

### Bi-directional Nasal Device Delivers Drug on Exhalation

**T**raditional nasal spray pumps face a common challenge: they cannot efficiently deliver drug to the regions of the nasal passages where diseases originate. To address this problem, OptiNose AS (Oslo, Norway, [www.optinose.no](http://www.optinose.no)) has developed a patented bi-directional delivery system that can target the olfactory region. The "OptiMist," a single-dose device designed by Team Consulting (UK), is currently in pilot-scale production by spray pump manufacturer Pfeiffer GmbH (Figure 1). Pfeiffer is providing the internal spray system.

According to Per G. Djupesland, MD, PhD, chief scientific officer of OptiNose, the bi-directional breath-actuated delivery technology exploits a natural reflex that isolates the nasal passages from the lungs during drug delivery. "By combining particular anatomical and aerodynamic features of the nose, I discovered a unique opportunity to improve nasal drug and vaccine delivery," says Djupesland.

The patient inserts a tight-fitting nozzle into one nostril and places the device's mouthpiece into the mouth. When the patient blows into the device, drug particles are released and are carried with the airflow into the narrow passages of the nasal cavities. The airflow turns 180 degrees through an opening behind the septum and exits through the other nostril. The positive



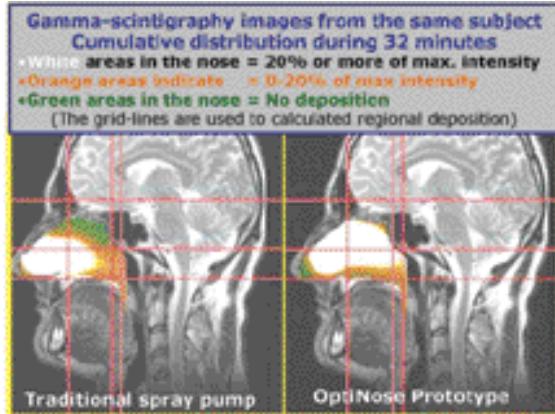
**Figure 1:** The "OptiMist" breath-actuated, single-dose nasal drug delivery device.

driving pressure opens the nasal passages to the drug particles (see figure 2). Studies with radio-labeled particles have shown significantly improved deposition patterns with a bi-directional device, according to OptiNose (see figure 3).

When the patient blows into the device, the positive pressure closes off the soft palate in the back of the mouth. Separation of the mouth and nose prevents the inhalation of small drug particles into the lungs. "You can use smaller particles to reach more difficult areas like the sinuses without them being inhaled," Djupesland explains. By selectively modifying the nozzle design, flow rate, and particle size, the device can target specific areas in the nasal cavity with either liquid or dry-powder formulations. According to OptiNose, two clinical studies with vaccines have shown several-fold increases in the immune responses.

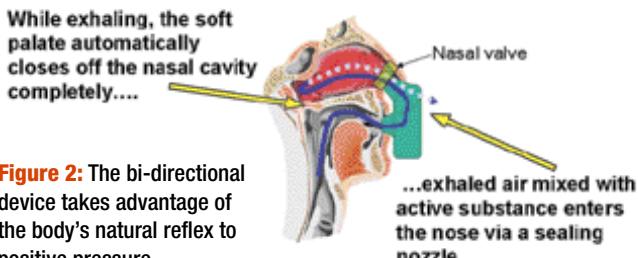
The OptiMist's design also lessens the possibility of user failure. Local irritation and dosing variability are frequent problems with traditional spray pumps. "We believe patient compliance and comfort will be much higher with the OptiMist because patients simply exhale to receive the dosage." To measure patient response to the device, OptiNose has conducted two user trials. Study participants found the OptiMist intuitive and easy to use.

OptiNose, which recently established



**Figure 3:** The OptiNose prototype can target the upper regions of the nose.

a subsidiary in the UK, is currently developing and combining its technology with selected off-patent drug substances in-house and is seeking to partner with pharmaceutical companies that have relevant drugs and vaccines in their portfolios and pipelines. The company believes its technology could provide an excellent delivery method for



**Figure 2:** The bi-directional device takes advantage of the body's natural reflex to positive pressure.

treating allergic rhinitis and sinusitis, as well as migraine and neurological diseases such as Parkinson's and Alzheimer's diseases. According to Djupesland, "The olfactory region is the only place in the body that does not have an intact blood-brain barrier. Because OptiMist allows us to target this region, we believe we can deliver drugs from the nose into the brain."

-Kaylynn Chiarello

## Directed Evolution Speeds Small-Molecule Manufacturing

Codexis, Inc. (Redwood City, CA, a subsidiary of Maxygen, Inc., [www.codexis.com](http://www.codexis.com)) has entered into a multiyear collaboration with Pfizer (New York, NY, [www.pfizer.com](http://www.pfizer.com)) to develop biocatalysts to improve manufacturing efficiencies for several small-molecule drugs.

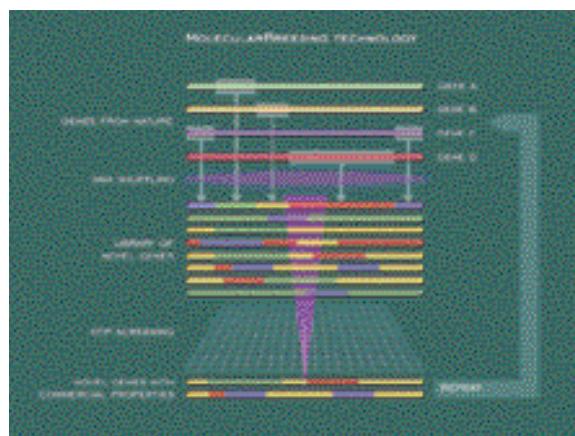
Codexis carries out genetic engineering to create new enzymes (biocatalysts) that can be used in fermentation processes to synthesize small-molecule drugs with fewer process steps and less waste than in fermentation using wild-type enzymes or in conventional chemical synthesis.

Under the new agreement, Pfizer has the option to license Codexis's technology for application to several drugs in Phase I and Phase II development. Previously however, Codexis helped Pfizer

increase the manufacturing efficiency of a product already on the market—doramectin, a veterinary antiparasitic drug. Before working with Codexis, Pfizer manufactured the active pharmaceutical ingredient (API) using a wild-type biocatalyst in a fermentation process with *Streptomyces avermitilis*. The original process, however, generated lower quantities of the desired molecule (B1) than of a byproduct (B2), in a ratio of 0.6 to 1. A year later, Codexis produced a genetically engineered biocatalyst that reversed that proportion, producing the API and by-product in a ratio of 2.5 to 1. Another six months of work increased the production ratio to 15 to 1. According to Tassos Gianakakos, vice-president of corporate development at Codexis, the increased efficiency allowed Pfizer to reduce the cost of goods by more than 10%, and free up several months' worth of plant capacity per year to manufacture other products.

Creating new biocatalysts is an iterative genetic engineering process (see

Figure 1). When presented with a new molecule to be produced through biocatalysis, Codexis' teams of chemical process development and molecular biology specialists first look for a suitable enzyme in the company's library. If none is available, the team selects organisms (usually genetically engineered *Escherichia coli*, yeast, or fungus) that



**Figure 1:** Codexis's "Molecular Breeding" technology involves multiple rounds of DNA recombination and screening.

possess genes they think will be good "parent genes." Those sets of genes, and sometimes whole genomes, are then recombined through sexual reproduction of the microorganisms in proprietary processes the company calls "Molecular Breeding" and "DNA Shuffling." The resulting library of gene variations is then put into an expression system and screened for the desired enzymatic expression. The best sets are chosen as parent genes for the next round of crossing and the results of that round are then screened again. The process is repeated until a suitable enzyme is produced.

"The main difference between the way Codexis carries out its directed evolution processes and what other companies do," says Gianakakos, "is that Codexis has harnessed sexual reproduction *and* mitosis. This makes our processes more efficient." Codexis researchers also use bioinformatics tools that increase evolutionary speed by predicting points where beneficial crossover recombination is likely to

occur. "Our processes produce highly active, intact proteins," Gianakakos says. "The viability rate is high." Once Codexis identifies the desired genetic sequence, the company usually outsources the DNA production, because it has outstripped internal capacity.

The process also received an internal corporate award at Pfizer for green manufacturing processes, Gianakakos says. "By reducing by-products and the use of harsh chemical reagents, the application of our technology generally results in environmentally friendly manufacturing," he explains, adding that increased manufacturing efficiency can also reduce capital expenses such as heating and cooling.

