IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 7 Issue 7, July 2020
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

Manufacturing Automation Technologies and Processes Currently Employed by Pharmaceutical Industries

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Abstract

Manufacturing in the Pharmaceutical Industry presents its own set of unique challenges. These range from constantly changing drugs and medicines, to machine standards, to the amount of a desired medication that is required to be produced. The world of pharmaceutical manufacturing is constantly changing. To keep up, the industry has fully adopted production line automation to keep up with the demand and to produce drugs and medicines that will adhere to the strictest of standards. The equipment capable of performing such tasks have undergone years of research and development and are still being changed to this day. All factors when manufacturing drugs must be taken into consideration. This includes everything from batch size, to dose size, to environment in which the drug is manufactured, to the packing requirements of each medication and much more. Because of the large number of requirements and standards set on the manufacture of drugs, the use of Industry 4.0 and other advanced automation equipment and software have been developed specifically for the pharmaceutical industry. These processes and technologies may be changing and being updated at a rapid pace, however certain technologies and processes remain similar among multiple different products and companies alike. The recent outbreak of the COVID-19 (Coronavirus) is an example as to how the pharmaceutical industry adapts and changes to new challenges and it shows how the machinery, software's, and workforce must adapt to combat this outbreak.

Keywords: *Pharmaceutical, Automation, Robotics, Industry Standards, New Technologies, COVID-19*

1. Introduction

The Pharmaceutical industry is held to some of the strictest standards in terms of productivity, cleanliness, and safety. There are multiple different processes and functions of those processes that must be controlled for the finished product to be safe for the consumer to use. Automated processes require less human intervention and are therefore less prone to human errors. Once the process is setup and the system are showing repeatable, reliable results, the system can run without any human interference. This all looks very good on paper, however getting these processes setup and producing these repeatable results takes a lot of time and in most cases require a large investment from the company implementing these processes. There is also a large amount of assumed risk when a company sets up a new automated process, especially in pharmaceutical industries. Batches of raw material handled by these processes may be worth millions of dollars and if the machine or process malfunctions, breaks down, or creates a finished product that does not hold up to the rigorous standard set by The Food and Drug Administration (FDA) and related firms, the entire batch, and millions of dollars, are wasted. The key for pharmaceutical companies is to have reliable, sound automation systems that produce reliable results with a minimal capital investment. Which will be the subject matter of this research paper. In addition, Remdesivir is an example of a treatment that has been shown to be effective in combating the COVID-19 outbreak and also shows how the pharmaceutical industry must be able to produce a large amount of a treatment that is effective, safe, and adheres to the standards that the industry must adhere to.

2. Pharmaceutical Industry Standards

Known for some of the highest and strictest standards in the manufacturing world, pharmaceutical companies have the responsibility to create quality, safe, and clean drugs that will always hold up to strict regulations set in place by FDA. The biggest regulatory standard the industry must uphold is the Current Good Manufacturing Practices (CGMPs). This essentially ensures that every batch of product is safe and effective for the user. This includes every part of the manufacturing process from raw material procurement to finished goods, and every operation in between [1]. This is important to the manufacturing process as all automated parts of the process must adhere to the FDA's CGMPs in order to produce product. Quality must be built into every step and this includes all automated steps of the process. These standards govern the drugs themselves and there is an entire separate standard put in place for the machines the pharmaceutical industry uses.

The American Society for Testing and Materials (ASTM) hold specific sets of standards the pharmaceutical industry must abide by. These standards cover every facet of machinery used in pharmaceutical manufacturing, covering process control, design, and performance, as well as quality acceptance and assurance testing [2]. The current list of categories the ASTM established for the pharmaceutical industry consists of general biopharmaceutical standards, general pharmaceutical standards, process understanding and Process Analytical Technology (PAT) system management implementation and practice, and terminology [2]. In the general biopharmaceutical standards section, topics such as low temperature and cryopreserved materials storage design, inventory control, and standard practices when handling biological materials are covered. In the general pharmaceutical standards section, pharmaceutical manufacturing systems and equipment standards, standard practice in demonstrating compliance, cleaning standards, and the like can be found. In the process understanding and PAT system management implementation and practice section, standards for practicing pharmaceutical process design, risk assessment/control, application of continuous processes, and sampling guides can be found.

