INTRANASAL DELIVERY

Sniffing Out New Sources For Growth

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INTRODUCTION

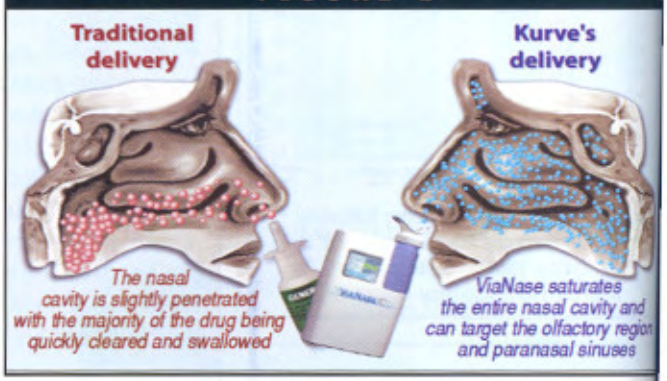
The pharmaceutical industry is constantly looking to improve its products, and at the same time, find new avenues for revenue generation. This is done through a multitude of drug development scenarios, including reworking an existing product and investigating new ways of dosing and delivery. Research and clinical development is ever ongoing in terms of improvements of human in vivo performance. Often, when drug products are discussed, the focus revolves entirely around oral and injectable methods of delivery. That type of myopic discussion misses the fact that there are other areas, such as intranasal delivery, which have the potential to perform as well, or often give superior treatment results. In addition to being a delivery path for new products, intranasal delivery can also serve as a way to transform and innovate products already in the market. The intranasal drug delivery market in the United States was estimated at $2.4 billion in 2005. Future growth and expansion of the intranasal sector is expected to continue, especially as companies continue to move focus from converting existing products to novel drugs that are designed as an intranasal product from the ground up.

WHY THE NOSE?

For most people, the nose is perceived as merely the portal for the sense of smell, and it serves in that capacity in terms of enabling people to sense things around them, malodorous and not. The nose, however, has other important tasks to perform that benefit the body. In addition to sensory applications, it plays a vital role as a particle filter and also warms and humidifies the air that passes through it. The nose therefore keeps the lungs protected and enables any undesirable matter to be disposed of.

The nose is also an ideal portal for drug delivery and presents a number of key selling points to the market. First, there is the aspect of needle elimination for products currently delivered through injection. Patient self-administration of an injectable product is often a burden, not only in terms of preparation and disposal, but in terms of added stress and discomfort due to the fact that it utilizes a physically invasive delivery mechanism. For those injection products for which a patient needs to return to a clinical setting in order to be dosed, an additional hurdle is created and adds to the difficult stack of potential reasons why a patient may have problems adhering to treatment. Intranasal delivery presents the potential opportunity for patients to take their medication in the comfort of their own home, office, or wherever they may be during the day, and at the same time can place the product in a much more attractive light and allow for increased probability of adherence to prescribed therapy. Nasal dosing also offers patients with the potential for the fastest method for drug delivery. This is really a prime area of differentiation, especially in the pain sector, as quick onset of action is a key point that can differentiate products in the market. Quick onset of pain relief has a number of potential uses, especially in cases of trauma, military field applications, the emergency room, and during cancer treatment. An additional aspect of nasal delivery that can be exploited for the purpose of product innovation is the direct route to the brain, bypassing the hurdle of getting a drug to cross the blood-brain barrier. This is especially important for products with CNS applications. There are also a variety of products currently in the market, both OTC and prescription based, that are slotted for localized disease treatment in the nose. This, however, is not the endpoint for what can be achieved from a nasal approach to drug delivery. Systemic product delivery via the nasal passage is really the bigger picture and provides a variety of potential advantages and positive points of approach that benefit both patients as well as the companies involved. Intranasal vaccination also has the potential to perform well due to the combination of local and systemic exposure to the vaccine, creating a larger shield for the patient.

