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Drug delivery market looks to deliver results: strong growth is projected for the drug delivery market as companies emphasize an integrated approach to pharmaceutical development - Focus 2003: Active Pharmaceutical Ingredients - Industry Overview

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Still proportionally small, drug delivery is an important and growing part of the pharmaceutical market. Some observers project double-digit growth for the sector as the market realizes not only opportunities in traditional functions such as extending product life cycles, but also in emerging technologies for protein- and peptide-based drugs.

The drug delivery market accounts for roughly 6 percent of the pharmaceutical industry, and is projected to account for 20 percent of global pharmaceuticals sales by the year 2005, according to Technical Insights, a division of Frost and Sullivan, a consulting company. Debra Bingham, vice president of Technology Catalysts International (TCI), a Falls Church, Va.-based consultancy, offers a slightly larger percentage and estimates that drug delivery product sales now constitute well over 10 percent of the total pharmaceutical market. TCI estimates the global drug delivery market to be over $40 billion in product sales in 2001.

In the US, the overall market for drug delivery technologies is expected to increase from $19 billion in 2000 to more than $41 billion by 2007, with revenues expected to increase at a compound annual growth rate of roughly 11 percent, according to Frost and Sullivan.

The strong growth rates for drug delivery are tied into the utility of the technologies in improving product life cycles for existing drugs as well as increasing sales through better patient compliance. "Pharmaceutical companies are realizing that, not only can improved delivery convey particular drugs more effectively or conveniently, it can also increase patient compliance, and extend the life cycle of these products as they lose their coveted patent protection," says Katherine Austin, analyst, biotech and pharmaceuticals, Technical Insights. Generics companies are also increasingly interested in novel drug delivery technologies for making their products competitive.

Other market drivers include expansion of company pipelines, product differentiation, and reduction of health care costs, according to Technical Insights. Since the 1970s, more than 35 drug delivery systems have been marketed, including transdermal patches, time-release pills, osmotic pumps and depot implants.

Over 300 companies are currently involved in drug delivery research and development. Key players include Nektar (previously Inhale Therapeutic Systems), Alkermes, Cima, Skyepharma, Eurand, Cardinal Health, Johnson & Johnson's Alza and Shire, according to TCI.

"The drug delivery market is now recognized as an important life-cycle management tool," adds TCI's Ms. Bingham. "It is also now being looked at much earlier in the development of pharma products. There are a number of drug delivery companies that are involved in early-stage development projects for new chemical entities (NCEs)."

Oral Still Leads Delivery Technologies

In terms of technology, oral delivery is still the route most preferred by patients and physicians, and therefore it will continue to dominate the market. Oral drug delivery currently accounts for roughly 50 percent of the total drag delivery market with a potential to reach over $30 billion by 2005, according to TCI. Oral drug delivery advances are now being applied not only to prescription pharmaceutical drugs but also to over-the-counter drugs and to consumer products. New oral technology is being developed to improve product perfor-mance and patient acceptance in products such as painkillers and mouth fresheners.

The search for technology that will enable the delivery of large molecules via the oral route is still ongoing. There are a couple of companies, including Nobex, which have been successful in clinical trials. Oral delivery of large-molecule drugs other than insulin currently represents an estimated $15 billion market, according to Frost and Sullivan. Industry experts peg oral controlled-release formulations as accounting for about 50 percent of the total drug delivery market with the potential to reach over S30 billion by 2005. However, with the increased development of biologics (typically very large molecules), other methods (mainly injection) have been growing, and oral delivery is expected ultimately to decline.

New technology developments in oral delivery include the use of carrier vehicles to increase gastrointestinal absorption; colon-specific drug delivery so that the drug is not degraded by the high pH of the stomach; sustained-and controlled-release formulations to reach and maintain safe but effective blood levels; and rapid-dissolve tablets that dissolve in the mouth thereby making them easier to swallow without the need for water.

