandwidth. To communicate with IDTs, the BS switches the channel to it and captures its data to then send them to the Communication Program. On the other hand, the IDT functionality included serving as the RFID reader, input/output reader, and transfer device. Per Wang et. al, the RFID reader can work at the frequency of 125 KHz or 13.56MHz, which are also the most universal frequency in RFID field. The network module supported three modes: TCP/IP via UTP; RS422 via cable; 433MHz via wireless. In this particular case

study, 433 MHz via wireless was the chosen configuration, which was utilized without issue (pg. 50). The research, as discussed above, validates proof of concept and a provides a feasible design for a mid-size biopharmaceutical company.

Wireless sensor networks. Similar to RFID technology, wireless sensory networks (WSN) is a culmination of autonomous of wireless-capable sensory devices (embedded nodes) that work harmoniously to achieve a common objective (Mourtzis, Vlachou & Milas, 2016). However, the distinction between RFID and WSN is that RFID aides in detection and identification of objects, whereas WSN, as the name implies, senses and monitors the condition of the object and/or environment (Vishwakarma & Shukla, 2013). Nonetheless, WSN can be used in tandem with RFID to optimize real-time monitoring of manufacturing and process data. According to Xu, He, and Li (2014), "by integrating data acquired by intelligent sensors (WSN) with RFID data, more powerful IoT applications that are suitable for the industrial environments can be created (pg. 2237)". For example, the RFID can identify an object for which the WSN can provide additional information, such as environmental or process conditions for the RFID. WSN also enables multi-hop wireless communication, which can improve coverage and data throughput (Mourtzis et al., 2016).

Per Potdar, Sharif, Potdar and Chang (2009), the general design of a WSN includes a server/base station, sink nodes, WSN nodes, and RFID tags. The data from the WSN nodes come to the sink node first (over wireless link) and then from the sink node, it is passed to the server by either use of wired/optical medium or wireless transmission through the use of a radio frequency (RF) protocol (Potdar et al., 2009). The base station is typically a computer coupled with an RF transceiver to receive and decode of the inbound packets; however, to minimize costs, the computer can be replaced with a microprocessor (Li & Kara, 2017).

To further expand on the architecture of WSN, Li and Kara proposed a two-step framework for an optimized design for WSN integration in a large-scale manufacturing facility (2017). The first step is the physical design of the WSN as describe through four-layer approach. Briefly, the first layer is data acquisition and transmission via the WSN. Next, WSN interfaces with the computer or microcontroller to deliver the data in the second layer. In the third layer, the authors highly suggest pursuing a cloud-based approach, rather than a static server, for data storage and/or data analysis to accommodate to large data sets and large volumes of incoming data. This can be achieved through subscription to a Software-as-a-Service (SaaS) or Platform-as-a-Service (PaaS). The last layer of the first step is data visualization via retrieval through cloud computing or a PC. The second step of the two-step framework is essentially a proposed qualitative guideline to select a software/hardware product for each aforementioned layer based on the type of infrastructure and facility in question (Appendix A). Although there has been little research done in regards to WSN integration in a biopharmaceutical facility at this point in time, the research and proposed model discussed indicates compelling evidence that it will meet the needs of big data utilization in the biopharma industry.

Cloud computing. As alluded to from the two-step framework for WSN design, cloud computing is necessary when dealing with big data as it acts as a repository to store and/or analyze large volume of data. Therefore, cloud computing provides a backend approach for handling large streams of incoming data from various disparate sources. According to Ren and Zhao (2015), resource allocation is achieved by multiple cloud data nodes, which makes the data closer to the users and therefore the response time of the system is shortened and the productivity of the enterprise is increased. Ultimately, cloud computing allows for ubiquitous connectivity and access to data flow for real-time monitoring, as well as store historical data to use for predictive analytics (Zhong, Shulin, Xu, Dai & Huang, 2015). Mourtzis et al. suggest that non-relational (NoSQL) databases are more convenient compared to relational (SQL) databases that are not flexible when changes in the schema are required, which could be due to variety of data acquisition devises

used in the manufacturing area (2016). Nonetheless, cloud computing is the underpinnings to support RFID and WSN applications from the manufacturing floor and thus is necessary to support big data analytics with medium to large-size organizations (Zhong, Xu, Klotz & Newman, 2017). To further enhance use of stored data via cloud computing, open-source software such as Hadoop® or Cassandra®, can be used within cloud computing to analyze and extract meaningful information from volume, variety and veracity of data (3V) to improve production processes and reduce rate of errors. This is the heart of predictive analytics as well as a subset of data science.

