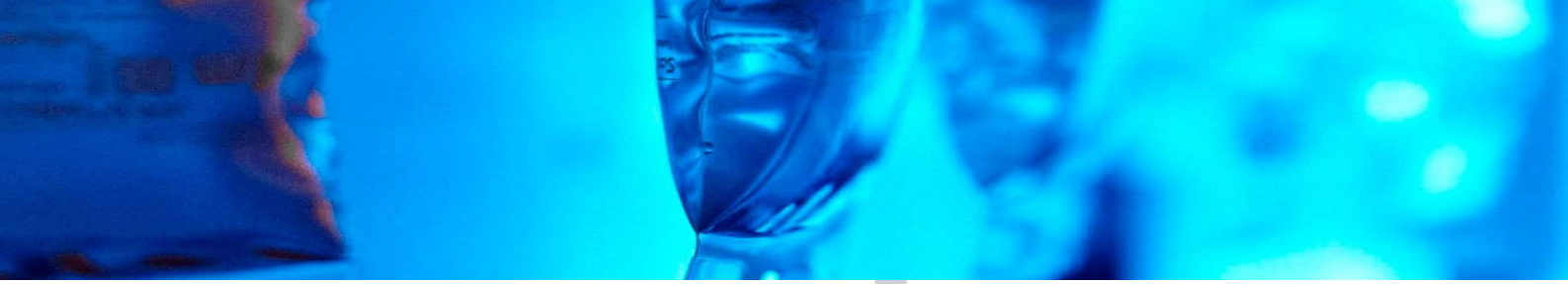

Continuous Quality is Essential in Parenteral Manufacturing

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Marta started her career at Merck, joining Grifols two years later; she has maintained a focus on quality throughout her career. Marta served as Quality Control Manager at Grifols for more than 20 years, before assuming the role of Technical Director of the Barcelona plant. In her current role, Marta is the Technical Director of Laboratorios Grifols in charge of Quality Assurance, Quality Control and Pharmacovigilance for all production facilities. Marta holds a pharmacy degree with a specialization in quality control.

Ensuring quality is the first concern of any pharmaceutical company in the development, manufacture and control of drug products. The highest level of quality is essential for achieving optimal patient safety, especially in the manufacture of parenteral drugs. The use of a quality-by-design (QbD) approach and compliance with requirements for parametric release are two key components of a successful and effective quality program.

Unique Quality Issues

The manufacture of sterile liquid injectable drug products presents a unique set of challenges separate from oral dosage form production. Final sterile formulations must be manufactured under sterile conditions from ingredients that are compatible with the glass or plastic product container and container closure. Sterilization must be achieved in a manner that prevents any degradation of the active pharmaceutical ingredient (API) or any other components of the final formulation. To ensure compatibility and confirm that no components of the container will contaminate the drug product, stability and extractable and leachable studies must be completed. Parenteral drugs based on APIs sensitive to oxygen, moisture and/or light have additional special handling and packaging requirements.

Resulting problems can include contamination, product leakage and variability in filled volumes. In recent years, the biggest challenge has come from the presence of visible particulates. There have been recalls of injectable products due to product quality issues, many of which have been caused by the presence of foreign particulate matter, such as metal particles, fiber and glass particles and silicone fragments.

To avoid these types of issues, it is essential to have an appropriate quality culture that includes a commitment to continuous improvement and an emphasis on designing quality into parenteral manufacturing processes from the start.

At Grifols Partnership, the CDMO business of Grifols, we have implemented a quality-by-design approach to process development and enhanced our process control capabilities. We have secured approval for the parametric release of products in the EU and expect to gain approval in the United States in 2019. We also have an established change management control system and have introduced automation technologies to further minimize the potential for error and contamination in our parenteral products.

A QbD Approach

Designing quality into a process from the start using a QbD approach ensures that the quality target product profiles (QTPP) are well defined from the outset. With the application of a standardized approach early on, it is possible to identify the critical quality attributes (CQAs) of the product that can be impacted by material attributes and process conditions, early on.

Grifols uses this approach for all processes, including preparation of the product solution, filling, sterilization, packaging and storage. Importantly, a team comprising representatives from the analytical, R&D, production, quality assurance and regulatory affairs departments is involved from the beginning of a project through product registration so that everyone has the same knowledge and understanding of the process.