New injection technologies include sustained release of drugs that are transported in biodegradable polymers (microspheres and hydrogels) that can be less painfully injected. Several companies are also working on needle-free injection technologies that include dry powder injection, which uses pressurized helium to mechanically and painlessly deliver tiny particles of drugs though the skin. Yet another method under development involves the use of arrays of tiny blades or microneedles to pierce only the nerve-free surface layer of the skin.

The current size of the injectable drug delivery technology market is roughly $1.8 billion, and it is projected to grow to roughly $6.3 billion by 2007, according to Frost & Sullivan estimates. It is anticipated that needle-less drag injectors will capture a significant share of the market from hypodermic needles. The needleless injection devices market is expected to reach more than $500 million in the next few years, and will command 70 percent of the worldwide disposable drug injection market by 2010, according to Technical Insights.

Transdermal drug delivery can be customized to deliver from one to seven days of medication through a single patch placed on the skin, according to Technical Insights. "This noninvasive approach provides a sustained release of medication that not only frees patients from needles or difficult-to-swallow pills, but can also reduce the risk of side effects."

Passive transdermal delivery systems are in development by several companies for pain management, contraception, cardiovascular treatment and several other indications. Active transdermal technologies such as sonophoresis, thermal activation, phonophoresis, microneedles, iontophoresis, electroporation and dry-powder injection are being developed for delivery of larger biomolecules such as peptides and proteins.

Industry experts put the current worldwide transdermal market at less than 10 percent of the overall drug delivery market, according to Technical Insights. This segment, though, has recently experienced a healthy

annual growth rate of 25 percent, a rate that outpaces oral drug delivery (2 percent) and the inhalation market (20 percent).

Inhalation delivery systems are receiving a lot of attention because the surface area of the lungs is very large and the tissue lining of this organ is much easier to penetrate than the skin. Limited success was achieved with past drug delivery systems, though, because cilia in the lung collect larger particles, and smaller molecules typically cannot penetrate deeply enough into the lungs.

New systems under development are overcoming these barriers, according to Technical Insights. Handheld electronic inhalers that target the bloodstream through the small airways and alveoli (air sacs) of the lungs allow precise doses of tiny liquid particles to be inhaled through the mouth. Technologies being investigated include electrohydrodynamic devices for pulsatile pulmonary delivery; pocket-sized, breath-actuated and motorized dry-powder inhalers (DPI); and adaptive liquid (aqueous mist) aerosol delivery that adjusts drug dosing to the patients' breathing patterns during delivery.

The pulmonary drug delivery market was estimated at $9 billion in 2000, and may exceed S36 billion in sales by 2005, according to SRI Consulting, a Menlo Park, Calif.-based consultancy. The potential of this market is high because it has the possibility of including one of every five US consumers in terms of drug delivery use. Intranasal delivery products command roughly $2 billion of the US pharmaceuticals market, according to some industry estimates.

Areas of the body that may be treated with targeted drug delivery systems include the peritoneal cavity, brain tissue, the eyes, the heart, liver and other organs, and solid tumors among others. Use of targeted drug delivery for cancer treatment is of great interest because cancer drugs are often highly toxic to healthy cells as well as to the undesirable cancer cells. Active targeting relies on the use of tumor-specific molecules such as monoclonal antibodies or ligands for tumor-related receptors.

Passive targeting is based on the enhanced permeability and retention (EPR) effect, where rumor blood vessels have different properties than those of normal tissue. Macromolecular anti-cancer agents such as liposomal or micellar drugs can more easily diffuse out of tumor blood vessels, reach the solid tumor tissue effectively and be retained for a longer period of time. Industry experts project sales of site-specific delivery systems to grow at an average annual growth rate of 26.5 percent, according to Technical Insights.

Liposomes have potential for delivering vaccines and gene-therapy molecules and have successfully been used for anti-tumor agents, anti-virals, anti-fungals, anti-microbials, vaccines and gene therapeutics. Micro-encapsulation techniques provide increased stabilization and controlled release of drags and can be administered orally, injected or inhaled, Use of polymer matrices to increase the water-solubility of drugs has also enabled transport of low water-soluble drugs into body tissues.