Other considerations in optimized network design. As the term "big data" implies, this is data that is high-volume, high-velocity, and high-variety that is beyond traditional technology abilities to process and store in a simple and efficient manner (Alghamdi, Ahmad & Hussain, 2015). To best meet these needs, a fifth generation (5G) wireless network would meet the network capacity to accommodate big data analytics, which would allow for spectrum expansion, spectrum efficiency enhancement, and network densification (Zhang, Yang, Ren, Chen, Yu & Shen, 2018). 5G wireless networks can transfer data more rapidly since it utilizes a higher-frequency band of the wireless spectrum, called a millimeter wave, than that of the lower-frequency band dedicated to 4G. However, the millimeter wave signals have smaller cells and therefore requires more, although smaller, antennas placed closer together. Nonetheless, 5G wireless networks are expected to be faster (10 – 200x based on various reports) than its 4G late term technology (LTE) counterpart (Fulton, 2019). In addition, 5G will likely migrate to a cloud-based layer network structure, as opposed to a base station cellular architecture (Bi, Zhang, Ding & Cui, 2015); so, 5G harmonizes with the needs of big data analytic as discussed above in regards to cloud computing. It must be noted that 5G is still in its infancy and has just very recently begun deployment by a few companies in select areas around the world. Nonetheless, this new technology should be watched closely by the biopharma industry as it will be necessary to support big data analytics as the platform grows in the future for this sector. According to Zhang et al., "5G wireless networks will play a very important role in the big

data processing chain due to the ubiquitous coverage as well as in-network storage and computing capabilities (2018)."

One of the top concerns in handling a massive amount of data is traffic and the ramifications of heavy traffic – in essence, a congested network and slow response time. Of course, this can be remediated by increasing bandwidth; however, Costa, Donnelly, Rowstrong, and O'Shea have proposed an alternative solution for traffic reduction while minimizing the need to increase bandwidth (2012). Traffic can be decreased by pushing data aggregation from the edge into the network via a platform called Camdoop, which distributes the functionality of the switch across the servers, as opposed to having dedicated switches. To provide conceptual context for the authors' model, Camdoop constructs aggregation trees where the branches serve as the intermediate data sources and the roots signify the servers performing the final reduction in traffic. Experimental test tuns of the proposed model by the authors had demonstrated a significant traffic reduction when compared to Camdoop running on a switch. In another study, Bi et al. contend that caching popular contents at wireless hot spots could effectively reduce the real-time traffic in the fronthaul links (2015). Thus, there are possibilities to consider for traffic reduction if increasing bandwidth is not a desirable option to pursue.

4. Method of Study

The research employed the quantitative literature review methodology, commonly called a meta-analysis, to conclude the overall findings and create a theoretical foundation for a feasibility study. This study was conducted by intensive literature review of peer-reviewed, recent (i.e. published within the last seven years) academic literature and case studies of similar nature to the research topic. Next, existing network communication and integration / constraint modeling methods has been identified based on a comprehensive review of current industry practices and academic researches. Finally, once the constraint classification and integration modeling techniques were identified using a large midwestern biologics

company as a case study, a conceptual framework for total integration / constraint management was outlined.