In addition, with knowledge of the targets for the product and the results of an initial risk assessment, it is possible to design an initial control strategy for the production of R&D batches. Once the critical process parameters (CPPs) are qualified, another risk assessment is completed, and the control strategy is modified as appropriate. Validation of the production process and production of batches for stability studies can then proceed. The ultimate goal is the development of more robust processes that yield products with consistently higher quality.

Enhancing Process Control

Quality standards are changing around the world, with process control emerging as a critical requirement. Rather than identifying problems by analyzing finished products — and having the product be wasted — the preference is to better monitor and control processes while they are underway.

At Grifols, CPPs are monitored during the process and statistical analyses are performed to identify process variations as they occur. For sterilization processes, in addition to the critical parameters, the bioburden is monitored to assure the sterility of the product.

Achieving Parametric Release

Parametric release is a release system that ensures that the product has the required quality based on the information collected during the manufacturing process — and according to the specific requirements of Good Manufacturing Practices related to parametric release. For injectable products, parametric release can only be established through the use of adequate and validated sterilization cycles. Once the sterilization is well understood, the physical parameters of processing are well defined and the lethality of the cycle has been microbiologically validated, the release of terminally sterilized batches or lots of sterile products — without having to perform the requirements under sterility tests — is a possibility.

Only companies that have historically shown excellent results in their sterility tests and repeated consistency in their overall quality systems can obtain this authorization. In 2007, Grifols was one of the first companies in Europe granted authorization for parametric release. Both plants in Spain (Murcia and Barcelona)

are certified.

To obtain this authorization, several steps were required:

- A control strategy that includes the description of the terminal sterilization process and how the process is monitored, controlled and evaluated (CPPs) was defined.
- The CPPs and their acceptance criteria were designated.
- A risk assessment was performed to evaluate the points for potential failure in the sterilization process (where there is a risk to the sterility of the product) and to identify actions to take to mitigate these problems.
- Historical data for the terminal sterilization cycle with the specific product, specific container closure system(s), specific load size(s), specific sterilizer(s) and the specific facility proposed for parametrical release were collected.
- Because parametric release is the method for finished product release instead of sterility testing, commitments were included in the submission to acknowledge the requirements for a successful parametric release program and the consequences of failure.
- For current terminally sterilized batches of drug product no longer being subjected to finished product sterility testing, the batch records are revised to indicate that an approved parametric release program is being used as the method to achieve sterility.

Currently, Grifols is in the process of obtaining authorization for parametric release in the United States. We have been manufacturing products for sale in the United States for over a year and are collecting the necessary data from these batches in order to receive authorization in 2019.

The Value of Automation

Implementing automation of processes involved in the production of parenteral drug products helps ensure the quality of those products by minimizing human interactions during manufacturing, which reduces the risk of contamination.

At both Grifols plants in Spain, automation systems have been installed to facilitate manufacturing and maximize product quality and patient safety. At our Murcia plant, form–fill–seal production lines for injectable solutions in polypropylene bags are fully automated, from the manufacture and printing of the bags through the filling, capping, overwrapping, sterilization and packaging of the product. The product is never touched by human hands until the point of use, which ensures the highest level of patient safety.

Bag molding was integrated into the process because it is a key point for potential particle generation, and Grifols prefers to maintain control over this critical aspect in the manufacture of an injectable solution. In addition, all of our systems are designed by our engineering team devoted to the design of pharmaceutical production plants, processes and equipment.

At our Barcelona facility, our lines for the production of products in glass vials are fully automated. The facility has implemented artificial vision systems for automatic

review of particles to avoid human error — the first to do so in Europe.

Building on Decades of Success

At Grifols, we focus on sterile products; we have extensive knowledge of the processes we use and the products we produce. Throughout our more than seven decades of manufacturing parenteral products, Grifols has been established as a leader with the highest reputation for quality.

Our focus on quality is not limited to blood products, but applies to all of our activities, from non-biological injectables to reagents and instrumentation for clinical diagnosis. Grifols Partnership has extensive experience working with both non-sensitive and highly sensitive APIs and broad expertise in the development of robust processes for the production of numerous types of products. The use of QbD, design of experiment and risk analysis approaches — combined with our quality culture — ensures the production of parenteral products of the highest quality.

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