Nanotechnology allows for targeted delivery of drugs and vaccines to specific cells and tissues and enables and enhances the ability to deliver poorly-water soluble compounds. Use of nanotechnology also provides the ability to achieve longer-sustained and controlled-release profiles and can increase the effectiveness of alternative routes of delivery such as inhalation and needle-free injection devices.

All of these technologies offer significant promise for the pharmaceutical industry. However, several challenges must be overcome, according to Technical Insights. The safety of these new drug delivery systems must be proven. Attractiveness to patience must also be achieved, The technologies must improve solubility and bioavailability of difficult drugs and demonstrate actual control of delivery including control of timing, quantity, duration and location of release. For those systems that sequester a drug, the technology must allow for appropriate release of the drug as well.

In addition, the market may not be ready for several of these technologies yet. Successful drag delivery systems to date have been based on simple concepts. "Both the pharmaceutical industry and the public need to be made more aware of the advantages of improved delivery systems, and selling new technology to 'big pharma' is not an easy task for a small company," says Technical Insight's Dr. Austin.

Many of the smaller drug delivery firms are also having difficulty raising funding. The costs of research and development and the necessary testing through clinical trails can be prohibitive. "While many novel delivery systems may offer enhanced functionality, they may also be extremely expensive to produce," notes Dr. Austin. "Initial outlays may be less important if the profit potential is huge. However, commercially successful drug-delivery products are often those that have made incremental improvements to functionality at modest cost."

Many drug delivery companies are emphasizing a solutions approach to their technologies, an integrated approach that not only involves partnering in the early stage of pharmaceutical development, but also involves the development of proprietary pharmaceuticals.

Top Players Position With Combinations Of New and Emerging Technology

In keeping with a diversified approach to drug delivery technology, Skyepharma, one of the leading drug delivery companies, has five major platform technologies: oral, inhalation, injectable, topical and enhanced solubility, according to Michael Ashton, CEO of SkyePharma. Each of these technologies comprises a range of drug delivery options.

Skyepharma's key oral drug delivery technology is Geomatrix, for which it has several drugs on the market. This includes Paxil CR, a controlled-release version of GlaxoSmithKline's Paxil (paroxetine), a leading selective serotonin reuptake inhibitors (SSRI) antidepressant. The Geomatrix formulation was designed to bypass normal gastric absorption of paroxetine, which in Paxil CR is taken up in the lower intestine. This reduces gastric side effects and significantly improves tolerability, an issue with all SSRI antidepressants and a major reason behind the problem of poor patient compliance. Paxil CR was launched in the US in April 2002 and already accounts for nearly one-third of all Paxil prescriptions.

Similar to Paxil CR, Skeypharma is also using its oral controlled-release technology to capture share from other marketed drugs. Another example is a once-daily version of Sanofi-Synthelabo's Xatral (alfuzosin), a selective alpha blocker for benign prostatic hypertrophy. This is on the market in Europe, where it has largely replaced the previous three-times-per-day version, and should reach the US market in the middle of this year.

The oral controlled-release delivery system can also be an important part of achieving the desired efficacy of active pharmaceutical ingredients, particularly when used in combination. An example is Roche's Parkinson drug Madopar, which incorporates in a single Geomatrix tablet two separate ingredients with different release profiles. L-Dopa is released gradually after an initial burst of the enzyme inhibitor benserazide, which helps to maintain a constant blood level of L-Dopa.

In the area of pulmonary drug delivery, SkyePharma's partner Novartis filed in December 2002, in the US and Europe, for the approval of a new version of formoterol, a fast-onset and long-acting bronchodilator for asthma. Novartis has recently appointed Schering-Plough to market this product in the US. This uses SkyePharma's proprietary multidose breath-activated dry powder inhaler device, together with a formulation that protects this labile drug substance and ensures repeatable dosing. The company expects to see the system on the market in 2004.

SkyePharma has two different sustained-release injectable technologies. DepoFoam is comprised of tiny particles of a lipid matrix that slowly erodes, releasing the drug active contained in water-filled internal compartments. In biospheres, the drug is suspended in starch microspheres coated with a lactic glycolic acid co-polymer. This is designed to carry large molecules and is offered as a powder that is administered after mixing with water.

