

SMALL MOLECULE INJECTABLE MANUFACTURING: CHALLENGES AND COMPLEXITIES

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Despite the growth of biologic drugs, medicines based on small molecules remain important in the treatment of all types of diseases. Small molecule injectable drugs are often necessary for the treatment of hospital patients. Production of sterile injectable projects is much more complex and challenging than oral dose manufacturing. A commitment to quality, robust processes and knowledge of the end user are essential for CDMOs providing these services.

DON'T COUNT OUT SMALL MOLECULES

These days small molecule drugs don't seem to receive the attention that biologics do. They are just as relevant today as they ever have been, however. In fact, they account for approximately two-thirds of drugs in the pharmaceutical industry pipeline.¹

In addition, the majority of FDA new drug approvals have gone to small molecule drugs in the past several years. Specifically, in 2015, 33 of the 45 new drugs approved by FDA were small molecules,² while in 2016, 15 out of 22 newly approved products were based on chemical active pharmaceutical ingredients (APIs).³ Furthermore, as recently as 2014, small molecule drugs accounted for 84% of pharmaceutical industry revenues.⁴ Five of the top 10 drugs in terms of revenue, and nine out of the top 10 most-prescribed drugs, were based on small molecule APIs.⁵

It is also worth noting that the global market for small molecule APIs is





plastic bags and deliver a fixed dose, ensuring accurate delivery of the drug to the patient and reducing waste.

QUALITY, QUALITY AND MORE QUALITY

Processes involved in the manufacture of sterile parenteral products are typically more complex than those required for the production of oral dosage forms. The stability of parenteral solutions must be assured. The product must be sufficiently stable to remain in solution (or within the freeze-dried cake) for a reasonable amount of time.

In addition, compatibility studies must be conducted to ensure that there are no interactions between the drug product/solution and the glass or plastic container, rubber stoppers, etc. Products packaged in plastic must also undergo extractable and leachable testing to ensure that no additives in the plastic contaminate the drug product. Sterility assurance is also essential. Studies must be conducted to confirm that there is no bacterial or fungal contamination of the formulated product. Transportation and logistics can also be an issue if low-temperature storage or other special conditions are required.

All of these issues relate directly to product quality. A culture of quality and effective quality systems are essential for successful production of complex products such as sterile injectables. It is imperative that all parenteral products be manufactured to the highest quality standards, regardless of whether they are branded drugs or generics. Because Grifols participates in the plasma-derived proteins market, we have made an extensive

GRIFOLS HAS NEVER EXPERIENCED ANY QUALITY PROBLEMS WITH ITS BLOOD DERIVATIVE PRODUCTS DUE TO VIRUS CONTAMINATION.

expected to grow at an annual rate of approximately 7% from 2016 to 2027, reaching \$279.7 billion.⁶

SMALL MOLECULE INJECTABLES' IMPORTANT NICHE

Within the small molecule drug market, the vast majority of products are formulated for oral administration. Oral dosage forms are generally the easiest for patients to take and the least costly for manufacturers to produce. There is a real need, however, for parenteral formulations of small molecule drugs.

The global sterile injectable drugs market will expand at a compound annual growth rate of more than 7% from 2016 to 2024, reaching a value of \$657 billion by the end of the forecast period.⁷ Notably, the market research firm sees small molecule injectable drugs gaining immense popularity.⁷

Intravenous infusion provides an immediate therapeutic effect by delivering

medication directly into the bloodstream. For small molecule drugs, such rapid delivery is needed to treat patients, and is most often needed in hospitals – either in an emergency room situation or when there are unexpected complications. In some cases, patients are incapable of taking medications by mouth, and injection or infusion is the most effective route of administration. In others, the API may be degraded in the intestinal tract and therefore require parenteral delivery.

The main small molecule drugs delivered parenterally include heart medications, antibiotics and analgesics. Standard solutions of glucose, potassium and saline are also administered in this manner.