When it comes to major standards to adhere to, there are 5 ASTM standards that are considered "essential" [3]. These standards are essential to all new products being developed and sold by the pharmaceutical industry. The first of these essential standards is titled "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (E2500)". This Pharmaceutical manufacturing system mainly deals with standards such as the design, installation, operation and its performance factors. Before the publication of this guide, it was harder for companies to adhere to this standard, the guide makes this process simpler to follow. This guide allows for easier adherence to the current standards as compared to what they were before they were published. The second essential standard is "Standard practice for Qualification of Basket and Paddle Dissolution Apparatus (E2503)". This standard addresses the product's ability to be dissolved in the stomach. A procedure is established to allow for the manufacturer to prove that their results from a calibration test of the product to be reproducible. The third essential standard is the "Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology (E2474)". This standard helps streamline the manufacture of large quantities of pharmaceuticals and focuses on risk management, continuous improvement, performance assessment, manufacturing strategy, data collection, and much more. The fourth essential standard is "Standard Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing (E2537)". To create a product that ensures that the process will produce consistent results based on the predetermined critical attributes of the product, the manufacturing process should focus on producing consistent results. The fifth and final essential standard is "Standard Practice for Process for Inactivation of Rodent Retrovirus by pH (E2888)". This standard focuses on the medical efficacy of drugs. This involves the use of rodent-derived cell cultures to ensure inactivation of non-defective C-type retroviruses [3]. It is from these standards that automation processes for the pharmaceutical industry can be built. These standards are incredibly strict and must be adhered to completely for a manufacturer to produce drugs and treatments.

3. Factory Control Systems and Software Used

As seen in the example in Figure 1, automation can be seen in almost every part of the pharmaceutical manufacturing process. From the handling of raw material to the packaging of the finished goods, automation is utilized. One major company that provides software for the pharmaceutical industry is Rockwell Automation. The Quality Management Systems (QMS) and Manufacturing Execution Systems (MES) are used in all major software providers such as Rockwell Automation which provides software called PlantPax MES and PharmaSuite MES. Both of these applications allow for

pharmaceutical manufacturers to update their operating systems with minimal downtime and require minimal amounts of training [4]. PharmaSuite MES manages all the processes from recipe checks to quality checks and can bring a manufacturing plant closer to "Industry 4.0". Industry 4.0 refers to the latest revolution in industry that makes use of interconnectivity, automation, machine learning, and real-time data. The Industry Internet of Things (IIoT) and smart manufacturing connect physical production and operations with smart digital technology, machine learning, and big data to allow monitoring and control of the entire supply chain and production system. Every company can benefit from this concept, not only for connectedness but also access to real-time analytics across processes, partners, products, and people [5]. Most software used in this industry are factory wide and usually bring said factories closer to being considered a part of Industry 4.0 as the operator performs minimal operations on the machine and process itself [6].

Another company that provides software specifically for pharmaceutical automation industry is Master Control. This company provides a software called Master Control Manufacturing Excellence. This software combines QMS and MES to automate a factory floor and make a process or processes more efficient in terms of operations. This software provides paper-less data entry and documentation and can cut production errors due to input and entry errors [7].