5. Analysis and Results

It must be recognized that a conceptual framework/model is not a one-size-fits-all approach. Based on the size, complexity and processes/systems utilized for process monitoring and data management, the framework could take on various forms to best suit the needs of the firm. Therefore, to provide a frame of context to create the conceptual model, a case study involving a midwestern, large-size animal health biologics company, Company Z, was utilized to fit the model. Briefly, Company Z is a leading producer in a variety livestock and companion animal vaccines, specifically poultry, equine and swine. The manufacturing operations include egg-based, tissue culture-based, fermentation and bioreactor methodologies to produce viral and bacterin vaccines. Company Z nets an annual revenue of $280 million and like many biopharma companies, it also recognizes and has a robust Lean Six Sigma program that deploys yellow, green and black belt training to the site organization. Nonetheless, despite the robust Lean Six Sigma program within the organization, Company Z had about $3.1 million worth of scrap in 2018 due to human error, out-of-specification material, contamination, etc.

To begin with, a major challenge with incorporating data science as a lean manufacturing tool within the biopharma industry has been the need to make production process flows electronic and more transactional in nature (Tormay, 2015). In the case of Company Z, manufacturing batch records are executed via manual transcription through paper batch records and/or disparate entities recording information, such as historians, building management systems (BMS), the bioreactor controller, zLIMs, etc. This data has to be integrated into a linked, central database using electronic batch records and interfacing technologies so that it can be readily retrievable when needed (i.e. investigations into scrap, suspected inefficiencies, unfavorable trends, etc.). These electronic systems would include electronic

laboratory notebooks for batch critical process parameters, laboratory information management systems (LIMS) for retrieval of in-process and finished product testing results, and enterprise resource planning systems (ERP), SAP, for product volumes, sales, inventory, and master data governance information (Sinclair, Monge and Brown, 2014). This would require labor intensive efforts and much change on the Company Z's initiative, but the efforts would be worth the outcome. A central database that provides access to critical process parameters, resulting outputs and other related information can promote a better understanding of the precursors to biologic product success and enable supervisors to focus on refining the production processes to optimize outputs and process performance. Nonetheless, it is the author's opinion that Company Z must first transition to electronic batch records prior to integration of big data and data science at the site. Without it, process data is incomplete and meaningful insights to improve yields could not be extracted from the data sets. Company Z plans to move towards electronic batch records in the near future, with implementation complete by yearend of 2020. However, all other systems (i.e. LIMS, SAP, BMS, bioreactor controllers, historian data) are electronic with datamining capabilities via SQL coding. To conclude, it is not only the biopharmaceutical firm's advanced lean manufacturing practices and views that must be changed to adapt to the new era of big data, but in addition, the wireless network infrastructure and supporting technology must be able to accommodate to these changes as well.

In line with supporting electronic systems, the production core and manufacturing facilities should be heat-mapped for wireless connectivity strengths to assure the manufacturing areas have the necessary bandwidth to meet wireless communication needs to support big data analytics. Surveying the manufacturing facilities via heatmapping also provides the opportunity to determine the need for additional wireless router access points (APs) or boosters to reconcile dead zones or areas with weak connectivity. In the case of Company Z, a survey of the facility was completed using the Ekahau® HeatMapper site survey tool. The heatmap indicated that about 75% of the manufacturing facility had strong wireless network

connection; however, a quarter of the facility did show weak connectivity or dead zones in certain areas[1]. Thus, Company Z would have to remediate these identified areas prior to the advent of implementing electronic batch records to include another AP or booster to ensure strong wireless connectivity for adequate wireless communications across the site.

WSNs are currently not used at Company Z; however, RFID tagging and scanner use has just been recently implemented at Company Z (2017 yearend), but used only for warehouse management of raw materials. Thus, company Z has the functionality to utilize RFID, although the enterprise would have to increase capacity of their RFID resources and wireless bandwidth to equip production process flows with RFID tags and WSNs at critical process parameter points; 433MHz wireless networks is necessary to accommodate the WSNs and RFIDs. Using these two wireless technologies in parallel provides identity and location of an object, but also provides information regarding the condition of the object carrying the sensors enabled RFID tag (Jain & Vijaygopalan, 2010). Therefore, when RFID-tagged materials and WSNs flow to RFID-tagged operators, real-time information, such as environment parameters by sensors, machine status and quality parameters by input, are collected into MES database. This will enable data collection for real-time analysis and communication between moving parts to ensure an optimized output.

