



PANEL MEMBER

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The Fertile Market of Sterile Injectables

Introduction

As life sciences firms have increasingly shifted their focus to therapeutic segments like Oncology, biologics have become a larger component of the pharmaceutical industry’s development pipeline. Further, novel drug delivery systems that provide targeted therapies are gaining prominence. These two factors, among others, have led to a rapid growth in the Sterile Injectable technologies and formulations’ market.

In this article, we provide an overview of the sterile injectable dose formulation market, the drivers behind its growth, and the various types of dosage forms that constitute the market. Following which, we assess the reasons for demand-supply inequity and the acquisitive strategies that have resulted thereof. We then conclude with a service provider’s view that summarizes how providers have responded to client needs and market trends.

Market overview

The global sterile Injectable market is at circa \$312 billion in 2014 and is projected to reach \$363 billion by 2017. The two largest segments are Biologics (52% share) and Small Molecule injectables (38% share), with a CAGR of 7% for the latter. Within Biologics, monoclonal antibodies (mAbs) account for the largest market share, followed by vaccines and insulin (see Chart 1). In the Small Molecule segment, Oncology and Anti-Infectives are the major contributors of the market (see Chart 2).

(Source: IMS, 2014)

Chart 1. 2014 Sterile Biologics Market US\$ 162 B

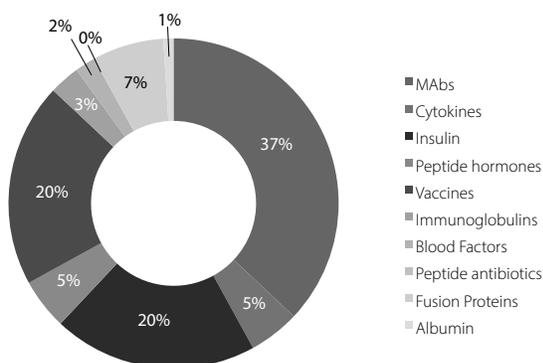
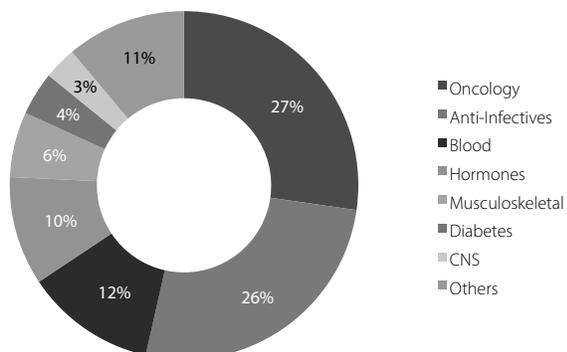


Chart 2. 2014 sterile Small Molecule Market US\$118 B



Market drivers

Approximately 2,400 injectable products are currently in the development pipeline (potent and non-potent), leading to growth on the innovative side of the market. Demand for cutting edge injectable capabilities should grow as ADCs and other high value products dominate the 'potent' development space. Nevertheless, the primary driver behind the growth in injectables is the generic market. Growth in the generic injectables is outpacing growth on the innovator side: The global, generic, sterile injectables market is projected to grow from \$37 billion in 2013 to \$70 billion in 2020 - a growth rate of 10%.

Market segmentation by technology

The Sterile Injectables formulation technologies market can be segmented into conventional and novel formulations. The 'Conventional Dosage' forms can be further categorized into Solutions, and Lyophilized / Water for reconstitution. Novel Drug Delivery Formulations have gained prominence in the last few years for enhanced disease targeting and to increase patient compliance. Some of them are:

- **Depot Injections – Microsphere & oil based:** A depot injection is an injection, usually subcutaneous or intramuscular, of a pharmacological agent which releases its active compound in a consistent way over a long period of time
- **Liposomes:** Liposomes are being used as carriers of various pharmacologically active agents like anti-neoplastics, antimicrobials, steroids etc. Liposome formulations are used to reduce toxicity and increase accumulation of the drug at the target site
- **Nanoformulation:** Nanoformulation enables the sheathing of drug particles with polymeric surfactants, which can then be layered onto a substrate for future delivery. This has helped in effective formulation of many insoluble molecules
- **PEGylated formulations:** PEGylation is the covalent attachment of Polyethylene glycol (PEG) to molecules of interest. It is the most commonly used non-ionic polymer in the field of polymer-based drug delivery. It increases solubility of the drug in aqueous medium, increases the half-life of the drug, reduces toxic side effects, stabilizes and improves therapeutic activity of the drug
- **Implants:** Implants are sterile solid preparations containing one or more active ingredients. They are of a size and shape suitable for parenteral implantation and provide release of the active ingredient(s) over an extended period of time

Key players in the innovator and generic space

Some of the large injectable players in the innovator (pharmaceutical and biotech firms) space are given in Table 1. Teva, Hospira, Hikma, and Fresenius Kabi, are some of the major generic players in this space.

Table 1: Key pharmaceutical and biotech firms with injectable products

Amgen	Genentech	Novo Nordisk
J & J	Sanofi	Abbvie
Eli Lilly	Pfizer	Roche Biogen

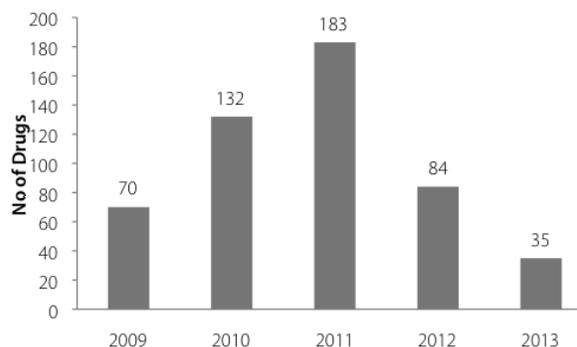
Market demand-supply equation

The development and manufacturing of sterile injectable products is both, complex, and capital intensive. Operational costs are high since injectables are toxic and infectious in their natural state and hence require a higher degree of quality and care in their manufacturing, packaging, storage, and distribution. Stringent regulations from FDA on manufacturing sites, pose a major challenge for both existing players, and for potential new market entrants. Competition from low cost manufacturing zones like India and China in the generic market has led to discontinuation of many products in the segment for economies of scale. Consolidation of captive/in-house manufacturing capacities have resulted in closure of many sterile manufacturing sites in the US and elsewhere which, in turn has led to product shortages in the US. Some of the other reasons for these shortages are:

- Mergers & Acquisition activities have resulted with single supply sources and capacity constraints
- FDA regulatory violations leading to Import alerts/bans at manufacturing sites
- Discontinuation of older injectable drugs in favour of newer, more profitable drugs
- Consolidation of supply chain by large pharma companies leading to shut down of their existing manufacturing sites
- Relatively less number of in the sterile injectable market that cater to the increasing demand of sterile dosage forms. The complex manufacturing process makes it even more difficult to transfer technologies freely between the sites. Some of the process related challenges are:

- Sterility: Bacterial and Fungal contamination
- Stability Issues (Crystallization)
- Extractables and Leachables from packaging materials: glass, metal or fibers in vials
- Transportation & Logistics

Chart 3: Sterile Injectables in short supply (Source: US FDA)



FDA has begun responding to shortages by expediting generic approvals for drugs that have shortages, shortening approval times for new production lines/new raw material sources to help increase supplies, and also allowing imports into the US for drugs under shortage from approved suppliers. This seems to be alleviating the problem, with the number of shortages reducing to 35 in 2013, from a high of 183 in 2011.

