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Injectables: The New Oral?

The growth trend of injectables continues across the pharma landscape.

It probably won't come as a surprise to many that the pharmaceutical industry has been increasingly embracing injectables as a consistently profitable business sector. It may be a surprise though, to find that seven of the top 10 pharmaceuticals by sales in 2014 were injectables (*Table 1*). This is a far cry from a decade earlier where only one product, Amgen's Epogen, managed to crack the Top 10, sitting in the Number 9 position. Eight of these Top 10 products were oral products, and one, Advair, was an inhalation product. The sharp move towards injectables is the result of a number of important trends that are worth understanding.

IT'S NOT JUST NOW, IT'S ALSO THE FUTURE

The decade long shift in the top rank of pharmaceutical products is likely to be the new order for some time. While the existing portfolio of marketed pharmaceuticals is still heavily weighted to oral agents, the emerging pipeline reveals a significant change (*Chart 1*). Among pipeline programs injectables rank far ahead of oral programs, and pretty much equal all other programs as defined by delivery route. Looking a little closer we see that these pipeline programs are increasingly dependent on drug delivery and formulation technologies to optimize performance and in many cases provide for enhanced intellectual property protection. Injectables are also increasingly likely to forgo simple aqueous formulations, in favor of sophisticated nanoparticle and protein fusion technologies. So exactly what underlies the attraction of injectables from a pipeline perspective and accounts for their position at the top of the charts?

IT'S ALL ABOUT BIOLOGICS

All of the injectables in the 2014 Top 10 list are biologics; there are no small molecule injectables. It shouldn't be a surprise that biologics are administered by injection; these are large, often labile, molecules sensitive to the gastric environment and, even if stable, inconsistently, if at all, absorbed following oral dosing. Similarly, these macromolecules are not candidates for transdermal administration. The lung is also a challenging delivery route for macromolecules. At present inhalation has proven to be best suited for the treatment of locoregional conditions using macromolecules such as Pulmozyme and Promixin. The great hope for defining the potential of the lung as a portal for the systemic delivery of macromolecules, inhaled insulin, seems to have hit a major bump in the road. Exubera was withdrawn a decade ago, and the latest iteration, Mannkind's Afrezza, is sitting in the slow lane of commercial acceptance.

That pretty much leaves injection as the only practical route for the delivery of macromolecules, and biologics in particular. But there is much more behind the rise of injectables to the top of the sales lists and the pharmaceutical pipelines of many companies.

IMPROVED SOLUTIONS FOR OLD PROBLEMS

The rising popularity of biologics is directly related to their ability to address challenging medical conditions with a degree of selec-

Product Rank	2004 Product	2004 Sales	2009 Product	2009 Sales	2014 Product	2014 Sales
1	Lipitor	11,727	Lipitor	12,651	Humira	12,543
2	Zocor	5,197	Plavix	9,455	Sovaldi	10,283
3	Plavix	5,110	Enbrel	8,489	Remicade	9,916
4	Norvasc	4,463	Advair	7,792	Enbrel	8,949
5	Zyprexa	4,420	Abilify	6,600	Lantus	8,435
6	Advair	4,019	Remicade	6,419	Abilify	8,404
7	Nexium	4,382	Diovan	6,091	Rituxan	7,553
8	Pravachol	3,679	Avastin	5,745	Advair	7,035
9	Epogen	3,589	Rituxan	5,620	Avastin	7,023
10	Prevacid	3,455	Humira	5,563	Herceptin	6,868
	Total	**50,041**		**74,425**		**87,009**

TABLE 1: Worldwide Product Sales, 2004-2014 (USD millions)

