

Drug Delivery[®]

Technology

June 2006 Vol 6 No 6

Identifying Parameters of Value

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AVEVA DDS, INC.: INNOVATIVE TRANSDERMAL TECHNOLOGY SOLUTIONS FOR PATIENTS, PARTNERS & PROFITS



Dr. Steven Sanders
Vice President, R&D
Aveva Drug
Delivery Systems

“At Aveva, no single process is employed in the development of transdermal drug delivery systems. We create individualized systems for each pharmaceutical production process and partner, creating unique products to meet specialized needs, cost effectively and in less time than others within our area of expertise.”

Aveva Drug Delivery Systems, located in Miramar, Florida, is a wholly owned subsidiary of the Nitto Denko company, one of the world's largest manufacturers of and a pioneer in transdermal drug delivery systems. Nitto Denko has a 20-year history of research and development of transdermal products. The medical division of Nitto Denko leverages the technologies available from other divisions of the company, such as proprietary, adhesive development and polymer synthesis to create innovative transdermal products. The US facilities have extended the core R&D and commercial production capabilities of Nitto Denko that have led to the success of numerous transdermal products in Japan. The opportunities for globalization of new transdermal technologies drive the current R&D environment within Aveva and Nitto Denko. Drug Delivery Technology recently interviewed Dr. Steven Sanders, Vice President of R&D at Aveva Drug Delivery Systems, to discuss how collaborations at his company's state-of-the-art transdermal research and manufacturing facility can strengthen product and development portfolios for its customers.

Q: What is Aveva's Mission Statement?

A: Aveva is committed to bringing innovative drug delivery solutions to the healthcare community through the commercialization of products with select industry partners. The fundamental aims of Aveva Drug Delivery Systems are much like the significant goals of Nitto Denko: develop products that are friendly to the environment and people; and help our industry partners by contributing to the prevention and prevention of disease and improving the quality of life for patients.

Q: How can transdermal products, especially those developed by Aveva, meet these goals?

A: Transdermal delivery is now a well-established and accepted route of administration for therapeutically beneficial medicines. The potential benefits that may be achieved using transdermal delivery include continuous, controlled release and absorption of medication into the body, avoiding presystemic metabolism that may occur following oral dosing, including both intestinal and hepatic first-pass metabolism, improving patient compliance by offering more convenient dosing regimens, such as once or twice weekly dosing, the ability to quickly discontinue treatment by removal of the system, etc. I could go on for some time about the benefits that may be realized with transdermal delivery, the key is to apply these benefits to a specific drug molecule and medical need in a manner that meets the goals. That is where the experience and expertise of the Medical Division Nitto Denko and Aveva comes into play: translating the technology into patient and environmentally friendly systems, which has been realized in our Gel Matrix adhesive, as well as improving the quality of life, such as with the only transdermal therapy for asthma, which is currently available in Japan. Our research and development scientists provide the backbone for product development. Our formulation development capabilities include proprietary computer-assisted transdermal feasibility evaluations, selection of excipients, adhesives, and structural film components based on function and compatibility, in conjunction with a high-capacity skin flux laboratory that

provides the in vitro basis for preclinical evaluation of product prototypes. This is all conducted with active intellectual property assessment and development to protect and enhance product investments. An example of these efforts is the Crystal Reservoir Technology, which maximizes systemic drug absorption while conserving requirements for drug product incorporation into the actual patch.

Q: What cGMP development and production capabilities are in place in the Miramar facilities, and what is your record with the FDA and other regulatory authority inspections?

A: Our state-of-the-art facility was designed for multiproject development and product production with maximum flexibility. The facility has over 117,000 square feet of working space that accommodates: multiple blending suites (2.5 to 650 gal); 4 coating suites; 5 packaging suites; 4 commercial-scale packaging lines; 2 pilot-scale packaging lines; 43 separately controlled air-handling zones; and cooling units for special applications. Depending on client needs, our packaging lines are equipped for rotary punching, male-female punching, and island-cut punching, with scalable, batched production runs. The one-to-one ratio for manufacturing and packaging provides maximum efficiency during production. Our Miramar, Florida, facility maintains excellent working relationships with local, state, and federal regulatory offices, successfully hosting numerous inspections by the FDA and DEA. Currently, we hold three DEA licenses that cover: Research (Schedules 2-5); Analytical (Schedules 1-5); and Manufacturing (Schedules 2-5). Most importantly, we have an excellent compliance history. To date, we have not received any citations for DEA violations.

Q: Nitto Denko is Aveva's parent company, can you tell me a little about Nitto Denko's company history?

A: Nitto Denko, a global technology company with sales in excess of \$5 billion, has facilities in 43 countries and employs more than 23,000 employees, 1,800 of whom are in the US.

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Nitto Denko has extensive expertise in polymers and adhesives. This focus has enabled them to be a pioneer and one of the largest manufacturers of transdermal drug delivery (TDD) systems in the world, and number one in Japan with three of the most successfully commercialized transdermal patches. These products have contributed immensely to their partners' businesses. The work Nitto Denko has conducted on transdermal drug delivery systems has led to a number of awards, including: 1993 Technology Prize of the Adhesive Society of Japan; 1998 Science and Technology Agency Director's Prize; and 2001 PSJ Award for Drug Research and Development of the Pharmaceutical Society of Japan. The advancements in transdermal drug delivery systems haven't stopped there. Nitto Denko remains committed to leading the development of transdermal drug delivery technology and to continuing their contributions in the field of medical care to improve quality of life.

