

EXPANDING US SUPPLY OPTIONS FOR LARGE-VOLUME PARENTERALS

→ BY MARGA VIÑES, GRIFOLS PARTNERSHIP

With limited numbers of producers supplying large-volume parenterals (LVPs) to the US market, shortages can result when natural disasters or manufacturing problems interrupt production operations. Grifols has implemented its vertical integration philosophy to ensure the consistent supply of high-quality Sodium Chloride 0,9% solution to its blood/plasma donor centers. The product will also be available to hospitals and compounding centers.



THE IMPORTANCE OF LARGE-VOLUME PARENTERALS (LVPs)

Drugs administered as parenteral solutions are prepared as either small-volume or large-volume products. Large-volume parenterals (LVPs) include intravenous solutions sold in bags or bottles containing 100 ml or greater (250 ml, 500 ml, 1 L). They are packaged in these large volumes because larger quantities are typically required. Common LVPs include solutions needed to correct electrolyte and fluid imbalances, provided important nutrients or act as a vehicle for the delivery of other drugs. The most common examples include sodium chloride solution, dextrose solution, Ringer's solution, and Lactated Ringer's solution, as well as combinations of dextrose and sodium chloride.

The market for LVPs is expanding due to an increase in the numbers of surgeries performed and the growing numbers of patients with chronic and other lifestyle-related diseases requiring hospitalizations.¹

LVPs provide a faster method for administering drugs to patients during surgery and when in the hospital. A growing preference by patients for single-dose administration of vaccines and drugs to treat chronic diseases is also driving demand for LVPs.

THE CHALLENGES OF LVP SHORTAGES

Despite the growing interest in large-volume parenterals, only a few manufacturers produce these important products for the US market. In fact, increased demand in combination with manufacturing delays and other problems has led to shortages of key LVPs in the United States.² Some manufacturers have also discontinued production of products in certain packaging or withdrawn from the market altogether. In its second report on national drug shortages in the US, the Council of Science and Public Health stated that quality problems, manufacturing delays, limited production capacity, particularly for generic sterile injectable products including LVPs, and

product discontinuations accounted for more than 80% of the drug shortages in 2014 and 2015.³

Currently, there are shortages of sodium chloride (saline) and dextrose solutions sold in large-volume bags for injection.² These shortages began in early 2014 and at the time were expected to be resolved by the summer.⁴ According to an Infusion Nurse blog post in March 2014, "Not having IV Saline solution available is like not have bread and milk at the grocery stores."⁴

A VERTICAL INTEGRATION STRATEGY

Production of sterile injectable drugs must occur in highly controlled environments in accordance with current Good Manufacturing Practices. Extensive process understanding is required to ensure the consistent manufacture of high-quality products. Advances quality programs combined with state-of-the-art automated aseptic processing systems are essential.

Grifols has been manufacturing par-

enteral products, including large-volume parenterals such as Sodium Chloride 0,9% solutions, for more than 50 years. To ensure the highest quality, the company has adopted a vertical integration model for control of the entire manufacturing process and implemented automation technologies (robotics) and advanced process controls (e.g. artificial vision) to reduce human interactions with injectable products and thus further minimize the potential for contamination.

Grifols' pharmaceutical production plants, processes and machinery are designed by Grifols Engineering, which because it is a Grifols company, is knowledgeable about the quality and compliance requirements for parenteral manufacturing. The bag molding process, often a source of particle generation, has been integrated into Grifols' filling operations through the adoption of Form-Fill-Seal technology. This approach allows Grifols to ensure complete control of this critical process.

This vertical integration philosophy is being extended to the production of LVPs for the US market. Grifols is one of the top three players in the plasma-derived proteins market. The company operates blood/plasma donor centers across the US. Each blood donor receives 500 ml of sodium chloride 0.9% solution, which currently is provided by another supplier. The shortage for several years of this important LVP has presented Grifols with an untenable situation. The company's blood donor centers, which are part of its core business, are at risk of being without this essential product. Vertical integration through the internal production and supply of LVP saline solutions eliminates this risk.

BACKED BY DEMONSTRATED QUALITY AND EXPERTISE

Grifols has successfully manufactured sodium chloride solutions for the European market at its Spanish manufacturing facilities for more than fifty years. Both its plasma-derived proteins and parenteral manufacturing businesses, and in fact all activities from non-biological injectable products to reagents and instrumentation for clinical diagnosis, are operated within a quality culture founded on a commitment

to continuous improvement and ongoing achievement of the highest quality levels.

