



NanoMarkets

White Paper

Quantifying the disruptive power of nanotechnology

Nano-enabled Drug Delivery Systems Market

**The Impact of Nanotechnology in Drug Delivery: Global Developments,
Market Analysis, and Future Prospects**

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As the pharmaceutical industry matures, meeting Wall Street's aggressive growth expectations becomes increasingly difficult. Many companies will continue to grow via merger and acquisition activity, and through internal development of high-value compounds. Nonetheless, over the next decade, several blockbuster drugs will go off patent, resulting in an estimated loss of \$30-\$40 billion in annual product revenues as generic drugs enter the market. This change is accelerating the industry's constant need to "build the pipeline" of new compounds, and to rapidly enter new markets.

Naturally, these trends are creating new challenges and opportunities in drug discovery. It is also a significant driver of change in Drug *Delivery* Systems (DDS), which are increasingly being used to alleviate some of the industry's concerns by extending product and patent lifecycles, creating New Chemical Entities (NCE's) via reformulation of existing and/or orphaned compounds, and subsequent creation of value for shareholders and consumers. When you add in the massive amount of nanotechnology and pharmaceutical R&D funding now available worldwide, the drug delivery industry is evolving rapidly and is nearly unrecognizable from its humble beginnings in the 1960s. This \$40-billion market has seen double-digit growth for the past two decades, and the industry's success has spawned intense competition.

NanoMarkets believes that important opportunities exist at the intersection of nanotechnology and traditional pharmaceutical R&D, though much uncertainty remains on how this will affect the industry. In early 2005, NanoMarkets will release the results of an in-depth research study that analyzes and quantifies market opportunities for nano-enabled drug delivery systems. This report will include an overview of nano-enabled drug delivery technologies, commercial applications and information on the companies pursuing them, information on nanotechnology initiatives and regulation in major international markets (North America, EU, Japan, Israel, etc.), as well as eight-year worldwide forecasts on the industry's anticipated growth and timing thereof. We believe that this report will be of key value to marketing professionals, corporate and strategic planners, R&D management, product development professionals, private equity analysts, angel investors, venture capital funds, academic institutions, and other industry watchers at all pharmaceutical, nutraceutical, diagnostic, therapeutic, life science and biotech organizations that may be impacted by nanotechnology. In this white paper, we summarize some of our findings to date.

Early Successes and Significant Potential Identified

In 2000, Elan Pharmaceuticals received FDA approval for its NanoCrystal technology, by reformulating Rapamune®, a Wyeth drug (sirolimus). The new formulation overcame the drug's relative insolubility by reducing the particle size to less than 200nm, and subsequently coating the active compound with GRAS (Generally Regarded As Safe) surface stabilizers. Perhaps the company's most significant benefit was an extension of the original compound's product lifecycle, due to the new formulation.

This practice can be particularly valuable near the end of a blockbuster drug's patent life, but outsourcing of the drug delivery function may also speed a compound's Time-To-Market (TTM), adding considerable credibility to claims by nanotech firms that they can help meet the pharmaceutical industry's formulation challenges.

NanoMarkets believes that nano-enabled drug delivery systems will make other considerable contributions to the pharmaceutical industry, including, but not limited to the following:

- **Solubility enhancements:** A fundamental advantage of nanoparticle-based drug delivery systems is their ability to quickly affect a target site. This is due in part to novel encapsulation technologies, coupled with a potentially rapid dissolution rate in the human body. To help quantify the potential benefit, a 10-micron particle could have a surface area of 2-5 m²/g (BET method), whereas 3-5nm nanoparticles may reach of 400-500 m²/g and beyond. Companies such as Elan Pharmaceuticals have developed advanced coating methods, allowing a degree of control never before seen in particles of this size.
- **Reduced development costs:** Nanotechnology R&D has created a need for a new breed of analytical methods. As these methods grow in popularity and commercial availability, they will likely drive R&D productivity enhancements in the drug delivery industry. Examples include nanoparticle-based biomarkers used in efficacy tests, and microarrays. Companies are using nanocrystals (typically silicon, germanium, etc.) to fluorescently tag compounds. Once in the bloodstream, researchers can use them to determine efficacy of delivery systems. Companies to watch include Quantum Dot Corporation, Evident Technologies, and Kereos.
- **Greater targeting ability:** The increased dosing efficiency afforded by nano-enabled drug delivery systems may lower the overall need for a drug, potentially lowering costs and undesirable effects in the human body. By way of example, ALZA has developed a unique lipid nanoparticle delivery system with a polyethylene glycol (PEG) coating, dubbed Stealth®. This technology has demonstrated an ability to evade certain immune system responses, enabling precise delivery of drugs to targeted areas. Ortho Biotech Products' Doxil® is the first marketed product to incorporate this technology, for treatment of ovarian cancer. Other methods involve the use

of external magnetic fields to accurately deliver coated magnetic nanoparticles.