An example of DepoFoam technology is DepoCyt, a sustained-release injectable version of cytarabine. DepoCyt is on the market in the US and Canada and has received approval in Europe and is used to treat neoplastic meningitis, a late-stage complication of many forms of cancer. With this new delivery system, patients only require an injection once every two weeks instead of four to five times per week.

SkyePharma's topical delivery technologies include the use of hyaluronic acid (HA), a long-chained polysaccharide that is attracted to and adheres to specific receptors on cell membranes which can be found in increased numbers at sites of damage and disease in the body, particularly on the skin. Drugs can potentially be targeted to and held at the site where the drug is needed.

One example is Solaraze, which is on the market in the US and Europe for the treatment of actinic keratosis (AK), a form of skin cancer developed from overexposure to the sun. Conventionally the affected area is either removed surgically or with liquid nitrogen or treated with 5-fluorouracil, which is painful and causes unsightly blistering. Solaraze is a topical gel that uses SkyePharma's HA technology to deliver diclofenac, the active drug, to the epidermal area and hold it there for an extended period of time. The treatment is not only effective but also painless and invisible.

Another technology focus of SkyePharma is in the solubilization of highly insoluble drugs, an increasing problem for the pharmaceutical industry. Enhanced solubility is an enabling technology that can be used alone or to complement one or more of the other delivery options, notes Skyepharma's Mr. Ashton. The company is working both internally and with external partners to develop drug delivery systems that use nanoparticles.

SkyePharma has developed several products that will be reaching the market in the next couple of years. Mr. Ashton believes that the most important of these is DepoMorphine for the treatment of moderate to severe postoperative pain in procedures such as hip and knee arthroplasty, Caesarian section and abdominal surgery. This uses DepoFoam technology to maintain therapeutically effective levels of morphine for 48 hours after a single pre-operative epidural injection. This not only achieves superior pain relief but also avoids the need for the patient to have an indwelling spinal catheter for continuous infusion. SkyePharma will be filing in the US around the middle of 2003 and expects to have the product on the market in mid-2004.

Endo Pharmaceuticals recently agreed to pay $25 million (with up to $120 million in total on achievement of milestones) for North American rights to DepoMorphine and a second product. This is a new formulation of the injectable anaesthetic and sedative propofol, used to calm down post-operative patients in intensive care units. Compared to current versions of propofol, the SkyePharma version will be much easier to administer and will reduce the likelihood of contamination. SkyePharma expects the product to be on the market in 2005-2006.

In addition, SkyePharma has considerable expertise in metered-dose aerosol inhalers that use hydrofluoroalkanes (HFAs) as a propellant in place of environmentally unacceptable chlorofluorocarbons. SkyePharma is developing for AstraZeneca an HFA aerosol of Pulmicort, an inhaled steroid for the treatment of asthma, and expects to file in 2004 for this product. SkyePharma has also developed its own HFA aerosol version of formoterol.

SkyePharma has a very healthy pipeline with three drugs in Phase III trials and four in Phase II studies. "Our strategy for success has changed over the last few years," says Mr. Ashton. "In the future we will be using drug delivery technologies to develop new drugs in areas where there are unmet medical needs or where current systems are poor performers. In some cases we will bring these products to the market ourselves, and where appropriate we will form strategic partnerships."

Over the last five years SkyePharma has broadened its technology base through the acquisition of smaller drug delivery companies with unique technology capabilities and near-term product opportunities, including Depo-Tech, Hyal and RTP. Currently the company is not looking to make any further acquisitions, but rather to use the royalties flowing from products on the market to fund internal research and development efforts, according to Mr. Ashton.

Mr. Ashton adds that SkyePharma has been very successful because it not only has capabilities in multiple technology areas, but also the company has expanded its offerings beyond drug delivery itself. "We have groups involved in clinical studies and regulatory issues in order to get our drug candidates to market as quickly as possible," he explains. "Companies need to be creative to succeed today. They need to look for opportunities where new drug delivery technologies can improve existing drugs, and then bring these new products to market efficiently and effectively."

