A HOLISTIC INTERPRETATION OF COMMITMENT TO QUALITY

→ BY **ORIOL PRAT**, GRIFOLS PARTNERSHIP

Quality is the first concern of any pharmaceutical manufacturer. Translating that concern into a quality strategy comprising effective procedures and practices is another matter, and can be particularly challenging for injectable drug products. Outsourcing of fill/finish activities adds an additional layer of concern because it introduces the risk of losing control over manufacturing quality. Therefore, selection of a contract service provider with a holistic approach to quality and a clear track record of quality performance in all aspects of injectables manufacturing is essential.

Demand for injectable drug products is increasing at a healthy rate, due in part to growth of the biologics market and because injectable formulations offer a mechanism for increasing the efficacy, while reducing the side effects, of many small-molecule drugs. In some cases, fewer doses of injectable drugs are required, which can increase patient adherence (particularly for self-injected therapies). *Markets and Markets* predicts that the injectable drug delivery market will increase at a CAGR of 12% from $326.1 billion in 2015 to $574.8 billion by 2020.[1]

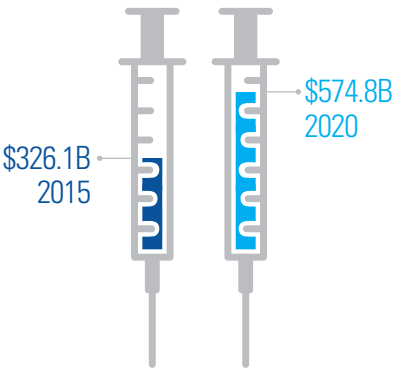
Quality issues have plagued the injectable drug market in recent years. Numerous recalls due to product quality issues have contributed to shortages of many injectable products in the United States. This troubling situation underscores how the lack of appropriate quality strategies,

and a quality culture, can directly impact patients.

A key indicator of the quality of injectable drug products is the extent of foreign particulate matter. One of the leading reasons for recent recalls of injectable drug products is the presence of visible particles.[2] During the period of 2008-2012, 22% of FDA recalls of sterile injectable drugs were attributed to the presence of visible particles.[3] Examples of recalls in 2015-2016 have included the injectable anticancer drugs gemcitabine, carboplatin, cytarabine, fluorouracil and methotrexate; saline injection products have also been the object of several recalls.

Various pharmacopeias include standards for the production of injectable products, but meeting requirements for the manufacture of products that are "essentially free" of particles is very challenging.[4,5] Materials found in recalled drug products have included metal particles, fiber and glass particles, silicone fragments and insect parts.

While several practical measures can be taken to prevent contamination of injectable drugs with particulate matter, from the use of appropriate cleanroom and vial/stopper designs to the use of isolators and sterile filtration, doing so will achieve only limited success without an overall culture of quality.



12% INCREASE

INJECTABLE DRUG DELIVERY MARKET CAGR FROM 2015 TO 2020

BENEFITING FROM BLOOD PLASMA INDUSTRY EXPERIENCE

The plasma-derived proteins market, in which Grifols is one of three top players, is particularly sensitive to quality issues, largely due to significant quality problems that occurred during the 1980s-1990s, related to virus contamination. Unlike most other companies in the sector, Grifols has never experienced any quality problems due to virus contamination, and this track record of performance has placed the company in a prestigious position in the plasma-derived proteins market.

This commitment to quality and our culture of continuously striving for the highest quality levels are also applied across all of the company's activities, from non-biological injectable products to reagents and instrumentation for clinical diagnosis.

PARTICULATE CONCERNS

In addition to being a crucial indicator of quality for injectable products, the presence of particulates in finished pharmaceutical sterile products can have significant consequences for patients. Clinical effects can range from minor problems to serious complications and even death.[6] In the U.S. alone, approximately 190 million liters of intravenous fluids are administered to patients each year, and thus particulate matter contamination is a real concern for the pharmaceutical industry.[6]

Given the increasing number of recalls due to contamination by visible particulates in parenteral drugs and the heightened concern of the FDA and other regulatory agencies, Grifols is actively working to improve its manufacturing operations and enhance its existing quality programs. In addition to adopting a vertical integration model for control of the entire manufacturing process, Grifols has introduced automation technologies (robotics) and implemented

ONE OF THE **KEY OPPORTUNITIES** FOR PARTICLE GENERATION OCCURS DURING THE **BAG MOLDING PROCESS.**

advanced process controls, such as artificial vision, to reduce human interactions with injectable products and thus further minimize the potential for contamination.