The future of pharmaceutical manufacturing will rely heavily on constant quality control and risk management in conjunction with US FDA standards for DDS's (Drug Delivery Systems) especially as new drug technologies become more and more advanced. Systems managers and engineers alike will have to learn to "catch up" with the new drug technologies to create DDS's that adhere to FDA and ASTM standards, but are also low cost and can provide continuous manufacturing. In order to be effective, Quality Risk Management (QRM) must be applied to the entire life cycle of a pharmaceutical product. QRM can be defined as an integrated action aiming at first identifying, assessing, and prioritizing risks; and second, at minimizing, monitoring, and controlling the related undesired result. From a manufacturing standpoint, QRM is most effective when a team with adequate knowledge and background on the given product can analyze said product and the processing required to make that product. Teams are usually multidisciplinary and have members that have experience in a broad range of fields from dosage form design, to manufacturing, process engineering, and quality functions [8]. Risk management, especially in the pharmaceutical field, is a continuous process that never truly ends. It is a constant process that risk management teams must always update and re-evaluate their own processes and guidelines to ensure the product they are producing is safe and effective.

Figure 1. Example of how most pharmaceutical industry processes can be automated (© F. Lagrange / CC-BY-SA-3.0)

4. Machine Vision Usage in Pharmaceutical Manufacturing

Machine vision systems have been heavily invested in over the last several decades as this technology helps prevent mislabeling, mispacking, and general mistakes. A single labeling or packaging mistake can result in litigation for the company and potential death for the user of the drug or product. Another major issue is that the globalization of the pharmaceutical industry leads to local regulations that are in many cases different from the regulations the FDA already have in place [9]. Such machine vision technologies are also employed in the earliest stage of the Research & Development (R&D) process [10]. These technologies scan the individual molecules of a new drug and compared them with desired

results. With all this in mind, machine vision technologies must be incredibly accurate and reliable to ensure the safety of the consumer and of the supplier, as the industry is beginning to rely more and more on these technologies to replace human interference now more than ever.

The pharmaceutical industry is known for their use of High Throughput Screening (HTS). This technology allows for thousands of molecules of a drug to be scanned and tested This dramatically reduces laboratory testing and scanning time versus scanning and testing one molecule at a time. This machine vision technology only scans the chemical entities of a new drug and determines specific characteristics of the drug and these characteristics are compared to the desired results for the drug . This replaces the human need to check for chemical identities once a new product is created. Critics of HTS say that the process simply "attempts to find what sticks" or that the technology is a trial and error approach to finding what works in a new drug. Chemists, pharmacologists, biologists, and related fields fear that this technology will take their jobs away and diminish a part of the job that has been personally refined over many years. However, HTS technology simply speeds up a laboratory's ability to identify new chemical entities that have not been known before at a higher rate than the current process. This specific technology can process chemical identities at a rate much higher than that of a human. This technology allows for HTS systems and laboratory professionals to work side by side finding new chemical entities and relationships that have not been known before at a rate several times faster than that of 20 years ago [11].

The industry also uses machine vision to perform quality control on filled glass serum vials. These systems can be broken down into two parts. The first being calibration; this step consists of the software learning the shape of the bottle and the overall dimensions of the bottle with the required solution inside. The second being the actual quality control; this consists of ensuring the actual bottle is filled with the correct solution and that there is the correct amount of solution in the bottle [12]. An important component of this process is edge detection. Texture analysis and motion detection are incredibly important as these two functions determine whether or not the vision system will see the vial. These two processes are difficult from a computing standpoint as texture analysis requires the camera system to be able to identify the material that is in front of the camera. Motion detection requires a lot of memory storage sequences and real-time processing to allow the software to determine whether there is a vial in front of the vision system [12] Digital photogrammetric methods are also applied to the vision system to compute 3D information, in this case, two cameras are used instead of one. Digital photogrammetric systems are especially useful when robotic arms are used, and the movements of the arms are determined based on the orientation and placement of the vial [11].

5. The Impact of COVID-19 on Pharmaceutical Companies

The Pharmaceutical companies around the world are taking a hit from the spread of COVID-19. Countries are closing their borders and limiting what's entering their countries, which is negatively affecting the prices and supply chain of raw materials and drugs. The issue arises more with generic drug types, unlike brand name drugs, as the probability of a drug shortage is high during these times. As solutions are being determined to fix this drug shortage issue, the main priority is trying to determine a possible vaccine for the Coronavirus. Additionally, since this virus is new and still in the unknown phases, precautions have been implemented all around the world for the safety of the public.