These drugs can be formulated as concentrated admixtures or diluted, premixed solutions. Admixtures, often freeze-dried and packaged in glass vials, require dilution prior to administration, which can introduce human errors. Premixed solutions are packaged in flexible

A CULTURE OF QUALITY AND EFFECTIVE QUALITY SYSTEMS ARE ESSENTIAL FOR SUCCESSFUL PRODUCTION OF COMPLEX PRODUCTS SUCH AS STERILE INJECTABLES.

commitment to quality. Quality culture is at the roots of our company and it branches out to all of our businesses, including our sterile fill-finish operations.

Grifols has never experienced any quality problems with its blood derivative products due to virus contamination. In addition, we received no 483 complaints following our most recent FDA audit in June 2015. Furthermore, Grifols was one of the first companies in Europe in 2007 to obtain approval for the parametric release of parenteral solutions in glass and flexible containers from its EMA- and FDA-certified production plants in Barcelona and Murcia, Spain. Parametric release is authorized for companies that have historically shown excellent sterility test results and high consistency in their overall quality systems. It is a guarantee that the product has attained the desired quality and is based on information collected during manufacturing according to Good Manufacturing Practices (GMP).

AUTOMATION IN INJECTABLE MANUFACTURING

As mentioned above, injectable products must be manufactured to very high quality and sterility standards. One aspect of Grifols' commitment to quality has been extensive investment in automation technologies to reduce the risk of error and contamination, and increase both operator and patient safety.

We have both "Form-Fill-Seal" technology for the production of polypropylene bags and fully automated glass vial filling lines designed to minimize human interactions with drug products. Artificial vision systems (developed in collaboration with Diagnostic Grifols) also enable the automatic inspection of injectable products

for particulates, avoiding the potential for human error in this important unit operation. Automation systems also help reduce the chance for incorrect container manipulation and ensure accurate labeling.

UNDERSTANDING THE NEEDS OF YOUR REAL CUSTOMERS

With the emphasis in the pharmaceutical industry today on increasing patient medication compliance through the development of patient-centric drug products, it has become more important than ever for drug manufacturers to understand the needs of their ultimate customers. For small molecule parenteral products, those customers are typically nurses and doctors with hospitals, clinics and organizations that provide in-home patient care.

Grifols has a 75-year history developing plasma-derived medicines, and during that time we have worked directly with nurses and doctors. As a result, we have extensive knowledge regarding their preferences for parenteral product design. We also have insight into how changes in process or product design might impact final product acceptance. This knowledge can be highly beneficial for drug manufacturers looking to differentiate their small molecule parenteral products, whether they are introducing a new branded therapy in a glass vial or looking to extend the life cycle of a generic premixed solution in flexible plastic packaging.

FOCUSED ON SMALL MOLECULE INJECTABLES

As a CDMO with a focus on the fill/finish of small molecule injectable products, Grifols offers both concentrated and diluted small molecule parenteral formulation options. Our state-of-the-art, automated,

multiproduct lines are used to produce high-quality, small molecule injectable drugs that can withstand terminal sterilization. We continue to expand our capabilities in response to customer needs; one example is the latest addition of a fourth "Form-Fill-Seal" line for the production of premixed products in plastic bags that will be operational by the end of 2017.

As a business unit within a global pharmaceutical manufacturer, Grifols Partnership has access to financial, technical, regulatory and other resources not readily available to standalone CDMOs. In addition, the same equipment, which is designed specifically for Grifols by Grifols Engineering, is used for both internal and external projects. As a result, operators have extensive experience working with these systems. This vertical integration also fits with Grifols' quality culture; it enables us to control the entire process, ensuring achievement of the highest quality. ■

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Marga Viñes holds a degree in pharmacy and an MBA in pharmaceutical management from the University of Barcelona. She has more than 17 years' sales and marketing experience in the pharmaceutical industry and healthcare business, defining and implementing marketing strategies for international and domestic markets. In addition, she has nine years' experience in the field of strategic marketing and business development in the contract manufacturing business on an international level.

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