- **Consumer-friendly end products:** Perhaps most important, nanotechnology may make life easier for the driving force behind the pharmaceutical industry -- the customer. Nano-enabled drug delivery methods may present an answer to the ever-present demand for increased user-friendliness and convenience. For example, several new drugs are being formulated for pulmonary delivery, regardless of whether the respiratory system is the intended target. Nektar Pharmaceuticals & Pfizer recently completed Phase 3 trials for a pulmonary system for insulin. This principle is the basis for other compounds, which require rapid onset and/or may be affected by the digestive tract.

The Market is Heating Up

Our research indicates that the market is taking account of this potential and, as a result, nanotechnology-enabled drug delivery systems are the subject of fierce competition. Examples of which include:

- **Creation of a nanotechnology class within the USPTO:** Nanotech patent filings are on the rise worldwide. This is partially due to favorable changes at the U.S. Patent and Trademark Office (USPTO), which recently created a registration category for nanotechnology inventions, called Class 977. This is very similar to the development drug classes (including 424 & 514) in the 1980s, which streamlined the patenting process for pharmaceuticals and biotechnology, but also created an Intellectual Property (IP) “free-for-all” as companies scrambled to take advantage of the opportunity to fortify their patent estates. Forward-thinking organizations are rapidly filing patents in this new nanotechnology class, which may allow them to define the subclasses for future benefit and broad claims. This may result in a new and potentially lucrative layer of IP protection for those who act quickly. It should be noted that the cost of doing nothing may be quite expensive.
- **“Genericization” and new business models driving a critical need for new drug delivery R&D methods:** Over the past few decades, drug discovery companies positioned themselves primarily as “technology companies.” The “Genericization” of the drug delivery market is pressuring some companies to move further upstream in the pharmaceutical value chain -- that is, towards the drug discovery segment of the business. Now that drug delivery companies are engaged earlier in the drug development process, there is a critical need for methodologies optimized for qualification of much smaller amounts of material. Nanotechnology companies are helping to address these challenges. NanoMarkets expects M&A activity to result from this phenomenon, as drug delivery companies seek strategic “bolt-on” acquisition in the start-up community, as well as partnerships with mid-size and large pharmaceutical companies.

In addition to the specific trends mentioned above, there are other general trends that we see as favorable for nanotech-enabled drug delivery. These include:

- **Increased availability of seed and early-stage venture capital:** Although, total VC investment actually declined this year, we believe that investors will begin to re-evaluate nanotech. We also expect large pharmaceutical companies to become increasingly involved with nano-enabled drug delivery via partnerships and M&A activity. Furthermore, several new and existing venture capital (VC) funds have identified nano-enabled drug delivery as a target investment area.
- **Rapidly increasing interest in nanotech R&D:** Nanotechnology has truly captured the imagination of the R&D community in a fundamental way. This phenomenon is highlighted by continued growth in the number of technical publications on nanotechnology. Pharmaceutical and biotech R&D accounts for a significant portion of this activity
- **Increased government funding for nanotech:** Major government programs to fund nanotech R&D have been launched in the U.S., U.K., China, Germany and many smaller nations in Europe and Asia. The U.S. has appropriated roughly \$3.2 billion for nanotechnology R&D to-date, beginning with the National Nanotechnology Initiative in 2000. Funding for this program increased during the Bush Administration. The U.S. is expected to spend \$6.9 billion on nanotech between 2000-2008. To put this in perspective, the entire Human Genome Project cost the United States approximately \$2.7 billion in FY 1991 dollars.

Challenges Still Abound

All this, we believe, should be very encouraging for widespread commercialization of nano-enabled drug delivery systems. But before this can be accomplished, the following challenges will have to be addressed (*note: this is only a partial list*):

- **Health and Environmental concerns growing:** The definable wave of progress in nanotech has drawn criticism from health advocacy groups, environmentalists, and other non-government organizations. The pharmaceutical industry has also seen its share of increased oversight and widespread criticism. The combination of nanotech and pharmaceutical technology may prove an irresistible lightning rod for many self-appointed watchdogs. Nanotechnology industry organizations and governments are scrambling to avoid the scenario faced by Genetically Modified foods in Europe, ultimately resulting in a six-year moratorium.
- **Politics, the FDA, and consumer sentiment:** The traditional role of the Food and Drug Administration (FDA) is evolving, as consumers rebel against high drug prices and rapidly increasing healthcare costs. Highly publicized events, such as Merck's Vioxx recall and a rash of prescription drug abuse, have brought

increased scrutiny on the industry and calls for more government oversight. Though political interference will always be a risk to the pharmaceutical industry, it has developed a strong global lobbying capacity and has been quite successful in minimizing government intervention. Nano-enabled drug-delivery may help offset some of this criticism due to its relatively “clean” image; the high cost of nanotechnology R&D may help justify pricing, and the fact that consumers will often flock to new technologies.