Next, Company Z would have to implement a comprehensive data repository to integrate the disparate sources of information to one interface to support big data analytics for compilation, storage and data management. This can be achieved through procuring an open source operating system (OS) designed especially for node integration (e.g. Hadoop® or Cassandra®). Such OSs utilizes a component-based architecture that enables rapid implementation, while minimizing code size as required by the memory constraints in sensor networks (Jain & Vijaygopalan, 2010). For example, and more specifically, Hadoop® is a top-level, java-written, open source framework that stores data by distributing it on computer clusters

[1] Company Z's heat map grids could not be provided within the report due to confidentiality of the plant.

(Hadi, Lawey, El-Gorashi, & Elmirghani, 2018). Therefore, Hadoop® not only has the ability to store and assimilate all kinds of data, but can do so while performing other tasks via clustering (Goyal, Monga & Mittal, 2017). This is especially useful for an enterprise like Company Z since over fifty different operations could be in-process simultaneously. By utilizing cloud-based big data analytic platforms (such as Hadoop® and related OS), the organization can handle large data volumes capable of handling 4.2 TB of data per day supplied through 123 Gbps links at low cost and high performance (Hadi et al., 2018). It must be noted that other traditional cloud computing can also be used for data storage and management as well, although the advantage of Hadoop® over other traditional cloud computing platforms is that Hadoop® takes it a step further by assimilating the data into data nodes and clusters.

In addition to data storage and management software, a datamining and reporting tool is necessary to enable the organization's capability to utilize big data analytics. An example of this tool would be RapidMiner®, which can be configured with Hadoop® to perform and streamline predictive analytics using neural networks. Over time, the assimilated process data from Hadoop® should theoretically have a large sample size to assure meaningful insights. Thus, these datasets would be fed in RapidMiner® to determine optimal process parameters for yield improvements. RapidMiner® would then use a neural network approach to identify explanatory variables in unison to optimize operating parameters to improve yield. The limitation at this point would necessitate the need for the site to acquire the skillsets, such as a data expert, statistics analyst, or datamining (DM) expert, to be able to perform the analysis. This would be necessary to understand and provide valid interpretation of the results obtained by RapidMiner® to determine its significance and outputs (Fahey & Carroll, 2016). Although hiring of these experts would be an ongoing investment, scrap reduction due to quality improvements in manufacturing would yield a significant return on investment (e.g. Company Z had $3.1 million in scrap in 2018).

Table 1 has outlined a generalized concept model for integrating big data analytics into the biopharma industry with consideration to overcoming constraints and challenges. Although Company Z is considered to be a global leader in manufacturing animal health biologics, the case study has highlighted a major gap between the site's current utilities and facilities versus the capability for improvement by big data analytics. In addition, by reviewing the current wireless technologies that can enable big data, in addition to current practices within the biopharma industry, gaps have been identified within the field. Nonetheless, it must be recognized that these tools are still in its infancy and thus it is an opportune time for the biopharma sector to begin preparing for these changes (i.e. close the gaps), as discussed above, that will undoubtedly be coming down the pipeline. Most importantly, biopharma companies should include training on datamining and statistical analysis to ensure valid interpretations of results to enhance understanding to make sound, data-driven decisions. This will begin to change the overall mindset and prepare its employees for the future of biopharma manufacturing and the data-driven revolution.

Table 1. Stepwise model for big data analytics in the biopharma industry and associated constraints.