M & A Activity

The last few years have seen significant M & A activity in the sterile Injectable space. In a bid to quickly participate in a rapidly growing market, firms are acquiring specialist sterile injectable players to enhance their product portfolio and manufacturing capabilities. Some of the recent key deals are listed below:

- **Pfizer- Hospira (\$17 billion):** This provides a growing revenue stream and a platform for growth for Pfizer’s Global Established Pharmaceutical (GEP) business by combining Hospira’s generic sterile injectables products, including acute care and oncology injectables
- **Pfizer – InnoPharma (\$360 million):** At the time of the announced acquisition, InnoPharma’s portfolio included 10 USFDA approved generic products, a pipeline of 19 products filed with the FDA, and more than 30 injectable and ophthalmic products under development
- **Hikma - Bedford laboratories (\$300 million):** Hikma acquired Bedford’s product portfolio, intellectual property rights, contracts for products marketed under license,

raw material inventories, R&D and business development pipeline. This strengthened Hikma’s position in the US generic injectable market

- **Sun Pharmaceutical - Pharmalucence Inc.:** Pharmalucence was a privately held company based in Billerica, Massachusetts, which has sterile injectable capacity supported by R&D capabilities
- **Mylan – Strides Arcolab:** In December 2013, Mylan Inc. completed the acquisition of the Agila injectables businesses from Strides Arcolab Limited for up to \$1.75 billion. Through this acquisition, Mylan expanded its injectable product portfolio, pipeline, and capabilities, and as of December 2013, had more than 1,200 approved injectable products globally and more than 900 injectable products pending global approvals
- **Piramal - Coldstream Laboratories:** In early 2015, Piramal acquired Coldstream Laboratories, a Kentucky based injectable manufacturer to augment its formulation offering, while augmenting its ADC fill finish capabilities

Sterile CMO Market

Presently, the injectable CMO market is at US\$6bn and growing at a CAGR of 11% compared to the overall global CMO market which is growing at a CAGR of 7%. Outsourcing in the Sterile Injectable segment is still skewed towards US, followed by the EU. We anticipate this market to continue growing at 10% annually for the next 5 years and US to remain the most preferred outsourcing destination.

Some factors driving the growth are,

- Specialised technologies and dedicated capacities required for biopharmaceuticals products leads to high outsourcing of these products

- Preference to outsource products that require handling of high potency materials and containment suites
- Rapid growth of Pre-Filled syringes’ market leading to spike in the demand of CMOs
- De-risking of supply chain by brand manufacturers by adding a second source to their product manufacturing
- High growth in emerging markets resulting in local players looking at local CMOs to enter the geography

The major CMOs in the sterile injectable space include: Catalent, Baxter, Pfizer Centersource, Akorn, Althea, Vetter, Piramal Pharma Solutions (ColdStream Laboratories), and IDT Biologica.

The Future

With over 900 approvals in the injectable space since 2000, the market is growing rapidly as firms invest more into development of new molecules and generics and ramping up their production capacities through acquisitions.

- Drug Delivery Systems like Liposomes, PEGylation, Depot Injections will see a spurt in the growth – especially in therapeutic segments that require efficient targeting of drugs
- Compliance issues and the high cost of injectable drugs will

propel the Pre-Filled syringe market to attractive growth

- Biologic molecules will contribute to more than 50% of the research spend by top 15 companies globally, serving as a macro catalyst for injectables long term prospects
- Generic segment will continue its growth, and we expect that top generic players will consolidate their position with adding manufacturing infrastructure
- Emerging markets will drive the generic market expansion, with China and India leading the pack

Summary

The increase focus in biologics and targeted therapies, especially in the area of cancer has led to an increase in the need for injectable drugs. While biological drugs have a larger part of the injectable market, the small molecule injectables will have the higher growth. The complex process of manufacture, high capital and operational costs, and the compliance requirements for success has

led to a smaller number of players. These firms are being further reduced due to acquisitive activity in a sector that is rapidly consolidating. The supply crunch that was present a few years ago has been mitigated to some extent by FDA actions. In the future, we see a continued demand for injectable drugs especially in drug delivery systems and Pre-Filled Syringes.

References

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