As a result, the company has never experienced any quality problems with its blood derivative products due to virus contamination or any recalls of its parenteral products due to particulate contamination. An FDA audit in June 2015 generated zero 483 observations. In addition, Grifols was one of the first companies in Europe to obtain approval for the parametric release – which requires historical demonstration of excellent sterility test results and highly consistent quality system performance – of parenteral solutions in glass and flexible containers from its EMA- and FDA-certified production plants in Barcelona and Murcia, Spain.

ENTERING THE US MARKET

To implement its vertical integration philosophy for large-volume solutions used at its blood donor centers in the US, Grifols required FDA approval. An application for a 500-mL product was submitted to the Center for Biologics Evaluation and research (CBER) within the FDA, the group within FDA with which Grifols has a long-standing relationship. FDA approval was received in May 2017.

Production of sodium chloride 0.9% solution for the US market in 500-ml bags was initiated at the Grifols manufacturing plant in Murcia, Spain in late 2017, and export of the product began in early 2018.

A fourth, completely automated Form Fill Seal line will be operative in the coming months to guarantee that it has sufficient production capacity to supply to blood donor centers, hospitals and compounding centers. With these automated lines, the operator uploads the polypropylene rolls and the bags are formed, filled and sealed and then sent for overwrapping; interactions between the operator and the process are avoided, minimizing any risk of contamination and human error. Inspection of injectable products for particulates is also automated using artificial vision systems developed in collaboration with Diagnostic Grifols.

CONCLUSION

Production of high-quality, sterile parenteral products involves complex processes. There are few manufacturers willing to take on the challenges associated with parenteral manufacturing for inexpensive, ba-

Minibags are Coming Too

➔ In addition to shortages of LVPs offered in large plastic bags, there are shortages of smaller “minibags” in volumes of 50 ml, 100 ml and 250 ml. The hurricanes that devastated Puerto Rico earlier this fall have affected production of these products.⁵ Such shortages are having an impact on hospitals, home infusion pharmacies and infusion centers. The greatest shortages exist for 50 and 100-milliliter minibags of sodium chloride 0.9%, dextrose 5%, and I.V. nutritional products, according to the American Hospital Association.⁵

To address the shortage, FDA is allowing the temporary importation of products from over-

seas, including minibags of sodium chloride 0.9% injection bags, dextrose 5% injection bags, and metronidazole injection.⁵ The agency is also expediting the review of any new product applications that will help resolve the shortages.

Grifols will submit the approval of its saline solution in 50 ml, 100 ml, 250 ml and 1000 ml to the FDA. In addition to hospitals and pharmacies, compounding centers use saline solutions in minibags to reconstitute lyophilize antibiotic and oncology therapies. The company will be marketing the minibags to all users throughout this year.

seas, including minibags of sodium chloride 0.9% injection bags, dextrose 5% injection bags, and metronidazole injection.⁵ The agency is also expediting the review of any new product applications that will help resolve the shortages.

Grifols will submit the approval of its saline solution in 50 ml, 100 ml, 250 ml and 1000 ml to the FDA. In addition to hospitals and pharmacies, compounding centers use saline solutions in minibags to reconstitute lyophilize antibiotic and oncology therapies. The company will be marketing the minibags to all users throughout this year.

Grifols will submit the approval of its saline solution in 50 ml, 100 ml, 250 ml and 1000 ml to the FDA. In addition to hospitals and pharmacies, compounding centers use saline solutions in minibags to reconstitute lyophilize antibiotic and oncology therapies. The company will be marketing the minibags to all users throughout this year.

seas, including minibags of sodium chloride 0.9% injection bags, dextrose 5% injection bags, and metronidazole injection.⁵ The agency is also expediting the review of any new product applications that will help resolve the shortages.

Grifols will submit the approval of its saline solution in 50 ml, 100 ml, 250 ml and 1000 ml to the FDA. In addition to hospitals and pharmacies, compounding centers use saline solutions in minibags to reconstitute lyophilize antibiotic and oncology therapies. The company will be marketing the minibags to all users throughout this year.

REFERENCES

1. Market — *Global Industry Analysis, Trends and Forecast — 2024*
2. “Current Drug Shortages List.” *Drugs.com, Drugs.com*
3. *REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-15), National Drug Shortages: Update*
4. “Large Volume IV Solution Shortages.” *Infusion Nurse Blog*, 27 Mar. 2014.
5. “Drug shortages loom from hurricane-impaired manufacturing in Puerto Rico.” *American Pharmacists Association*, 14 Nov. 2017

ABOUT THE AUTHOR



Marga Viñes

Business Development Manager, Contract Manufacturing, Grifols Partnership

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.

LinkedIn www.linkedin.com/in/marga-viñes-a9aa748

Email marga.vines@grifols.com