No.	Step	Activity	Constraint / Challenge	Comments
			All critical points and parameters in the process needs to be monitored.	RFID and WSN to be deployed at a critical process parameter points.
1	Run Manufacturing Process per Product	Monitor process from starting operations to finishing operations.	Production core and manufacturing suites must be equipped with wireless communication networks and strong bandwidths.	Heatmap facilities to determine wireless capability and connectivity strengths. Mitigate dead zones and weak areas by additional APs or boosters.
2	Collect LIMs (QC data), Batch Record (process data), BMS (temperature, humidity, pressure), SAP (ERP data), bioreactor controller, historian data.	Data collection at all points in the production flow.	All data collection needs to be performed electronically.	With the advent of electronic batch records and other electronic systems, the biopharma enterprise must make these investments to eliminate gaps in the data analysis and therefore prevent spurious analysis.
3	Conglomerate Data in Hadoop®	Funnel all data from disparate sources (listed in step #2) into Hadoop to store and manage the data into structured formats.	Requires an open source system (Hadoop, Cloudera, Cassandra, etc.) to store, assimilate and manage data by distributing it on computer clusters.	Investment by biopharma enterprise to obtain and maintain software platform.
4	Datamine in RapidMiner®	Configure Hadoop to RapidMiner or other data science platform to streamline predictive analytics	Requires an open source data science platform to streamline your predictive analytics	Investment by biopharma enterprise to obtain and maintain software platform.
5	Perform Predictive Analytics	Evaluate dataset models within RapidMiner for statistically significant operating parameters	Requires skillsets within the organization to read, understand and interpret valid statistical inferences from the data science platform.	Enterprise should consider hiring these specific skillsets, if not already within the organization.
6	Trial optimized process parameters in Manufacturing Suite	Hone processing parameters to fit optimized model. Trend results.	N/A	These steps are cyclical. Process data will continue to be collected and evaluated over time for continuous improvement and refinement.

6. Summary and Conclusion

Company Z faces several challenges in that 1.) the main source of process data to elicit the most valuable information is still recorded in manual form; 2.) the major electronic data acquisition systems are

not linked or interfaced into a heterogenous network; and 3.) overall, the site is not capable of generating or utilizing big data to improve manufacturing processes to improve products and/or increase yields and therefore would need significant initial investment to implement the proposed systems. Nonetheless, the proposed model in Table 1 illustrates a path for integration and implementation, while addressing current constraints within the biopharma industry, such as Company Z.

The research presented in this paper provided a breadth-first review of the research relating to big data in the biopharma manufacturing sector to promote a better understanding of a new and pervasive area. The biopharma manufacturing sector possesses many unique challenges due to the complexity of processes, inherent process variability and capacity limitations that encompass biologics manufacturing. However, these process-type industries sit on a plethora of untapped data that could reveal and transform processes to an optimized state. Although biopharma companies still have a long road in refining and utilizing advanced data analytics, data science, in addition to lean six sigma methodologies, can be a critical tool for realizing improvements in variability and yield. Due to the large and complex nature of manufacturing biologics, big data analytics allows the investigator to take an exploratory approach to correcting root cause, rather than confirming or refuting hypotheses. However, big data analytics is by no means intended to supersede Lean Six Sigma as an advance manufacturing tool; rather it is meant to work in parallel with this methodology as a quality improvement strategy. In conclusion, data science as an advanced lean manufacturing tool is a feasible solution to give the biopharma industries the competitive edge needed to maintain operations that could provide economically justified prices on drugs and biologics to those who need it most.

7. References

Alghamdi, A.S., Ahmad, I., Hussain, T. (2015). Big Data for C4I Systems: Goals, Applications, Challenges and Tools. *International Conference on Innovative Computing Technology (INTECH),* 89-93.

Auschitzky, E., Hammer, M., Rajagopaul, A. (2014). How data can improve manufacturing. *McKinsey & Company*. 1 – 4.

Bi, S., Zhang, R., Ding, Z., & Cui, S. (2015). Wireless communications in the era of big data. IEEE Communications, 53(10), 190-199.

Brue, G. (2002). Six sigma for managers. Madison, WI: McGraw-Hill Companies, Inc.

Ciampa, M. (2013) CWNA guide to wireless LANs (3rd ed.). Boston, MA: Course Technology, Cengage Learning.

Evans, I. (2010). Follow-on biologics: A new play for big pharma. *Yale Journal of Biology and Medicine, 83*(2), 97 – 100.

Fahey, W., Carroll, P. (2016). Improving biopharmaceutical manufacturing yield using neural network classification. *Bioprocessing Journal, 14*(4), 39 – 50. DOI: 10.12665/J144.Carroll.

Fang, H., Zhang, Z., Wang, C. J., Daneshmand, M., Wang, C., Wang, H. (2015). A survey of big data research. *IEEE network, 29*(5), 6 – 9. DOI: 10.1109/MNET.2015.7293298.

Fulton, S. (2019, February 19). What is 5G? Retrieved from https://www.zdnet.com/article/what-is-5g-everything-you-need-to-know/.

Goodwin, G. (2014). Attitudes on How Big Data will Affect Manufacturing Performance. *LNS Research.* Retrieved from: http://blog.lnsresearch.com/blog/bid/194972/Attitudes-on-How-Big-Data-will-Affect-Manufacturing-Performance-DATA

Goyal, Y., Monga, Y., Mittal, M. (2017). Study and analytical perspective on big data. *International Journal of Computational Systems Engineering, 3*(4), 193-202.

Hadi, M. S., Lawey, A. Q., El-Gorashi, T. E., & Elmirghani, J. M. (2018). Big data analytics for wireless and wired network design: A survey. Computer Networks, 132, 180-199.

Harding, J., Shahbaz, M., Kusiak, A. (2006). Data Mining in Manufacturing: A Review. *Journal of Manufacturing Science and Engineering*, 128, 969 - 976. Retrieved from DOI:10.1115/1.2194554.

Hazen, B.T., Boone, C.A., Ezell, J.D., Jones-Farmer, L.A. (2014). Data quality for data science, predictive analytics, and big data in supply chain management: An introduction to the problem and suggestions for research and applications. *International Journal of Production Economics*, 154, 72 - 80.

Henschen, D. (2017, December). Merck optimizes manufacturing with big data analytics. *Information Week.* Retrieved from *https://www.informationweek.com/strategic-cio/executive-insights-and-innovation/merck-optimizes-manufacturing-with-big-data-analytics/d/d-id/1127901*

Holweg, M. (2007). The genealogy of lean production. Journal of Operations Management, 25, 420-437.

Ismail, A., Ghani, J.A., Rahman, M.N.A, Deros, B.M., Haron, C.H.C. (2013). Application of lean six sigma tools for cycle time reduction in manufacturing: Case study in biopharmaceutical industry. *Arabian Journal for Science and Engineering, 39*(2), 1449 - 1463.

Jain, D.P., Vijaygopalan, K.P. (2010). RFID and Wireless Sensor Networks. *Proceedings of ASCNT – CDAC* in Noida, India, 1 – 11. Retrieved from: https://pdfs.semanticscholar.org/47ae/cbb03c54d74911e11266d24289586ac72e2a.pdf?_ga=2.230 02171.1272462875.1555268644-1720434243.1555268644

Lee, I., Lee, K. (2015). The internet of things: Applications, investments, and challenges for enterprises. *Business Horizons, 58*, 431 – 440. Retrieved from: http://dx.doi.org/10.1016/j.bushor.2015.03.008.

Li, W., Kara, S. (2017). Methodology for Monitoring Manufacturing Environment by Using Wireless Sensor Networks (WSN) and the Internet of Things (IoT). Procedia CIRP, 61, 323 – 328.

Melton, T. (2005). The benefits of lean manufacturing: What lean thinking has to offer the process industries. *Chemical Engineering Research and Design, 83*(6), 662 - 673. DOI: doi.org/10.1205/cherd.04351

Mourtzis, D., Vlachou, E., Milas, N. (2016). Industrial Big Data as a result of IoT adoption in Manufacturing. Procedia CIRP, 55, 290 – 295.

New Vantage Partners (2012) Big data executive survey 2012. Consolidated summary report. http://newvantage.com/wp-content/uploads/2012/12/NVP-Big-Data-Survey-Themes-Trends.pdf.

Pavlovic, K., Bozanic, V. (Eds). (2010). Lean and six sigma concepts - Application in pharmaceutical industry. Proceedings from: *4th International Quality Conference.* Faculty of Mechanical Engineering, University of Kragujevac.

Pokharkar, D., Jadhav, V., Gholve, S., Kadam, V. (2010). Six sigma: golden opportunity for pharmaceutical industry. *International Journal of PharmTech Research, 2*(2), 1160 – 1164.