PEGylation is Key for Nektar Therapeutics

PEGgylation technology is the key capability for Nektar Therapeutics, which changed its name from Inhale Therapeutic Systems in January 2003 to reflect its broadened drug delivery capabilities. Nektar gained advanced PEGylation and supercritical fluid technology in 2001 as part of its acquisitions of Shearwarer Corp. and Bradford Particle Design, respectively.

In early 2002 the company announced a broad strategic alliance with Enzon Corp, which included development and licensing agreements. "This alliance significantly expanded Nektar's ability to offer a wider range of PEGylation technology--a technology that we believe can benefit almost every protein, peptide, and antibody fragment and many small molecules," says Christopher Searcy, vice president of corporate development with Nektar Therapeutics. "In addition, it strengthened our pipeline significantly with several new product collaborations." Last month Enzon and NSP Pharmaceuticals agreed to merge in a $1.6 billion deal. Enzon brings it PEGylation royalty stream from Schering-Plough, and NPS has several drugs in late-stage development.

Currently there are four products on the market in the US that use Nektar's technologies, including Roche's Pegasys (peginterferon alfa-2a) for hepatitis C, Amgen's Neulasta (pegfilgrastim) for neutropenia, and ScheringPlough's PEG-Intron (peginterferon) for hepatitis C. Pharmacia's Somavert (pegvisomant) is filed for approval in the US and approved in Europe. The company's partners have an additional four products in late-stage clinical development including inhaled insulin with Pfizer; Macugen for macularde-generation with Eyetech; CDP 870 with Pharmacia for rheumatoid arthirits; and SprayGel with Confluent Surgicals for the prevention of surgical adhesions.

Last year, Nektar signed additional agreements in 2002 with ten new collaborative partners for development of 12 compounds for the treatment of chronic hepatitis C, cancer, rheumatoid arthritis, endometriosis, lung infections and others. Some of these drugs are already in phase II or III clinical trials. The company has also announced in 2003 collaboration with The Straumann Group to develop dental regeneration (both bone and tissue) products for dental implants.

Nektar says it is taking a solutions approach by offering development, formulation and manufacturing capabilities. Its Nektar Molecule Engineering capabilities are based on Advanced PEGylation technology that improves the performance of both macromolecular and small molecule injectable drugs. Nektar Particle Engineering methods use proprietary technology that improves drug absorption, solubility, formulation, and taste-masking as well as the delivery of powders to the deep lung for inhalation. NektarDelivery Solutions are for pulmonary, injectable and oral modes of administration and enable drug administration routes to be specifically tailored for particular treatment needs and patient benefits.

The company emphasizes that solutions approach is important as the nature of the drug delivery market evolves. Historically, drug delivery was focused on life cycle management of older products facing patent expiration or seeking product line extensions, according to Nektar's Mr. Searcy. "Today the concept of drug delivery is evolving to go far beyond its original focus on finding alternative modes of administration in order to reduce drug side effects and prolong drug action over time," he says. "Applications of drug delivery technology are increasingly considered an integral part of the development process--one that can often enable superior and in some cases breakthrough therapies." He adds that it is now recognized that drug delivery spans the entire development process, with an earlier need to rescue or optimize drug candidates, and a premium on faster and more efficient drug development.

Newcomers Enter The Drug Delivery Fray

A relative newcomer to the drug delivery market (founded in 1997) is Vectura, a venture capital funded speciality pharmaceutical and drug delivery company, spun out from the University of Bath. The company acquired its Aspirair inhaler technology and device development team from Cambridge Consultants in February 2002. It also moved into a new cGMP facility in December of 2002. Vectura signed option and licensing agreements with GlaxoSmithKline and Zambon, and co-development agreements with Arakis and Ranbaxy. The company also has underway feasibility studies with several top pharmaceutical firms.