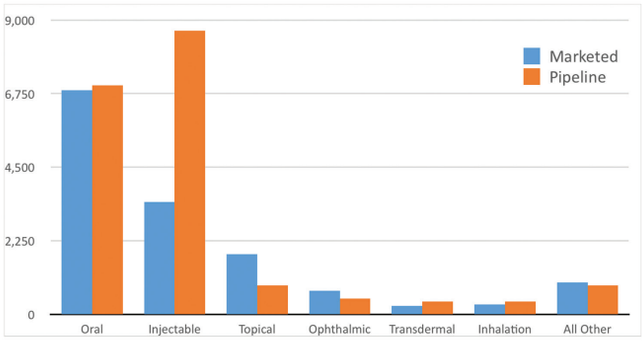

CHART 1: Marketed and Pipeline Pharmaceutical Programs – 2016

tivity that was unimagined even two decades ago. Autoimmune conditions such as arthritis, which had been treated symptomatically for decades, are now treated at a more mechanistic level with biologics such as Humira, Remicade and Enbrel. At the same time a number of aggressive cancers are being managed with antibody based biologics such as Rituxan, Avastin and Herceptin, once again selectively targeted to specific biologic processes.

PROVIDING EXCLUSIVITY

Like any Top 10 album, it's one thing for a pharmaceutical product to make its way onto the list of best selling pharmaceuticals, it's another thing altogether to stay in sight of the top of the list. This is where biologics have a huge advantage over small molecules. Unlike small molecules there is no simple regulatory pathway for the approval of generic versions of biologics. And unlike small molecule products, once approved, biologics cannot be simply substituted at the prescription level. That, combined with an extended regulatory exclusivity period for biologicals, pretty much assures that if a biological can get into the top tier of product sales it will sit there for a decade or more. This is quite unlike the situation with small molecule products that can work their way into the Top 10, sit there for a year or two, and quickly fade as substitutable generics grab share and erode sales. While the most successful small molecule products like Lipitor and Plavix struggled to secure even a decade of market exclusivity, biologics such as Herceptin and Rituxan are cruising along nicely almost two decades after first launch. And when substitution with biosimilars arrives it still promises to provide approved biologics with a smooth landing, rather than the crash and burn seen with many small molecule pharmaceuticals at the end of their patent life.

INCREASINGLY PATIENT FRIENDLY

The emerging market for injectables is increasingly targeted to outpatient treatments for chronic conditions. Injection has, for decades, been largely limited to inpatient use, with health professionals actively involved in administering doses intravenously, intramuscularly and subcutaneously. This continues to be the standard of care when it comes to intravenous, intramuscular and infusion-based therapies, but not for subcutaneous injections. What started as a burden for patients with diabetes, multiple daily subcutaneous injections, has evolved into a manageable dosing strategy for a variety of medical conditions.

The improvement in subcutaneous dosing has been led by advances in three areas: more patient friendly injection devices, reduced dosing frequencies, and reduced injection volumes. The introduction of prefilled syringes and injection pens has reduced the intimidation associated with outpatient injections. These syringe and cartridge based injectables also reduce the possibility of errors in preparing and administering a subcutaneous injection. Pain and discomfort are also reduced with the use of short, and very fine bore, needles.

Equally important has been the trend towards the adoption of formulation technologies, ranging from polymer conjugation to protein fusion, that stretch out the interval between dosing. What might have required daily dosing a decade ago is now managed with once-a-week, or even once-a-month, dosing.

Combined with better efficacy and enhanced tolerability the prospect of self injection for the management of a chronic disease is increasingly found to be an acceptable trade-off for many patients. The top selling product, Humira, is most commonly dosed every two weeks using a pen or prefilled syringe. And Biogen's Plegridy, a PEG-polymer second generation treatment for multiple sclerosis, extends dosing from every week to every two weeks, using prefilled syringes and pens. At the same time there is no increase in injection volume with the new longer acting dosage form.

Injection, most certainly subcutaneous injection, has evolved from a being a last choice dosing option for patients and physicians to one that is more than acceptable for the management of chronic conditions. One subcutaneous injection every two weeks or an oral tablet twice a day that causes stomach upset? Injection can seem the better option.

THE INJECTABLES PIPELINE

So what is in the burgeoning injectables pipeline? Let's slice the data by indication, delivery route and molecule type (*Tables 2,3,4*).

In total subcutaneous and intradermal dosing accounts for about 30% of the injectable pipeline. That number is likely to be higher, but unfortunately a number of products, about 20% in the case of Phase 2 pipeline products, do not define a delivery route

more specific than injectable.

Cancer is the number one pipeline indication for injectable programs, followed by infectious and immune diseases. In the case of cancer, intravenous programs account for about two-thirds of the pipeline programs, while subcutaneous programs account for a bit less than a fifth. The situation is reversed for immune and endocrine indications, where subcutaneous dosing accounts for more than two-thirds of the pipeline programs.

The greater part of the developing pipeline for injectables is related to macromolecules, about three-quarters of the total, with molecules ranging in size from peptides at the lower end, to antibody therapeutics at the higher end.

THE FUTURE OF INJECTABLES

The future expansion of injectables is directly linked to the future of biologics. There is little question that we will be seeing more and more opportunities for these macromolecule sized pharmaceuticals to deliver oversized therapeutic benefits. Their specificity and selectivity will offer multiple new therapeutic options for a variety of challenging medical conditions. With the constant improvement in smart injectable devices, not just limited to subcutaneous treatments, it is likely we will see practical outpatient intramuscular and intravenous dosing options in the coming years.

Biologics are now starting to face challenges that were once limited to small molecule therapeutics; me-too competitors as well as generic, referred to as biosimilars. Approved in the EU almost a decade ago biosimilars are starting to receive approval in the U.S. Nonetheless, biologics have much less to worry about with the intrusion of these new, similar but not identical, competitors. Regulations restrict biosimilars from accessing the regulatory data of the innovator biologics for a period of ten to twelve years, in the EU and U.S. respectively. And even then biosimilars do not receive an automatic interchangeable label, permitting substitution for an innovator biologic. Interchangeability is determined on a country-by-country basis in the EU and state-by-state basis in the U.S. So, with all of these regulatory impediments in place biologics are likely to enjoy a long and profitable run in the marketplace.

This extended period of exclusivity for biologics should spur innovation in terms of injection devices, formulations and particle engineering that will add additional exclusivity to these biologics, and by extension injectables through the age-old process of patent protection.

The future for injectables looks rosy. The industry shift to biologics has established a growth market for injectables and supporting technologies. Given several layers of regulatory protection, and the usual exclusivity afforded by patents, it is quite likely that biologic injectables will enjoy strong commercial rewards for the next quarter century. Add in the innovation that is being seen with devices and formulations and it is hard to bet against injectables hanging on to their position at the top of the charts. **CP**

TABLE 2: Injectable Programs – Delivery Route by Phase

Route	Phase 3	Phase 2
Intramuscular	10%	9%
Intravenous	36%	39%
Subcutaneous / Intradermal	32%	25%
Other / Undefined	22%	27%
Total	**477**	**1,103**

Source: PharmaCircle Products & Pipeline Module

TABLE 3: Injectable Programs – Indication by Phase

Route	Phase 3	Phase 2
Cancer	28%	36%
Cardiovascular	6%	7%
Endocrine	5%	7%
Genetic	5%	1%
Immune	8%	8%
Infectious Disease	17%	14%
Other/Undefined	31%	37%
Total	**477**	**1,103**

Source: PharmaCircle Products & Pipeline Module

TABLE 4: Injectable Programs – Molecule Type by Phase

Indication	Phase 3	Phase 2
Antibody	23%	19%
Carbohydrate	1%	2%
Cell Therapy	5%	10%
Gene Therapy	3%	5%
Oligonucleotide	1%	3%
Peptide	10%	12%
Polymer	1%	<1%
Protein	21%	17%
siRNA	1%	2%
Small Molecule	25%	22%
Other / Undefined	9%	7%
Total	**477**	**1,103**

Source: PharmaCircle Products & Pipeline Module

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