In addition to Pfizer, Codexis has partnerships with various other pharmaceutical manufacturers to use DNA Shuffling and Molecular Breeding to produce small-molecule intermediates and APIs. Partners include Eli Lilly, Novozymes, Sandoz, and Gist-brocades NV, a subsidiary of DSM. Another DSM subsidiary, DSM Pharma Chemicals, does similar development work with biocatalysts (see *Pharmaceutical Technology*, March 2004, p. 17). Codexis's technology is currently used in five commercialized processes.

-Laura Bush

## Strategic Alliance for Prion Adsorbents

To market and further develop products that selectively adsorb pathogens (prions and viruses) from blood and blood-derived products, Prometic Life Sciences (Montreal, Canada), the American National Red Cross (Washington, DC), and Pathogen Removal and Diagnostic Technologies (PRDT, a joint venture of Prometic and the Red Cross), have formed a strategic alliance with MacoPharma (Lille, France).

The parties' commercial strategy, which will be implemented during the next few months, is to provide the first commercially available prion filter for red blood cells. The companies plan to launch the industry's first prion-removal product in 2005 in Europe.

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## CGMP Notes Redux

The Office of Compliance (OC) of the US Food and Drug Administration's Center for Drug Evaluation and Research has resumed publication of short question-and-answer guidance on Current Good Manufacturing Practices.

In August, CDER posted its first "Questions and Answers on Current Good Manufacturing Practices (cGMP) for Drugs" on the center home page ([www.fda.gov/cder](http://www.fda.gov/cder)). This "Q&A on CGMP" grew out of FDA's two-year-old initiative to clarify CGMP policies, moving towards a more timely and flexible, science-based regulation, according to OC Director David J. Horowitz.

### Pop Quiz.....

The first edition of "Q&A on CGMP" answers the following questions (the short answers appear at the end of the story):

1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?
2. Is there a list of approved drug manufacturing equipment?
3. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness?
4. A firm has multiple media fill failures. They conducted their media fills using TSB (tryptic soy broth) prepared by filtration through 0.2- $\mu\text{m}$  sterilizing filter. Investigation did not show any obvious causes. What could be the source of contamination?
5. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?
6. Can containers, closures, and packaging materials be sampled for receipt examination in the warehouse?
7. Do the CGMPs require a firm to retain the equipment status identification

The online publication (co-sponsored by the Centers for Veterinary Medicine and for Biologics Evaluation and Research, along with the Office of Regulator Affairs) is a "Dear Abby" for process managers and designers. The August posting is a trial version. FDA will discuss plans for expanding the Q&A when it unveils its CGMP update in mid-September.

The debut Q&A includes about a dozen specific regulatory questions, cross-indexed by 21 CFR 211 subparts (e.g., organization and personnel, buildings and facilities, equipment, production and process controls, and packaging and labeling control). Following

each question are a direct answer (often "yes" or "no"); a brief, clear discussion; some regulatory references; and the name and e-mail address of an agency contact.

These guidance notes aren't intended to break new regulatory ground. They focus, rather, on specific, well-settled issues, Horowitz said.

"Q&A on CGMP" picks up where the popular *Human Drug CGMP Notes* left off. *Notes* began answering processing questions in 1993, but suspended public distribution in September 2000, due to what Horowitz calls "internal regulation and procedural issues." (*Notes* continued to appear as an internal FDA newsletter until 2003, when it then ceased altogether.)

-Douglas McCormick

### Prion filter continued from page 16

"This strategic alliance capitalizes on the strengths of the parties and will accelerate the development and commercialization of this urgently needed first product, to be followed by next-generation devices," said Pierre Laurin, president and CEO of ProMetic Life Sciences. "MacoPharma and PRDT will combine unique and proprietary technologies, share in the development costs, and in the revenues of additional filters."

PRDT scientists say that the prion-removal ligands are the sole products that specifically deal with the selective adsorption of infectious prion proteins. The scientists recently confirmed they had identified lead ligands capable of specifically targeting viruses that remain a challenge to the blood industry. This might lead to a product line extension, providing on-site filtration of donor blood supplies in blood transfusion centers, reducing the risk of transmitting such viruses as West Nile and Hepatitis C (flavivirus and parvovirus families respectively).

Because more than 40 million blood units are collected worldwide every year, filters designed to reduce the risk of transmitting prions and viruses via blood transfusion represent a significant market.

-Megyn Bates