FIGURE 1



INTRANASAL DELIVERY

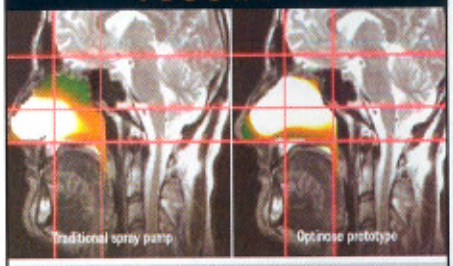
CURRENT TECHNOLOGY

There are a number of devices that can be used for intranasal delivery. The most common way that drugs are delivered via the nasal passage is through mechanical metered dose spray pumps. This technology is typically used for products to treat diseases, such as osteoporosis, migraine, and allergy products. Mechanical metered dose spray pumps are able to serve the purpose for many products, but the technology is not without numerous faults, which is why there are companies working on improved devices for intranasal delivery applications. Mechanical metered dose spray pumps currently have the greatest reproducibility success in terms of dosing. The pumps are modified by the respective product manufacturers to release a precise amount of liquid drug in a plume shape that expands out from the exit point on the device. The particle size for these products delivered in this manner is very important and is kept on the larger side (45 to 65 micrometers) in order to keep the amount deposited in the lungs to a minimum. Currently, the Food and Drug Administration has a limit that only 5% of the per dose dispersion is allowed to hit the lungs.

DEVICE IMPROVEMENTS

Technology improvements are being sought on the device side in order to create more effective methods to physically deliver an intranasal drug product. Current delivery methods, such as nasal spray bottles and metered dose inhalers, are constrained in their effectiveness by factors, such as suboptimal nasal cavity product penetration, as well as effectively balancing particle size with maintaining low levels of lung inhalation. This is not a trivial issue as many products only hit the anterior region, thereby missing the mark from where the technology should be to garner the best therapeutic result. Other aspects of current intranasal delivery devices that leave something to be desired include characteristics, such as post-dosing aftertaste, headache, and nasal irritation. Advancement in device technology is one area that is capable of making real headway in improving interest in this sector of the pharmaceutical market.

FIGURE 2



White areas in the nose: 20-100% of maximum intensity
Orange areas in the nose: 0-20% of maximum intensity
Green areas in the nose: no deposition
Gridlines are used to calculate regional distribution; Gamma-scintigraphy images from the same subject; Cumulative distribution during 32 minutes
Source: OnDrug Delivery 3rd issue August 2005. www.ondrugdelivery.com

Kurve Technology

Kurve Technology, Inc., with its Controlled Particle Dispersion (CPD) technology (Figure 1) has developed a delivery product that is able to saturate the entire nasal cavity, including the paranasal sinuses. Kurve's delivery product, Vianase can be utilized for both topical and systemic products to yield superior results over what is achievable with currently marketed nasal spray pumps. Vianase also has the potential to deliver products directly to the brain. This product uses "vortical flow" to achieve it's multiple advantage points over traditional technology. Kurve has also incorporated anticounterfitting and antitampering technology into its Vianase ID version in order to prevent potential unintended usage. This intelligent delivery system provides an important asset especially from the aspect of dose control, which is very important in application areas, such as pain management.

OptiNose

OptiNose AS, has approached delivery innovation from the concept of bi-directional delivery. This strategy looks at delivering both powder and liquid products while the patient is exhaling, thereby circumventing the issue of lung inhalation. Eliminating lung exposure during dosing with this device enables a smaller particle size to be used in the drug formulation. Exhalation into the device automatically triggers particle release at a moment where the positive dynamic pressure expands the narrow nasal passages, which in turn is able to aid the drug in achieving greater deli ery penetration. Through this delivery techno ogy, the airflow carrying drug particles to the target sites enters the nose through a sealing nose piece inserted in one nostril and exits through the other, allowing for both systemic and local topical delivery to the total nasal region, while significantly improving deliver to specific areas such as the olfactory region. Greater olfactory region exposure is important, as that is a point of direct access to the brain. The two-point fixation of the device enhances device stability and comfort during actuation.

WHAT'S IN THE PIPELINE?

Many companies are working on pipelin compounds that approach improving intranasal drug delivery by focusing on formulation technologies. For localized topical products, a minimal modification of formula tion is required to create an intranasal produc and this typically focuses on particle size in order to try to prevent the product from comi ing back out of the nose or moving easily int the throat or the lungs. Systemic products require more of a specific fine-tuning of the formulation's particle size. This is to both pre vent the same general issues that exist for a localized product, and at the same time, enable the proper dosing control that would b required to maintain safe and accurate deliv ery of the drug.

