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Drug Shortages and Excipient Opportunities: A Parenteral Excipient Market Analysis

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Reports of drug shortages surfaced in news outlets in 2010. By 2011, the number of drug shortages peaked. Of the 251 problem drugs published by the FDA, 183 involved sterile injectable products (FDA/ CDER Drug Shortage Program). While many of the shortages were related to the inherent manufacturing complexity and daunting quality requirements of parenteral products, the FDA has cited delays in receiving raw materials and components from suppliers as a siginificant contributing factor. Many of these supplier shortages are related to the challenges of producing high purity exipients which has resulted in an under capacity to the market. Due to efforts by FDA and CDER, reports of drug shortage reports started to wane by 2013, but drug shortages still persist today, particularly in the sterile injectable products sector.

It is frequently thought that the pharmaceutical industry is immune from such market dynamics. The dominating industry is quite mature maintaining a long standing presence, significant capacity and a robust intellectual property portfolio. But as older drugs give way to newer, more profitable medications with completely different delivery mechanisms, the economic forces shift the equilibrium status quo. The parenteral market has experienced rapid growth, with higher demand that outpaced a lower supply. Unfortunately, it has manifested in drug shortages.

Oral Solid Dosage Forms (OSDF) continue to dominate the pharmaceutical landscape. With higher patient compliance, tablets and capsules are the preferred delivery method, and economically speaking, OSDF are easily transported, chemically stable, and cost effective. New small molecule opportunities have been limited by solubility and permeability challenges. Efficacious, large molecules present great growth opportunities, but these also present a drug delivery challenge.

As of 2013, parenteral drug delivery represented a 30% share of the overall drug delivery technology market while oral formulations occupied 60%. However, 60-70% of drugs currently under clinical development phase are considered biopharmaceuticals, twice the historical precedent. This includes mABs, ADC and vaccines. The growth in the biopharmaceutical sector is vastly outpacing historical demands and the delivery platform change propels an increased demand for parenteral grade excipients. Targeted disease states and the promising large molecule candidates are dictating delivery by injection.

Globally, parenteral excipients account for 8% of the overall excipient market spend and this sector is rapidly growing compared to OSDF. The parenteral excipient market in the US and Europe is rising at CAGR of 12-13% due to the emphasis on biologics. Excipient manufacturers are beginning to recognize this shift in demand. However, few suppliers are positioned to meet the extensive purity analysis requirements, stringent regulatory scrutiny, and most importantly, the guaranteed requirement for low endotoxin levels.

Endotoxins are lipopolysaccharides which are released when gram negative bacteria become lysed. If entered into the blood stream, endotoxins can result in septic shock, organ failure and death, particularly affecting the young, elderly, and immunocompromised. Manufacturers can control excipient particle size via simple methods like screening or filtering, milling and drying conditions. Many of these filters can easily confine bacteria using 0.22 µm membrane filters; however, lipopolysaccharides are much smaller and can not pass through this barrier. Therefore, excipient manufacturers must use more sophisticated techniques. Specialized equipment, dedicated production suites, and specialized monitoring equipment are all standard practices. As a result, manufacturing and quality costs are expensive and suppliers must undertake the risk of marketing excipients that require costly, extensive impurity analyses while also recognizing that their products can have direct impact on patient health.

