Nanoparticle-based Therapeutics in Humans: A Survey

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ABSTRACT

With patent expirations on the rise, pharmaceutical and biotechnology companies are searching for new competitive business strategies. There is enormous excitement regarding nanomedicine's potential impact in the diagnostic and therapy arenas. Specifically, drug delivery via nanoparticles presents novel therapeutic opportunities for active agents (drugs or genes) that were previously unsuited to traditional oral or injectable therapeutic formulations, allowing active agents to be delivered efficaciously while minimizing side effects and leading to better patient compliance. Nanoparticle-based therapeutics have enormous potential in addressing the failures of traditional therapeutics that could not be effectively formulated due to factors such as poor water solubility or a lack of target specificity. Although there are only a few FDA-approved nanoparticle-based therapeutics on the market, these formulations are already impacting medicine and promise to alter healthcare. The initial impact of nanoparticle-based therapeutics will likely only accelerate in the coming years. However, as these products move out of the laboratory and into the clinic, federal agencies like the FDA and the U.S. Patent and Trademark Office continue to struggle to encourage the development of these products while imposing some sort of order. To date, numerous nanoparticles including luminescent quantum dots, magnetic nanoparticles, gold nanoshells, dendrimers, and block copolymer micelles have been studied for drug delivery. In this article, Dr. Raj Bawa provides a brief overview of different nanoparticle technologies with some comments on their commercialization potential. In particular, he highlights selected nanoparticle-based therapeutics that are undergoing clinical trials or have been approved for human use.

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I. THE DRUG DISCOVERY PROCESS

Drug companies in today's global economy face enormous pressure to deliver high-quality products to the consumer while maintaining profitability. They must constantly reassess how to improve the success rate of new molecular entities (NMEs) while reducing research and development (R&D) costs and cycle time associated with producing new drugs, especially new blockbusters. In fact, the cost of developing and launching a new drug to the market, although widely variable, may be upwards of 800 million U.S. dollars.[1] Typically, the drug appears some 10 to 15 years after discovery.[2] Furthermore, out of 5,000 compounds that enter preclinical testing, only five lead compounds make it to human testing and just one makes it to final clinical use.[3] Annual R&D investment by drug companies has risen from one billion U.S. dollars in 1975, to 40 billion today—while annual new approvals have remained flat at between 20-30 drugs.[4] Big pharma's business model, which relies on a few blockbusters to generate profits via enormous promotional campaigns, is clearly broken. Moreover, in recent years, patents on numerous blockbusters have been expiring. In fact, drug revenues worth 70-80 billion U.S. dollars will be lost by 2011 as various drugs go off-patent. This is altering the drug landscape in a big way.

Some argue that big pharma is too focused on shareholder profits rather than innovative therapies. A recent study shows that big pharma spends twice as much on promotion as R&D.[5] Drug companies are also facing other challenges that necessitate development and implementation of novel R&D strategies. [6]

Given this backdrop, there is a critical need for drug companies to alter research approaches and business models so that they can continue to discover and fill the pipeline with novel compounds and introduce them to new markets. Therefore, it is not surprising that drug companies today are focusing on technologies that support high-throughput, miniaturization and nanotechnology,[7] which enable faster drug target discovery and drug development.

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1 PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY 1 (Ram Mahato ed., CRC Press, 2007).

2 *See* R. Anon, *Health Informatics Into the 21st Century*. HEALTHCARE REP. FEB.: REUTERS BUS. INSIGHT (1999)

3 *See id*.; *See also* John Erickson, *Translation Research and Drug Development*, 312 SCI. 997 (2006).

4 *See* Norman L. Sussman & James H. Kelly, *Saving Time and Money in Drug Discovery – A Pre-emptive Approach*, BUS. BRIEFINGS: FUTURE DRUG DISCOVERY 46 (2003), *available at* http://www.touchbriefings.com/pdf/16/Sussman.pdf.

5 *See* Marc-Andre Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLOS MED. 29 (2008).

6 The industry is currently facing other hurdles as well, including: increasing costs for drug development (only 30% of drugs ever recover their R&D costs); weakened product pipelines; decreasing numbers of new drugs approved by the FDA and foreign drug agencies; an increase in the generics' share of the prescription drug market; international competition from countries like China and India; voluntary or forced withdrawal of several blockbusters; difficulty in delivering promising biomolecules, such as, peptides, proteins and other therapeutic biologicals (generated as a result of the rapid growth of the global biotechnology industry); pricing pressures due to high industry margins; a sharp decline in public confidence in the pharma industry; state and federal government's increased vigilance pertaining to hyper-aggressive business practices (e.g., illegal drug marketing and improper drug pricing); difficulty or inability in effectively formulating active agents (30–40% of all active agents identified via combinatorial screening programs have poor water solubility). On top of all this, the FDA and the U.S. Patent & Trademark Office (PTO) are in crisis. *See* Raj Bawa, *Nanotechnology Patent Proliferation and the Crisis at the U.S. Patent Office*, 17 ALB. L. J. SCI. & TECH. 699 (2007). Both federal agencies are plagued by quality and performance issues—lack of expertise and talent in certain technology areas; a high turnover; poor morale; and inadequate computer systems. *See id*. at 721-28.

7 One of the problems facing nanotechnology is the confusion, hype and disagreement among experts about its definition. One of the most quoted, yet inaccurate, definition of nanotechnology is the one used by the U.S. National Nanotechnology Initiative (NNI): ". . . the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications." National Nanotechnology Initiative, *What*

In theory, nanotechnology[8] should reduce the cost of drug discovery, design, and development. It should enhance the drug discovery process itself through miniaturization, automation, speed, massive parallelism, and reliability of assays. The resulting improved R&D success rate should enable faster introduction of new, cost-effective products to the marketplace leading to enhanced business revenues in the future. For example, nanotechnology can be applied to current microarray technologies, exponentially increasing the hit rate for promising candidates/targets that can be screened and accelerating the generation of novel NMEs. Inexpensive and higher throughput DNA sequencers based on nanotechnology can reduce the time for both drug discovery and diagnostics.

In reality, nanotechnology is offering solutions to fundamental problems in the drug industry ranging from poor solubility to a lack of target specificity. In fact, numerous companies are already commercializing nanomaterials and nanosystems for various biomedical applications.

As high-throughput screening technologies continue to lead to an increase in the number of poorly water-soluble NMEs, drug nanoparticle formulations have been proposed (see Sections II and III) and utilized (see Tables 1-3) to tackle such formulation problems as well. Furthermore, nanoscience research has also uncovered a need for novel analytical technologies that can directly impact aspects of therapeutic delivery, such as determining target efficacy and therapeutic outcome.

This article will focus on engineered nanoparticle-based therapeutics pertaining to the drug delivery arena. The toxicity, biocompatibility (e.g., the interactions between engineered nanoparticles and biological systems) and health-related issues of nanoparticles due to instability (either too rapid degradation or prolonged stability within the body) are topics left to a future article.

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is Nanotechnology? http://www.nano.gov/html/facts/whatIsNano.html (last visited May 31 2008). This definition excludes numerous devices and materials of micrometer dimensions, a scale that is included within the definition of nanotechnology by many. Government agencies such as the FDA and the PTO also use a definition based on a scale of less than 100 nm—this rigid definition is essentially copied from the NNI. However, this NNI definition of nanotechnology presents difficulties not only for understanding nanopatent statistics, but also for the proper assessment of scientific, legal, environmental, regulatory, and ethical implications of nanotechnology. This problem exists because nanotechnology represents a cluster of technologies, each of which may have different characteristics and applications. For example, although the sub-100 nm size range may be critical for a nanophotonic company where quantum effects depend on particle size (*e.g.*, quantum dot size dictates the color of light emitted therefrom), this size limitation is not critical to a drug company from a formulation, delivery or efficacy perspective because the desired or ideal property (*e.g.*, improved bioavailability, reduced toxicity, lower dose, enhanced solubility, etc.) may be achieved in a size range greater than 100 nm. Numerous examples from the pharmaceutical industry highlight this important point (see Tables 1 and 2). In view of this confusion, a more practical definition of nanotechnology, unconstrained by an arbitrary size limitation, has recently been proposed: *"The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property."* Raj Bawa, *Special Report - Patents and Nanomedicine*, 2(3) NANOMED. 351 (2007).

[8] Governments across the globe are impressed by nanotechnology's potential and are staking their claims by doling out billions of dollars, euros, and yen for research. According to a recent report, governments, corporations and venture capitalists in 2005 spent almost 10 billion U.S. dollars on nanotechnology R&D globally while emerging nanotechnology was incorporated into more than 30 billion U.S. dollars of manufactured goods. LUX RESEARCH, THE NANOTECH REPORT, 4th ed. (2006). This report predicts that by 2014, 2.6 trillion U.S. dollars in global manufactured goods may incorporate nanotechnology (about 15% of total output). U.S. federal funds are supplemented by state investments in nanotechnology (approximately 40 cents per U.S. dollar). The President's budget for 2008 allocated 1.44 billion U.S. dollars for nanotech as compared to 1.35 billion U.S. dollars in 2007.

II. NANOPARTICLES AS THERAPEUTIC AGENTS

Often, the efficacy and commercial viability of a drug depends upon its mode of delivery. This fact is highlighted by the existence of hundreds of specialty pharmaceutical companies whose focus is to develop innovative drug delivery systems (DDS).[9] A long-standing issue for drug companies is to deliver the correct dose of a particular therapeutic (small molecules, proteins, or nuclei acids) to a specific disease site. Since this is generally unachievable, therapeutics have to be administered in excessively high doses, thereby increasing the odds of toxic side effects. The concept of site-specific delivery of a therapeutic arises from this classic drawback of traditional therapeutics. Nanoparticles have enormous potential in addressing this failure of traditional therapeutics: *they offer site-specific targeting of therapeutics.* Such precision targeting via therapeutic nanoparticles will reduce systemic side effects, resulting in better patient compliance. Various approaches involving targeted multivalent drug nanoparticles are under investigation or on the horizon.[10] Indeed, nanotechnology is poised to deliver to the marketplace evolutionary as well as revolutionary products.[11] Some of these products could be available immediately while others are on the distant horizon.[12]

Nanoparticles are selected for properties such as biodegradability, biocompatibility, conjugation, complexation or encapsulation properties and their ability to be functionalized. There are two types of nanoparticle-based therapeutic formulations: (1) those where the therapeutic molecules are the nanoparticles (therapeutic functions as its own carrier); and (2) those where the therapeutic molecules are directly coupled (functionalized, entrapped or coated) to a carrier.

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[9] DDS are polymeric (or lipid) carrier systems that transport a therapeutic (*e.g.*, drug or gene) to its target binding site (receptor, active site, etc.) so as to impart maximum therapeutic activity with maximum safety (*i.e.*, protect the body from adverse reactions) while preventing the degradation/denaturation/inactivation of the therapeutic during delivery/transit. Targeting can be achieved by (a) linking specific ligands or molecules (*e.g.*, antibodies, glycoproteins, etc.) to the carrier system; or (b) altering the surface characteristics of the carrier system so that it evades the reticuloendothelial (RES) system.

[10] *See* Austin M. Derfus et al., *Remotely Triggered Release From Magnetic Nanoparticles*, 19 ADVANCED MATERIALS 3932 (2007), *available at* http://lmrt.mit.edu/publications/DerfusAdvMat2007.pdf; Wim H. De Jong & Paul Borm, *Drug Delivery and Nanoparticles: Applications and Hazards*, 3(2) INT'L J. OF NANOMED. 133 (2008); *See also* DEEPAK THASSU ET AL., NANOPARTICULATE DRUG DELIVERY SYSTEMS (Informa Healthcare USA 2007); TUAN VO-DINH, NANOTECHNOLOGY IN BIOLOGY AND MEDICINE: METHODS, DEVICES, AND APPLICATIONS (CRC Press 2007).

[11] *See* Raj Bawa, THE FUTURE OF NANOMEDICINE 266 (T. C. Mack ed., World Future Society 2007).

[12] The U.S. demand for drug delivery systems will increase by more than 10% annually to 132 billion U.S. dollars in 2012. *See* Bill Martineau, *Demand for Novel Drug Delivery Systems Rising*, 28 GENETIC ENG'G & BIOTECH. NEWS 14 (2008), *available at* http://www.genengnews.com/articles/ chitem.aspx?aid=2474. The U.S. demand for nanotech-related medical products is expected to increase by more than 17 percent per year to 53 billion U.S. dollars in 2011 and 110 billion U.S. dollars in 2016. *See* The Freedonia Group, *Nanotechnology in Healthcare to 2011* (2007). Nanotechnology-enabled drug delivery systems will generate over 4.8 billion U.S. dollars in 2012. *See* Antonio Regalando, *Nanotechnology Patents Surge as Companies Vie to Stake Claim*, WALL STREET J, June 18, 2004 at A1, *available at* http://www.signallake.com/innovation/061804WSJNanotechPatentsSurge.htm. The market for the use of nanotechnology-enabled drug delivery in 2005 was 1.3 billion U.S. dollars, with a 35% annual growth rate projected for the next five years. *See* Clare Kittredge, *FDA Seeks 'Little' Information*, THE SCIENTIST, June 1, 2006 at 78. As of mid-2006, 130 nanotech-based drugs and delivery systems and 125 devices or diagnostic tests were in preclinical, clinical, or commercial development. *See supra* note 8. The U.S. National Science Foundation predicts that nanotechnology will produce half of the pharmaceutical industry product line by 2015. *Id*.

1. What are Therapeutic Nanoparticles?

Nanoparticles are colloidal particles of approximately 10 nanometers to 1,000 nanometers (1 micron) in size and widely used in drug delivery.[13] Nanoparticles are diverse both in their shape and composition. