

INTRODUCTION

ORAL DRUG DELIVERY: THE NUMBERS BEHIND THE BUSINESS

For the pharmaceutical industry, extended release oral dosage forms provide multiple commercial benefits. Reduced dosing frequency improves compliance, which translates into higher unit sales. And better therapeutic outcomes due to improved efficacy and improved tolerability can lead to fewer medication switches and greater physician loyalty. New formulations can also extend market exclusivity.

With oral drug delivery becoming an increasingly mature technology it's worth looking at some of the numbers and parameters that impact the business of oral drug delivery. What was once a novel and high value technology has increasingly become a commodity platform. Is there still value to be found in developing novel oral drug delivery platforms? Perhaps the numbers can give us a sense of the past, present and future.

BACKGROUND

The numbers in this article focus on the US market. The US represents the largest global market controlled by a single, remarkably transparent, regulatory process. This permits trends and values to be more easily analysed.

"COMPANIES PROVIDING ORAL DRUG DELIVERY TECHNOLOGIES WILL NEED TO EVOLVE THEIR OFFERINGS AND BENEFITS IF THEY HOPE TO AVOID COMPETING IN A COMMODITY MARKET"

And what happens in the US doesn't just stay in the US; products and ideas often move overseas. While there are great oral drug delivery ideas coming from Europe and Asia, companies almost always look to the US as the most important market.

We will define "drug delivery" for the purpose of this article as a formulation technology that enables and/or enhances the use of a

pharmaceutical active. The acronym (DDEP) refers to these drug delivery enhanced and/or enabled products. Our definition will not include commonly available formulations considered to be part of a standard toolbox. This includes simple enteric coated products such as proton pump inhibitors. Extended release pseudoephedrine, ephedrine and antihistamines are also excluded because of the formulation toolbox nature of the technologies. All other oral sustained release and quick dissolve technology products are included.

ORAL DRUG DELIVERY PRODUCTS SALES

Table 1 provides a summary of the annual sales of oral drug delivery products in the US for the years 2000 to 2008. This list is limited to prescription oral drug delivery products (oral DDEPs) that were among the Top 200 Retail Products in terms of sales. These Top 200 products accounted for about 85% of all retail sales in the US.

Overall, oral DDEPs accounted for between six and 11% of the sales of all pharmaceutical products in the Top 200. The sharp increase in sales of oral DDEPs between 2000 and 2003 is accounted for by the strong growth of new sustained release formulations of antidepressant, incontinence and ADHD medications. Oral sustained-release (SR) product sales accounted for 96.6% of all oral DDEP sales, with ODT formulations accounting for 2.2% and Liquid SR the remaining 1.2%.

The top-selling oral DDEPs are all SR formulations with Effexor XR (venlafaxine; Wyeth/Pfizer) holding the number one spot with peak sales of almost \$2.7 billion in 2008. The second-place product was OxyContin (oxycodone; Purdue) with reported sales of \$2.5 billion in 2008. Other top products included: Wellbutrin SR (bupropion; GlaxoSmithKline), which had sales of \$1.7 billion in 2003; Wellbutrin XL (bupropion; Biovail/GlaxoSmithKline), with \$1.7 bil-

lion sales in 2006; Toprol XL (metoprolol; AstraZeneca) with \$1.5 billion sales in 2006; and Adderall XR (mixed amphetamines; Shire) which had \$1.4 billion of sales in 2008.

It is worth noting that the majority of these products address chronic central nervous system indications. All of these top selling oral DDEPs are reformulations of previously approved, and very successful, immediate-release products.

The top products in terms of peak annual sales are all reformulations of previously approved and marketed actives. Only when you get to the 29th product, Invega (paliperidone; J&J), do you find a new molecular oral DDEP. Sales of Invega were reported as \$246 million in 2008.

The top selling non-SR oral DDEP was Claritin RediTabs (loratidine; Schering-Plough/Merck) at the 17th position with sales of \$383 million in 2002. Other notable ODT formulation products include: Zofran ODT (ondansetron; GlaxoSmithKline) with sales of \$214 million in 2005; and Maxalt MLT (rizatriptan; Merck & Co) with sales of \$192 million in 2008. Tussionex (hydrocodone/chlorpheniramine; UCB), a liquid SR product for the treatment of cough, was in at the 28th position with sales of \$247 million in 2008.

ORAL DRUG DELIVERY PRODUCT DEVELOPMENT PARAMETERS

What about the development parameters associated with oral DDEP? How long does it take to develop these formulations? What are the expected success rates?

The figures from the recent Bionumbers report, *DD09 – Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity*, provide a good idea of development parameters for oral DDEP. The report looked at DDEP developed and approved over the last 13 years in the US. These numbers should be considered optimistic; products developed and approved in the last few years require longer development times and have lower success rates. The report provides detailed guidance on these trends.

For the period 1996 to 2008, it has taken on average 5.8 years to move a DDEP through

clinical development and approval. This is exclusive of any earlier formulation or preclinical activities. The average clinical development success rate for this period is 34% (see table 2). These figures now stand close to 6.2 years and 24% respectively.

The corresponding 1996 to 2008 average development time for oral DDEPs is 4.9 years, with an average of 2.7 years for ODT formulations and 5.6 years for oral SR products. These can be compared with the 5.8 year average noted in the previous paragraph (see table 2). It is reasonable to expect that these times have increased by at least 10% in the past few years.

The overall development and approval success rate for oral DDEPs is 43%, with a 47% success rate for oral SR DDEPs (table 2). This is about a third higher than the overall rate for DDEPs (34%). Current success rates for oral DDEPs are probably lower, but most likely above 33% (1 in 3).

It is interesting to speculate why the development and approval times for oral DDEPs are shorter than the average for all DDEPs and why the success rate is higher. The reason may be that oral DDEPs are targeted to enhance convenience. SR provides once-a-day dosing versus thrice daily, for example. And ODT gives the convenience of ‘melt in the mouth’ tablets. These product benefits often require little more than demonstrating bioequivalence with currently approved immediate-release products. Even if efficacy endpoints are required, the development program is often quite simple. And if the drug delivery platform is validated, the regulatory review period can be short.

MARKET EXCLUSIVITY

The attractive development parameters associated with oral DDEPs are offset to some extent by the relatively short market exclusivity periods for these products. The US FDA provides regulatory exclusivity of three or five years depending on whether a product incorporates a previously approved active (three years) or a new molecular entity (five years). This regulatory exclusivity is with regard to generic products approved solely on the basis of bioequivalence data (the ANDA process) and exclusivity runs in parallel with any patent exclusivity the product may possess.

In the case of products incorporating previously approved actives, the three year exclusivity provides no protection from functionally equivalent DDEPs. These functionally equivalent DDEPs incorporate the same active, but use a non-patent infringing drug delivery system. These products are approved on the basis of their own clinical data.

In the marketplace this means DDEPs enjoy market exclusivity from generics for the longer of the two FDA exclusivity periods, or any patent protection existing for the pharmaceutical active. But this does not prevent the introduction of functionally equivalent DDEPs where there are numerous technologies available and there is no parent molecule patent protection.

In the generic scenario a good example of the three year exclusivity period is seen

The third approach to securing exclusivity involves developing novel delivery systems that cannot be duplicated. This is difficult with oral drug delivery systems. As is the case within the electronic products market (computers, smart phones, televisions), once a company introduces a new technology competitors are quick to offer a comparable technology that does not infringe the originator company patents.

| Year | Top 200 Product Sales (US\$ billions) | Top 200 Oral Drug Delivery Product Sales (US\$ billions) | Proportion of Oral Drug Delivery Products (%) |
|------|---------------------------------------|--|---|
| 2000 | 90.0 | 5.5 | 6.1% |
| 2001 | 103.2 | 7.3 | 7.1% |
| 2002 | 111.0 | 9.9 | 9.0% |
| 2003 | 117.5 | 12.2 | 10.4% |
| 2004 | 117.3 | 12.3 | 10.5% |
| 2005 | 119.7 | 11.6 | 9.7% |
| 2006 | 126.4 | 12.9 | 10.2% |
| 2007 | 130.6 | 13.6 | 10.1% |
| 2008 | 133.2 | 14.5 | 10.9% |

Source: SDI/Verispan

Table 1: Top 200 Retail Product Sales – US

with Wellbutrin XL. A once-daily formulation of bupropion, this product was developed by Biovail and licensed to GlaxoSmithKline. With the underlying active having lost its patent protection long ago, the first generics appeared a little over three years after the approval of Wellbutrin XL, despite Biovail having issued patents that extended through 2018.