Within the United States, the FDA has been the protector of human health for many years. They are taking unprecedented action during these difficult times especially when it comes to expediting ways to test possible drugs in the hopes to combat the negative effects of the coronavirus. This organization is taking precautions, but still allowing more laboratories and manufacturers around the US to have a hand in the helping of finding a solution to this virus problem. For example, clinical trials of possible vaccines are allowed to happen sooner than later as it's their number one priority to solve this pandemic and to get peoples' lives back to normal. While COVID-19 is their focus, the FDA knows about the drug shortage in the country and is actively reaching out to pharmaceutical manufactures to identify the drug shortages going around [13].

A clinical trial that shows promise in combating COVID-19 symptoms, whether severe or not, is a drug called Remdesivir. Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity [14]. This drug has been tested first in animals to combat viruses similarly structured to COVID-19 such as MERS and SARS. Although this drug is not yet approved for humans anywhere around the world, the US FDA just recently approved it for clinical trials in small quantities. Some findings from the outcome of one clinical test, which was done between February 6 to March 12, 2020, showed some promise.

There were 237 people randomly selected for a Remdesivir test which all patients showcased coronavirus symptoms of different magnitudes. Out of the 237, 158 people received the Remdesivir drug while the other 79 received a placebo. Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less [15]. The effects of Remdesivir was shown to mitigate the coronavirus systems of the patients receiving the drug to the point where some patients on respirators didn't require said device to assist with their breathing any longer. Even to the point of bringing them back from the brink of death because of the complications from COVID-19 and to make a full recovery. However, adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients [15]. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early [15]. Although this drug shows much promise in helping people with severe symptoms of the coronavirus, it's still too early in the testing phase to trust this drug fully. Even though some test patients are recovering from the virus because of the help of this drug, it is still shown to have negative effects on some of the people being tested. Until this issue can be solved, more clinical trials would have to be run, whether it be with this drug or not, in the hopes of finding a stable drug & cure for COVID-19.

The benefits of Remdesivir are still something for doctors to look into as other solutions could become available. For this case, manufacturers would have to step up their production of this drug. Since Remdesivir is in liquid form, vials will have to be created to contain the drug contents. Machines such as the RW-500 vial washer from SP Scientific would be beneficial to use [16]. The speculation is that if machinists of this machine type can be taught how to operate it efficiently, the possibility of making large batches of this drug help increase the probability of distributing it to doctors for further clinical tests.

6. Conclusion

The Pharmaceutical Industry is held to some of the strictest standards compared to other industries. This in turn means that the software, machines, and technologies produced must be held to these standards. The US FDA and ASTM are two organizations that set the standards for the industry. Each organization has its own set of codes and standards that the pharmaceutical industry must adhere to in terms of product creation, machinery, and manufacturing processes. The US FDA focuses mainly on the creation and efficacy of new products, and the ASTM focuses mainly on the machinery, automation, and manufacturing processes. Industry 4.0 is a term that is widely associated with the pharmaceutical industry. Machine vision, advances in machine technology, and advances in automation software help bring the pharmaceutical industry closer to adhering to this standard. The COVID-19 crisis has introduced an entirely new challenge to the pharmaceutical industry as companies scramble in attempts to create a vaccine or a treatment for the virus. As it stands, the current treatment being used is Remdesivir which is packaged in liquid form in vials for distribution. Because of the massive demand for the treatment, pharmaceutical manufacturers have found that the scale of the manufacture and distribution of the treatment must be multiplied in order to keep up with the demand. This will call for experts in the fields of automation, engineering, product development, and quality control as these treatments will need to be effective and safe for the patient to use, however, an incredibly large quantity of the treatment must also be produced. Overall, the pharmaceutical industry has always been a large proponent of automation as it removes the element of potential human error and can create a clean, reliable, effective drug.

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