→ PARENTERAL DRUG MANUFACTURING

THE CRITICAL ROLE OF CONTINUOUS IMPROVEMENT IN PARENTERAL DRUG MANUFACTURING

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In the competitive pharmaceutical manufacturing landscape, the ability to continuously achieve improvements in efficiency and productivity is essential to success. Given the higher complexity of parenteral drug manufacturing, continuously improving production processes is also paramount for ensuring the highest level of quality.

A MANUAL HISTORY

Just two decades ago, most production operations in parenteral drug manufacturing involved manual manipulation and intervention. Human operators were responsible for controlling all aspects of the production process, including the steps involved in producing the containers for final drug products, the preparation of drug product solutions, filling those solutions into containers, and their final packaging before shipment.

MANY OPPORTUNITIES FOR IMPROVEMENT

Since that time, the pharmaceutical industry has undergone significant change. Price pressures on generic drugs are tremendous today. At the same time, quality standards have continued to rise and are becoming more globally harmonized. Many generic manufacturers in emerging markets have been issued warning letters or had their facilities closed, and key drug imports produced by these firms have been halted in Western countries until compliance issues are addressed.

Manufacturing processes must be ultra-efficient while still maintaining the highest level of product quality and safety. Grifols has taken on this challenge with an ongoing continuous improvement program that includes everyone involved in the production of our parenteral and blood plasma products, from process design engineers to operators. We have focused on replacing inefficient manual operations that create opportunities for human error with highly automated, multifaceted processes that dramatically boost both quality and productivity.

This ongoing continuous improvement program has enabled and will continue to enable Grifols to be a highly competitive and high-quality manufacturer of parenteral products with global approvals and recognition as a world-class pharmaceutical company.

ADVANTAGES OF AUTOMATION

The automation of parenteral manufacturing processes using robotic systems enables tasks to be completed repeatedly in the same manner. Robots can be programmed to perform the same motion, exactly the same way every time, something that is not possible for humans to accomplish. Automation also reduces the level of human contact with the products, which, in turn, reduces the risk of contamination. Furthermore, reduced reliance on human activities minimizes opportunities for human error. Overall, automated processes are robust and efficient and lead to more consistent and higher-quality products.

LEVERAGING TECHNOLOGY TO STREAMLINE OPERATIONS

Grifols is currently manufacturing many of the same products that were produced 20 years ago, but in an entirely new manner and in an upgraded, state-of-the-art facility. The new parenteral manufacturing plant relies extensively on automated processes, from production of the plastic containers to the preparation of drug product solutions, to filling, sterilization, and final packaging.

Advances in technology have made the implementation of many of these automated solutions possible – one important example is form–fill–seal technology. Previously, Grifols produced plastic containers in a separate manufacturing area. Once the containers were manufactured, they were boxed and then placed in the warehouse until they were needed for the fill-finish step. At that point, the boxes were moved to the filling area, and the bags were removed and used for final product manufacture.

This double handling of the plastic containers was highly inefficient and included a significant time effort that did not add any value to the final product, but did increase its cost. Our solution was to adopt form–fill–seal technology for the production of plastic containers and to incorporate this process in the same line as the filling operation. Today, robots control the entire process, from the manufacture of the containers, which occurs immediately before filling, to final packaging.

As a result, we have eliminated all of the non-value-added movement of materials used in the process and the product itself, dramatically increasing efficiency and productivity. In addition, quality has been enhanced, because we also reduced the potential for contamination and risks associated with human error.

AN INTERNAL ENGINEERING TEAM MAKES A BIG DIFFERENCE

One of our key strengths at Grifols is our focus on controlling processes. The founder of the company, Dr. José Antonio Grifols Lucas, pursued an integrated approach to business and was continually inventing new tools and solutions. This same philosophy remains infused throughout all aspects of the company. Our employees enjoy working in our facilities and are passionate about improving how they work. They are always looking for novel approaches to our processes and developing new solutions.

This philosophy also led to the establishment of Grifols Engineering, a business within the Grifols Group that provides engineering services to the pharmaceutical industry. Having an internal engineering business is unique in the pharmaceutical industry. Most importantly, Grifols Engineering has been intimately involved in the design and construction and/or upgrading of Grifols' facilities and various production lines.

The engineering team has extensive experience with process technologies employed across the company and brings this knowledge to each project. Engineering team members also collaborate closely with the production team to design process solutions that address their concerns down to the minutest details. The engineering group does not simply design and implement the process and hand it over to the production team – because the two groups work together, the operators also have ownership of the equipment and process and feel responsible for solving any problems that arise.