In the functional-equivalent scenario, there are two approved oral SR formulations of Tramadol, each of which was approved on the basis of its own technologies and studies.

There are at least three strategies for securing extended market exclusivity with oral drug delivery products. The first, as noted earlier, relates to having a patent on the underlying pharmaceutical active. This is often the basis for the exclusivity enjoyed by big pharma’s products and for which oral drug delivery formulations represent a lifecycle strategy.

The second strategy involves securing patent protection on non technology-related performance parameters of the DDEPs; for example, drug plasma levels. This strategy has been used effectively by Purdue Pharma with their OxyContin product line. First approved in 1995, this product enjoys market exclusivity until at least 2011, solely on the basis of patents related to serum levels of the active. Attempts to invalidate these patents, while initially successful, have failed and OxyContin continues to generate sales of more than \$2 billion annually.

In general one can expect to have no more than three to five years’ exclusivity with a new oral drug delivery product unless one also has patent protection on the underlying pharmaceutical active, has defined a unique product profile, or has a unique technology.

FUTURE OF ORAL DRUG DELIVERY PRODUCTS

There remains an important therapeutic role for sustained-release and quick-dissolve drug delivery products. Unfortunately commercial benefits are more limited than has been seen in the past with billion dollar products like Procardia XL, OxyContin, Wellbutrin XL and Effexor XR. Product exclusivity is limited and pricing flexibility will be limited.

Nonetheless there remain pressing oral delivery needs that can be exploited therapeutically and commercially. The first of these, sustained release liquids, is poorly served by current technologies. While products based on UCB’s Pennkinetic delivery system have been available for more than two decades, the delivery technology is crude and unlikely to meet current FDA standards for new products. However, the promise of new liquid SR platforms is starting to be realised with the recent approval of an extended release liquid formulation of clonidine by Tris Pharma.

| Product Type | Average Development Time* (years) | Average Success Rate |
|--------------|-----------------------------------|----------------------|
| DDEP | 5.8 | 34% |
| Oral DDEP | 4.9 | 43% |
| Oral SR DDEP | 5.6 | 47% |
| ODT DDEP | 2.7 | data not available |

* time from initiation of clinical development to approval

Source: *Bionumbers*

Table 2: Comparison of average development times and success rates for DDEPs, Oral DDEPs, Oral SR DDEPs and ODT DDEPs for the period 1996-2008.

The most exciting oral drug delivery opportunity may be in the area of abuse deterrent formulations for opioids and stimulants. There exists in the US a significant regulatory interest in reducing the levels of misuse and abuse of these products.

Embeda, from King Pharmaceuticals, is the first of the abuse deterrent formulations to be approved by the FDA. An oral SR morphine combined with naltrexone, Embeda provides sustained-release analgesia when taken orally as directed. But when crushed, the narcotic antagonist naltrexone is released antagonising both pain relief and opioid high. This should limit successful attempts to get a rapid high by crushing and swallowing, injecting or insufflating the product.

Additional abuse-deterrent strategies are in development ranging from the use of narcotic antagonists, to the inclusion of aversive agents, to the use of physical methods to make crushing and solubilisation difficult. If these technologies can match the efficacy and safety of current opioids and stimulants, but with little abuse potential, they will find significant market acceptance.

REFLECTIONS

Companies providing oral drug delivery technologies will need to evolve their offerings and benefits if they hope to avoid competing in a commodity market. The same

principles that make today's computer or mobile phone obsolete within a couple of years applies to drug delivery technologies. While these technologies are still useful and pharmaceutically valuable, they do not support the attractive margins they used to command even a few years ago.

An important test for the drug delivery industry will be whether it can rise to the challenge of true innovation. The numbers suggest oral drug delivery remains as relevant today as it did a decade ago. Who will lead the way to new technologies and products?

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The report, *DD09 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity*, is available from Bionumbers.

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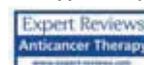
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