Nastech

Nastech Pharmaceuticals has approache intranasal applications through its focus on tight junction biology. Tight junctions exist throughout the body, and Nastech is looking to take advantage of that in several areas, on being nasal tissue. The company is looking fo compounds that increase permeability of the tight junction, without harming junction cell or altering the structure of the molecule bein delivered. In finding compounds that can open the barrier and allow for drugs to be passed through, the company is focusing on issues, such as how to deliver larger molecules, providing access of compounds to the

CNS directly, and improving the amount of a drug in the blood. Nastech currently has an obesity product, PYY3-36, in Phase II clinical trials. This peptide compound is an anti-obesity product focusing on appetite reduction. As the prevalence of obesity is an ever-growing problem, it requires a multifaceted approach to control and treatment. New ways to slot products into a patient's therapeutic regimen, especially those that are convenient to use and will therefore promote adherence to therapy, are very important to that type of chronic disease treatment. Nastech also has partnered with Proctor & Gamble for PTH1-34, which is a nasal version of Eli Lilly's Forteo (teriparatide) for osteoporosis. Forteo is currently delivered by subcutaneous injection. PTH1-34 is currently in Phase I clinical trials. This product is a good example of a drug that is not for a small niche area or presently generic being reformulated for intranasal delivery; it is that type of product that has the potential to contribute on the larger side to market revenues and at the same time provide an improved product to patients.

Javelin

Javelin Pharmaceuticals, through the utilization of its ChiSys carbohydrate polymer, has developed a way to achieve predictable blood levels of morphine via nasal delivery. Javelin's ChiSys technology is able to provide enhanced mucosal drug absorption and is able to prevent the drug from quickly leaving the sinus cavity through promoting high levels of drug adhesion to the mucosal layer. The company's Rylomine (intranasal morphine) product is currently in Phase II clinical trials and is a novel formulation of morphine with Javelin's ChiSys polymer. This product could provide an important new option for morphine use, as it would combine the fast onset of action inherent of injectable morphine with the ease of patient self-dosing currently seen with oral morphine. Javelin's intranasal morphine would have both of those important characteristics, thereby providing it with a potential competitive advantage.

THE FUTURE

Intranasal delivery is an area of the pharmaceutical market that has a very large amount of untapped potential. As companies look to the future and are forced to rethink more classical blockbuster product models in order to continue to create new sources of product revenues, concepts, such as technology transfer and extension strategies for life cycle management, are expected to come more to the forefront of the collective industry brain. The advantages and upside that intranasal products and the associated delivery technologies can provide to the industry across the board is a source-point of billions of dollars that is there for the taking.

How fast that growth occurs and the total peak of the associated revenues is governed by several factors. The combination of technology improvements from both the formulation side and the device side are expected to allow for continued overall interest and growth for the intranasal delivery sector. The products that provide new realms of growth for the market can come from either reformulation of existing products, or by designing new products specifically for intranasal use. In order for the market to really come into its own, industry focus will have to be more on products for diseases with larger patient populations as well as the development of novel products that are able to exploit the benefits of a properly delivered intranasal product. The real test of the future potential of intranasal drug delivery will be in a novel product designed for intranasal delivery from the outset for a widely prevalent disease incorporating one of the more effective device technologies currently in the works. Once a product like that hits the street, the industry could really see the larger potential of an intranasal drug delivery product's true capabilities.

BIOGRAPHY

Mr. Daniel Ruppar is a Research Analyst in the Pharmaceuticals & Biotechnology group of Frost & Sullivan. His primary coverage focus is in the area of cardiovascular diseases, with recent work focusing on the Cholesterol Market as well as the Anticoagulant and Antiplatelet Drug Markets in the United States. In that, he provides insight into individual drug forecasts, analysis of development pipelines, as well as evaluating treatment trends and clinical trial results. Prior to joining Frost & Sullivan, Mr. Ruppar spent 9 years in research and development in the pharmaceutical industry as a medicinal chemist. He has co-authored four journal publications for his work in chemistry in various peer-reviewed scientific journals, such as the Journal of the American Chemical Society, Tetrahedron Letters, and Bioorganic and Medicinal Chemistry Letters. He is also a co-inventor on four patents for his work in drug discovery. Mr. Ruppar was a long-standing member of the American Chemical Society, Organic Division. He earned his BS in Biochemistry with a minor in Economics from Trinity University and performed his research training in chemistry in the laboratory of Dr. Michael P. Doyle.