- **Public capital markets cautious of technology:** The successful commercialization of a new drug delivery technology is, and will likely always be very expensive. Highly visible failures in the life sciences industry (such as ImClone) and general skepticism of technology investment returns may affect early-stage companies’ ability to raise capital in public markets. This is especially true today, as witnessed by the recent withdrawal of the highly anticipated Nanosys IPO. Some nanotechnology and drug delivery start-ups will have problems in raising money, because their payouts are often very long-term, and their value propositions are often poorly understood by retail investors. When coupled with the fact that drug delivery firms have historically not achieved the valuations of drug discovery firms, it creates a difficult environment for new entrants.

Conclusions

Risk and uncertainty abound at the crossroads of nanotechnology and pharmaceutical R&D. And as we have seen in this paper, there are plenty of challenges that nano-enabled drug delivery firms must face. At the same time, nano-enabled drug delivery seems to meet the needs of the current drug delivery market place in a number of important ways. To date our research indicates that the three biggest opportunities in nano-enabled drug delivery are:

- **A. Use of novel nanomaterials in traditional drug delivery** – Nanoscale compounds have completely different properties than their macro-scale equivalents. This phenomenon is the driving force behind the majority of innovations in the field, and is expected to continue.
- **B. Pharmaceutical R&D by partnership and acquisition** – Due to massive amounts of R&D funds available for nanotechnology R&D worldwide, there is a wave of hungry start-ups entering the drug delivery field, bringing with them a relatively inexpensive and less-risky means of “filling the pipeline” with innovative products. These companies will require lots of cash, and in most cases will rely on large pharmaceutical companies to get to market.
- **C. Reformulation of existing drugs to increase product lifecycle** – Nanotechnology-enabled drug delivery systems have proven to be a weapon against generics. Novel reformulations may allow an existing compound to qualify as a New Chemical Entity. This may increase

profitability, expand a firm's intellectual property estate, and discourage competition during a drug's most valuable years.

Large and small companies alike are strongly encouraged to develop a nanotechnology strategy, but more importantly, to devote the necessary resources for successfully executing that strategy. Though the impact of nanotechnology may be minimal in the short term, the cost of doing nothing may be very high over time. If approached with sound planning and hard work, pharmaceutical R&D organizations will find a way to create breakthrough products with nanotechnology, save countless lives in the process, and generate long-term value for shareholders.

About the Author:

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Mr. Moradi is a successful serial entrepreneur in the nanomaterials industry, having founded or been a principal in three nanotech start-ups. He is a frequent invited speaker at major industry conferences and several state and regional events. He founded Venture Development Associates, a business-consulting firm that advises top-tier traditional and corporate venture capital funds, early-stage technology companies, and major R&D centers in all matters of technology commercialization and start-up growth.

Mr. Moradi was a co-founder and Vice President of SouthWest NanoTechnologies, a manufacturer of single-wall carbon nanotubes, where he developed and managed strategic partnerships with industry leaders including ConocoPhillips, Zyvex, and a leading Fortune 100 multinational semiconductor company. Mr. Moradi was previously Vice President of Business Development for NanoSource Technologies, where led the company's sale via asset acquisition to DuPont, which is widely regarded as the first major nanotech liquidity event. Mr. Moradi earned a Bachelor of Science degree in Biochemistry from the University of Oklahoma, and has been an adjunct instructor in the College of Engineering and Graduate College of Business. In 2003, he was awarded a community service commendation from the United States Congress, for his voluntary efforts in technology-based economic development.

About NanoMarkets, LC:

NanoMarkets analyzes the impact of nanotechnology on both established and emerging markets with a focus on the realms of communications, IT, semiconductors, bio-medical and energy. Through our reports, white papers and customized client engagements, we provide our clients with insightful analyses of both the commercial and technology related issues that will determine where and how nanotechnology will impact both their business operations and profit potential, as well as providing realistic quantifications of nanotech-based materials and solutions. The firm's web site can be found at www.nanomarkets.net.