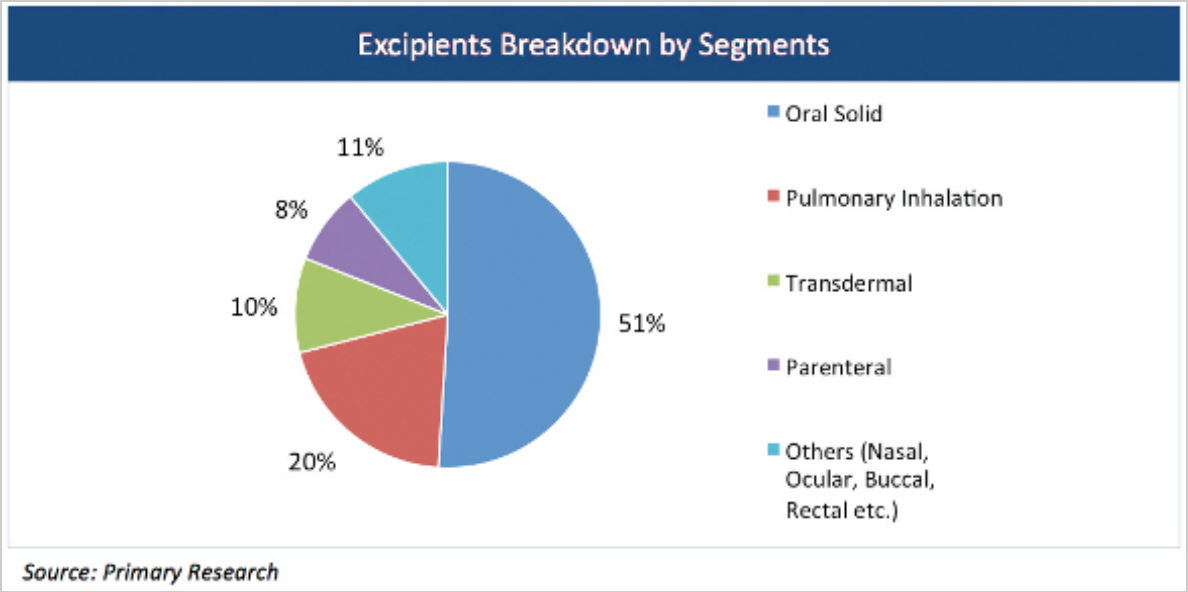

Figure 1.

All of these efforts result in parenteral grade excipients production having 3-5 times higher cost than manufacturing the same excipient designated for the OSDF market. Currently, the volume of these specialized excipients accounts for only 2-3% of the overall excipient volumes purchased by pharmaceutical companies, comparatively making sterile excipients a niche sector. For example, the global pharmaceutical industry consumes 25% of the gelatin production; however, only 5% is used in parenteral preparations. Similarly, parenteral grade succinic acid is just 2% of global succinic acid market. As a result, high cost, low volume, and limited supplier base substantially reduce the pharmaceutical buyer's bargaining power.

Nevertheless, while demand for these ultrahigh purity, cGMP excipients is growing at an accelerated rate, supply for these excipients has not matured at a rate fast enough to cater to the pharmaceutical industry's needs. Due to the stringent manufacturing requirements, there are very few excipient suppliers willing to undertake the necessary investment or risk needed to produce low endotoxin excipients meeting parenteral application regulatory standards.

The industry needs suppliers who can manufacture high purity parenteral excipients with proficient technical expertise while meeting customers' and regulatory authorities' expectations. In this market, the number of qualified suppliers is limited.

Some suppliers are recognizing this opportunity and capitalizing on it. A typical excipients manufacturer's strategy is to convert standard pharmaceutical grade excipients to parenteral grade, often resulting in low product quality and a high number of rejected batches. Dedicated manufacturing has become the preferred solution.

To ensure consistent supply, drug makers often enter into supply contracts having clauses that define production expectations, tight specification limits, guaranteed volumes and assurances that suppliers do not make any changes impacting product quality without prior notification. For many excipient manufacturers, this translates into custom manufacturing. Since many excipient manufacturers began as simple food or chemical suppliers, production facility

capital and operational changes are required to meet or exceed strict quality requirements to meet FDA drug products guidelines. This greatly influences operations and cost models at older facilities.

Based on the current market situation, opportunities exist for excipient suppliers to develop and expand parenteral grade manufacturing. There is a market gap in both the capacity and technologies available for parenteral drug delivery. Companies like Evonik Industries have increased capacity while also acquiring companies like SurModics, which focuses on controlled release parenteral applications. In addition, Evonik also acquired complimentary technologies like Boehringer Ingelheim's RESOMER® platform. All these efforts expanded their presence and capabilities in a move satisfying increasing sterile market opportunities.