Potdar, M., Sharif, A., Potdar, V., Chang, E. (2009). Applications of Wireless Sensor Networks in Pharmaceutical Industry. International Conference on Advanced Information Networking and Applications Workshops, 642 - 647.

Potyrailo, R. A., Surman, C. (2013). A Passive Radio-Frequency Identification (RFID) Gas Sensor with Self-Correction Against Fluctuations of Ambient Temperature. Sensors and actuators. B, Chemical, 185, 587–593. DOI: 10.1016/j.snb.2013.04.107

Price, W.N., Rai, A.K. (2016). Manufacturing barriers to biologics competition and innovation. *Iowa Law Review, 101*(3), 1023 - 1063.

Proano, R.A., Jacobson, S. H., Zhang, W. (2012). Making combination vaccines more accessible to low-income countries: the antigen bundle pricing problem. Omega, 40(1), 53 – 64.

Rantanen, J., Khinast, J. (2015). The Future of Pharmaceutical Manufacturing Sciences. *Journal of Pharmaceutical Sciences, 104*(11), 3612 - 3638. DOI: 10.1002/jps.24594.

Ren, S., Zhao, X. (2015). Framework and key technologies for big data based on manufacturing. 2015 International Conference on Materials Engineering and Information Technology Applications, 380 – 383.

Schuhmacher, A., Gassmann, O., Hinder, M. (2016). Changing R&D models in research-based pharmaceutical companies. *Journal of Translational Medicine, 14*(105), 2 – 11. DOI: 10.1186/s12967-016-0838-4.

Shanley, A. (2005). Operation excellence: walking the talk. Pharmaceutical Manufacturing. Retrieved from https://www.pharmamanufacturing.com/articles/2005/400/.

Sinclair, A., Monge, M., Brown, A. (2014). A framework for process knowledge management. BioProcess Int, 10(11), 22–9.

The Economist. (2014). Pharmaceuticals: Going Large. Retrieved from https://www.economist.com/news/business/21637387-wave-new-medicines-known-biologics will-be-good-drugmakers-may-not-be-so-good.

Tormay, P. (2015). Big data in pharmaceutical R&D: Creating a sustainable R&D engine. *Pharmaceutical Medicine, 29*, 87 – 92.

Vishwakarma, U. K., Shukla, R. N. (2013). WSN and RFID: Differences and integration. International Journal of Advanced Research in Electronics and Communication Engineering, 2(9), 778 – 780.

Wang, M., Dai, Q., Zhang, X., Luo, X., Zhong, R. (2010). A RFID-enabled MES for Real-time Pharmaceutical Manufacturing Supervision. *IEEE International Conference,* 49-53.

Womack, J., Jones, D.T., Roos, D. (1990). The Machine That Changed the World: The Story of Lean Production. New York: Rawson and Associates.

Xu, L.D., He, W., Li, S. (2014). Internet of things in industries: A survey. IEEE Transactions on Industrial Informatics, 10 (4), 2233 – 2241.

Zellers, E.T, Han, M. (1996). Effects of Temperature and Humidity on the Performance of Polymer-Coated Surface Acoustic Wave Vapor Sensor Arrays. Analytical Chemistry, 68, 2409–2418.

Zhang, N., Yang, P., Ren, J., Chen, D., Yu, L., & Shen, X. (2018). Synergy of big data and 5g wireless networks: opportunities, approaches, and challenges. IEEE Wireless Communications, 25(1), 12-18.

Zhong, R.Y., Shulin, L., Xu, C., Dai, Q., Huang, G.Q. (2015). Visualization of RFID-enabled logistics Big Data in Cloud Manufacturing. The International Journal of Advanced Manufacturing Technology, 84(1-4), 5 – 16. DOI: https://doi.org/10.1007/s00170-015-7702-1.

Zhong, R.Y., Xu, X., Klotz, E., Newman, S.T. (2017). Intelligent manufacturing in the context of industry 4.0: A review. Engineering, 3 (5), 616 – 630. Retrieved from: https://doi.org/10.1016/J.ENG.2017.05.015.

8. Appendices

APPENDIX A