Vectra's products include an active dry powder inhaler device (Aspirair), a formulation system to maximize the efficiency of dry powder inhalers (PowderHale), an easy-to-use without water system for the direct dosing of powders to patients (Accustar), unit dose systems for controlled topical drug delivery (Pandermal), systems to improve the bioavailability of poorly soluble drugs (Maxsol), and a cost-effective oral controlled-release system with extended patent life (Gencontab).

Vectura is also emphasizing the companies' solutions approach to drug delivery. The company offers technologies that fit its clients' current processing equipment capabilities, according to director of business development Doug H.R. Smalley. "We also work with client companies on their new drug programs to optimize product performance from the onset, and ensure that our technology is correctly evaluated during the initial phases of any project," he notes. Mr. Smalley also adds that today many drug delivery companies are adding value to their technologies through clinical exemplification and funding of their own product pipelines.

"Our drug delivery technologies and expertise are being employed in our own product development programs, providing IP protection and enabling existing compounds to be rapidly developed for new therapeutic applications with enhanced performance and patient benefit," says Mr. Smalley. The company intends to license out these products at Phase IIb to major pharmaceutical companies.

Watson Still On the Acquisition Path

Watson Pharmaceuticals says it will continue to use acquisitions as a means to fuel growth as it prepares for a launch of a new product. Watson has historically made acquisitions, mergers, alliances, and this type of

activity will continue to be part of its growth strategy, says Chuck Ebert, senior vice president of research and development with Watson Pharmaceuticals. Recent deals includes the acquisition of TheraTech and Zetachron for drug delivery technologies and Circa for gum technologies.

The main drug delivery products of Watson Pharmaceuticals include various transdermal patches such as Androderm, Alora, and Oxytrol (currently under review with the Food and Drug Administration (FDA)). Other transdermal products include Emsam, a transdermal selegiline patch for the treatment of depression, under development with Somerset Pharmaceuticals (a joint venture between Watson and Mylan) and pending resubmission to the FDA this summer.

Non-transdermal products include nicotine gum and the recently launched nicotine lozenge by GlaxoSmithKline (a product licensed to GSK from TheraTech, which was recently acquired by Watson) and other oral drug delivery products in development.

Watson's transdermal and topical drug delivery technology focuses on patch design technologies and permeation enhancement technologies. The company offers oral transmucosal (delivery of the drug into the oral cavity) technologies, including gum technologies (Watson is one of the largest manufacturers of pharmaceutical gums), non-sugar based lozenge technologies, and self-adherent mucosal tablet technologies for oral transmucosal delivery. In addition, the company has oral drug delivery technologies based upon swellable/erodible tablet matrix technologies, hydrophobic drug solublization technologies, and filmcoating technologies.

"With the recent successful launch of Evra, a transdermal contraceptive patch by J&J, as well as the pending launch of our Oxytrol product (once FDA approval has been received), the market for transdermal products is expected to grow in the near future," notes Dr. Ebert

Watson is preparing for the launch of Oxytrol, pending final FDA approval. This transdermal patch has been developed for the treatment of overactive bladder (OAB), which includes symptoms of urgency, urge incontinence and frequency. Oxytrol delivers the drug oxybutynin (recognized as the gold standard for the treatment of OAB) through the skin, avoiding the pre-systemic metabolism of oxybutynin that occurs with oral administration.

"Our clinical research has demonstrated that Oxytrol can effectively treat the symptoms of OAB but has reduced dry mouth, constipation and sleepiness, relative to existing oral products for OAB," says Dr. Ebert.

Watson also hopes to see some uptick in demand for transdermal technology as result of the recent Women's Health Initiative (WHI) actions involving oral hormone replacement therapies that have led many medical experts to recommend transdermal estrogens over oral estrogens, although the long-term safety of these products must still be evaluated. "As a leader in transdermal drug delivery technologies we will leverage our capabilities to maximize the opportunities afforded by this growing market," adds Dr. Ebert.

In addition to the Emsam patch, Watson is also completing Phase III clinical trials in 2003 on an innovative topical product for the treatment of onychomycosis, or fungal infections of the toe and finger nails. If these trials are successful, Watson will submit a new drug application for the product in the first half of 2004.