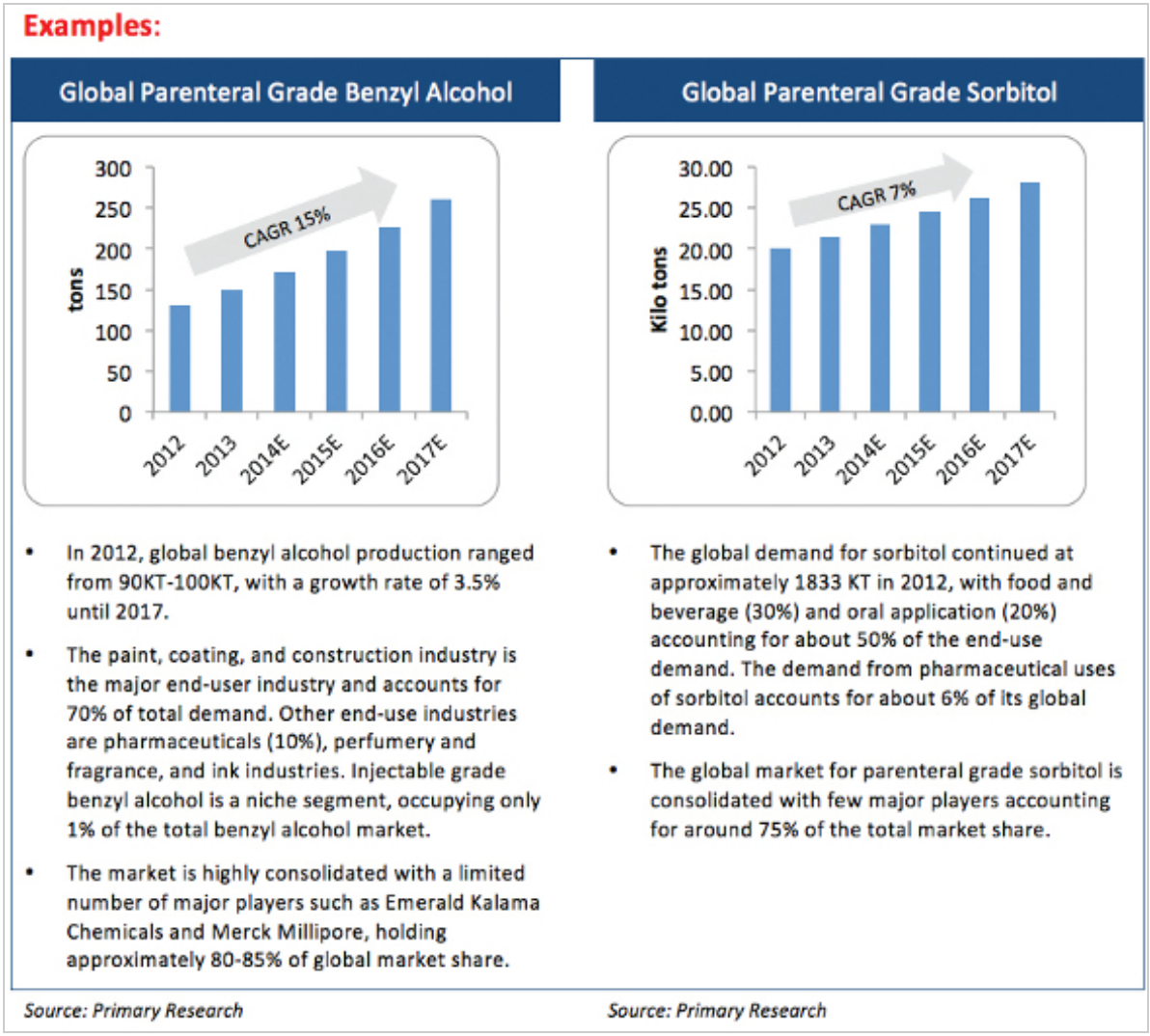

Figure 2.

Recent News on Parenteral Excipients

Suppliers	Products Portfolio	Year of News	News on Suppliers
Pfansteihl	Sucrose, Maltose, Mannitol	2015/ 2014	In 2015 & 2014, Phansteihl introduced high quality parenteral grade maltose and mannitol for pharmaceutical formulations respectively. They have also planned to launch new parenteral excipients (combination of protein stabilizers and solubilizers) which can be used in prefilled syringes, a fast growing segment.
Roquette Pharma	Dextrose, Mannitol, Sorbitol, Sodium Glyconate	2012	Roquette pharma, which started a new dedicated line for manufacturing parenteral dextrose monohydrate in France at the end of 2011, had successfully completed US FDA inspection.
Emerald Kalama Chemicals	Benzyl Alcohol, Benzoic Acid	2013	It had expanded benzoic acid plant capacity in Rotterdam, The Netherlands by 20KT. Benzoic acid is used in different industries such as food & beverage, pharmaceutical, coatings etc.
Avantor Performance Materials	NA	2013	Avantor had added high purity polysorbates 20 and 80 to cater needs from biopharmaceutical and small molecule drug industry.

Source: Supplier websites and news; NA: Not Available

Figure 3.

Excipient suppliers can also collaborate with the pharmaceutical industry for product customization or innovation and thus stay competitive in a changing market. For example, while a CMO/ pharma partnership is commonplace, the industry has witnessed CMO alliances with excipient suppliers to develop optimal drug delivery mechanisms. Companies like BASF have allied with Bend Research and Catalent Pharma Solutions to collectively develop drug delivery solutions for newly developed and difficult active pharmaceutical ingredients. These strategies are evidence of the opportunties to expand the capabililty, technology, capacity, and promise of parenteral excipients.

With the number of parenteral excipients suppliers being limited to few qualified producers and the market growth for selected excipients, it is likely that new players will enter this sector. It is important to understand the technical attributes, but also the market dynamics. Hence, throughout drug product life cycle management, category managers and excipient producers must understand the factors that enable sustainable sourcing and the impact on patient safety and well being.

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