GREATER CONTROL WITH VERTICAL INTEGRATION

The use of Form-Fill-Seal technology at Grifols Partnership provides a good example of how vertical integration results in the highest quality performance. The process involves the formation, filling and sealing of plastic (polypropylene) containers (bags) in one step and in a fully automated manner without any human interaction. To ensure complete control of the process, Grifols manufactures components, including ports and stoppers, employed in the Form-Fill-Seal process and uses equipment developed and manufactured by Grifols Engineering.

One of the key opportunities for particle generation occurs during the bag molding process. For this reason, Grifols has integrated this process into its filling operations through the adoption of Form-Fill-Seal technology in order to maintain control over this critical aspect of injectable solution manufacturing.

Grifols Engineering is a Grifols company devoted to the design of pharmaceutical production plants, processes and machinery for both Grifols and other pharmaceutical manufacturers. Because it is part of a pharmaceutical company, Grifols Engineering is particularly knowledgeable about the quality and compliance requirements for pharmaceutical production processes and the design of manufacturing facilities.

With this vertical integration approach, Grifols has control of the entire process from start to finish, ensuring that all parts of the manufacturing process are performed following the same high-quality standards.

AUTOMATION ADVANTAGES

At the Grifols Partnership plants in Spain, where non-biological injectable drugs are manufactured, high levels of automation are employed to reduce human interactions with drug products and thus minimize the risk of contamination. No further operator intervention is required on the Murcia plant "Form-Fill-Seal" production lines for injectable solutions once the plastic rolls are loaded; bag production and printing, filling, capping, over-wrapping, sterilization and packaging are fully automated, and the final product is not touched by anyone until the point of use. Fully automated glass vial production lines at the Barcelona plant also minimize human interactions with products.

ADVANCED INSPECTION TECHNOLOGY

The Barcelona plant has also pioneered the implementation of artificial vision systems in Europe. Developed in collaboration with Diagnostic Grifols, another Grifols company that has extensive knowledge of artificial vision technology, the systems enable the automatic inspection of injectable products for particulates, avoiding the potential for human error.

PARAMETRIC RELEASE

Parametric release is a system of release that gives assurance that the product is of the intended quality and is based on evidence of successful validation of the manufacturing process. The information collected on process monitoring carried out during the manufacturing process, and the compliance with the Good Manufacturing Practices, provides the desired assurance of the quality of the product. Companies that have shown high consistency in their overall quality systems can be approved for parametric release for sterility. In 2007, Grifols was one of the first companies in Europe to obtain this authorization.

CONCLUSION

Products manufactured by the Grifols Partnership CDMO are of vital importance to patient health and quality of life. Safety is therefore more than just a regulatory requirement; at Grifols it is a philosophy that goes hand-in-hand with quality, and both apply not only to our products, but our internal manufacturing, communication and operational processes. Our holistic approach to quality has resulted in a robust and reliable quality system and positioned Grifols Partnership as an ideal strategic partner. P

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ABOUT THE AUTHOR

Oriol Prat Director Contract Manufacturing, Grifols Partnership

Oriol has been working in pharmaceutical marketing and sales, with a focus on the hospital business both domestic and internationally, for 30+ years. He has spent the last 15 years devoted to the strategic business growth of products and markets. In the past 10 years, he has concentrated on the development of the contract manufacturing business unit at Grifols, designing the strategy of positioning and communication, as well as driving the company towards necessities of the market.

LinkedIn www.linkedin.com/in/oriol-prat-8952354
Email oriol.prat@grifols.com

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