ATTENTION TO DETAILS PAYS OFF

As part of our continuous improvement efforts at Grifols, we have learned that paying attention to even the smallest details can have a huge impact on the efficiency of facility operations. One example relates to the design of the trays used to supported filled plastic bags when they are being sterilized in an autoclave.

To simplify the process, one of the goals for our new facility was to have one tray that could be used for all of the plastic bags we produce, regardless of their size and volume. In the process, bags are placed on trays and the trays are stacked one on top of the other. With the initial design, when smaller-volume bags were sterilized, a large amount of empty space existed between each of the stacked trays.

The engineering and production teams challenged themselves to develop a tray

design that would still meet the goal of having just one type of tray yet provide different stacking options for bags of larger and smaller volumes. The solution was a tray that stacks differently when it is aligned with other trays in a parallel versus perpendicular orientation. One orientation leaves less space between the trays and is appropriate for small-volume bags, while the other results in a bigger gap between the trays to allow sterilization of large-volume bags. Paying attention to that little detail had a huge impact on productivity: the number of bags that could be sterilized was doubled.

Throughout the new Grifols facility, there are many other examples where collaboration between the engineering and production teams to address small issues has resulted in measurable improvements in performance.

BUILDING ON EXPERIENCE IS ALSO VALUABLE

Ongoing collaboration between the engineering and production groups also enables Grifols to build on its experience. For each new production unit that is installed, improvements are incorporated based on the lessons learned when operating existing equipment and systems.

In one example, on a filling line, operators followed instructions on a touch screen for the preparation of the product solution. To start, they selected this option to gain access to instructions for connecting the appropriate hoses. While this system provided some guidance to operators, it was still possible for them to connect the hoses incorrectly. This could lead to mistakes during the preparation of the solution.

For the new filling lines, the software has been upgraded, and additional controls have been implemented. Barcodes have been placed at each point where tubing can be connected, allowing the operators to confirm that they have attached the hoses correctly. In addition, the system will not allow the operator to proceed unless the tubing has been properly connected.

These types of improvements are routinely made at Grifols as a result of production personnel sharing their experiences and challenges with the engineering team. We are always looking for ways to learn from our mistakes, and the close collaboration among the operators and engineers makes it possible to develop increasingly effective solutions.

RESULTS TELL THE STORY BEST

The cumulative results of our continuous improvement efforts at Grifols are significant. Twenty years ago, in our older facility, production processes were based largely on manual operations. In our new state-of-the-art parenteral production plant, we have multiplied the number of units produced by 10 times.

Due to the advanced automation and digital solutions that Grifols has implemented in the facility, we can track each individual product unit that is manufactured in the plant. For a batch of 45,000 units, at the end of the process in the packaging area, we can detect the loss of just one bag – something that was not possible two decades ago.

In addition to a tremendous gain in efficiency and productivity, therefore, continuous improvement has resulted in enhanced and highly consistent product quality and a significant increase in the confidence Grifols and our customers have in our processes.

MOVING FROM REACTIVE TO PROACTIVE

Continuous improvement is a never-ending process that becomes increasingly challenging as major inefficiencies and inconsistencies are eliminated. We strive to continue improving our processes at Grifols every day.

Perhaps most importantly, we are moving from a reactive mode to a proactive approach to continuous improvement. Rather than rely on errors and mistakes to identify opportunities for improvement, we conduct extensive risk analyses to determine areas where potential improvements are needed. In this manner, we are improving processes before any issues occur.

RATHER THAN RELY ON ERRORS AND MISTAKES TO IDENTIFY OPPORTUNITIES FOR IMPROVEMENT, **WE CONDUCT EXTENSIVE RISK ANALYSES TO DETERMINE AREAS WHERE POTENTIAL IMPROVEMENTS ARE NEEDED.**

CURRENT CHALLENGE: HUMAN AND ROBOT COLLABORATION

At our new state-of-the-art facility, most of the processes have been largely automated, from the manufacture of the bags to the preparation of product solutions, bag filling, sterilization, and final packaging. However, there are still processes that, due to their complexity, require the intervention of manual operators.

At Grifols, we are working to develop a solution that will enable humans and robots to collaborate in the same area. Where appropriate, we will incorporate robots, but for some operations we will continue to rely on human operators. It is a very challenging mission and one that Grifols is tackling head-on as a component of our ongoing continuous improvement program. P

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Antonio Gómez holds a degree in industrial engineering from UPCT and an MBA from ENAE Business School. He joined the Grifols group in 2001 and has developed his whole career at Laboratorios Grifols, where he is the head of the Pharmaceutical Production Division. Antonio also collaborates regularly with ENAE Business School, where he teaches about operations and logistics.

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