Q: You previously mentioned a couple of Aveva's leading-edge capabilities, can you provide some additional details on these transdermal technologies?

A: Two of the exciting technologies include our proprietary Gel Matrix adhesive and the Crystal-Reservoir drug-in-adhesive design. At the forefront of innovation, Aveva and Nitto Denko produced the first and only marketed transdermal patch using a revolutionary Gel Matrix adhesive system for an unequal balance of adhesion reliability and gentleness. This acrylic polymer-based system combines the "skin-friendly" properties that are commonly associated with hydrophilic gels or plasters with the adhesion reliability of traditional acrylic matrix systems. Because the Gel Matrix adhesive cause only minimal effects to the stratum corneum, these patches can be removed and actually reapplied with minimal to no skin irritation. This leads to better tolerability of the transdermal product, improving patient experience and minimizing problems that patients may have with patch application and removal. Despite the gentle effects on the skin, the patches adhere consistently with minimal adhesion problems, lifting and actual patch fall-off occur rarely, also improving patient's satisfaction with treatment, which may lead to increased persistency and compliance. One of the most successful advancements in transdermal drug delivery systems is our Crystal Reservoir Technology, which has resulted in the ability to design smaller patches with better control of drug release. Techniques to oversaturate an adhesive polymer with medication leads to a partial and controlled crystallization of the drug in the adhesive matrix. The presence of drug molecules dissolved in the adhesive and

in solid crystal form maximizes the thermodynamic activity that drives the absorption process. This provides a long-acting, consistent supply of drug in each patch as crystals redissolve. This technology also allows the potential use of lower amounts of drug in each patch with attendant economic and environmental benefits. Nitto Denko also brings innovative polymer synthesis capabilities that will aid in the development of future transdermal products. Critical for all polymer-based development projects is the ability to combine monomers into longer-chained polymers that retain the desirable characteristics of the initial building blocks. This technology has been applied to plastics and adhesives in a number of industries. Now, biopolymers are being utilized to incorporate DNA, siRNA, and proteins into biological systems, which are rapidly advancing the field of biotherapeutics and may find their way into transdermal systems of the future.

Q: Are there specific therapeutic areas of interest for transdermal products? What have been the limiting factors in developing more transdermal products?

A: There is no limitation on therapeutic area for the development of transdermal systems. Some therapeutic areas stand out, including sex hormones and pain management, due to the successful marriage of the individual drug molecules and available product technologies. To date, however, there are numerous transdermal products that have gained significant commercial success and provided unique benefits for patients. In addition to those mentioned previously, smoking cessation, hypertension, overactive bladder, and motion sickness are other areas with important transdermal products available. In some cases, the dominance of oral products in the US market has limited the entry of and better acceptance of transdermal products. The estrogen and combined estrogen/progestin treatments for menopausal symptoms represents one area where the benefits of transdermal therapy are not well understood. Continued research is necessary to fully appreciate the benefits of transdermal treatments, where transdermal delivery not only avoids effects on the liver that occur with oral dosing, but also provides treatment that matches the physiologically produced hormone. Certainly, challenges remain for the development of transdermal systems. Aveva is committed to finding new solutions that will minimize skin irritation or other effects that may be associated with transdermal delivery. By continuing our research, we can also break down the barriers that limit the types of drug molecules that may be delivered through the skin, with increased molecular size and complexity presenting current obstacles.

Q: What are some of Aveva's commercial successes, and what is in the pipeline?

A: In the commitment to improving the lives and well-being of patients, Aveva and Nitto Denko have driven numerous transdermal drug delivery systems successfully through the product development process. Aveva transdermal products are in various stages of development, ranging from initial research to regulatory review. We also have several proprietary developments with our partners that include both industry-leading pharma companies, as well as specialty pharmaceutical companies. The future looks very good for new transdermal products as technologies for improved designs continue to evolve. In addition, the current economic environment has placed an increased emphasis on discovering new value opportunities for currently marketed products as well as examining previous pipelines for potential missed opportunities in light of new drug delivery technologies. Aveva has demonstrated strength in the transdermal arena and will be seeking new alliances and opportunities to expand our available drug delivery platforms.

Q: Any closing comments for our readers about how they can work with Aveva to improve their pipelines or extend the life-cycle opportunities of their current products?

A: Bringing products to fruition efficiently and cost effectively deserves nothing less than a solid foundation of successful experience, coupled with a full range of research, development, and manufacturing capabilities, utilizing a number of sophisticated technologies. To accomplish this, our US and Japanese personnel work in a complementary, synergistic fashion. At Aveva, no single process is employed in the development of transdermal drug delivery systems. We create individualized systems for each pharmaceutical production process and partner, creating unique products to meet specialized needs, cost effectively and in less time than others within our area of expertise. Our strengths at Aveva and Nitto Denko are reflected in our successful collaborations with pharmaceutical and biotechnology partners. These include the following Transdermal Delivery Systems (TDDS): TEVA (Confidential); Pfizer (Confidential); Wyeth for the development of Lidocaine TDDS; Watson Laboratories, Inc., for the development of Nicotine Transdermal Systems; Par Pharmaceuticals, Inc., for the development of Clonidine TDDS; and Toa Eiyo for the development of Isosorbide Dinitrate TDDS. ♦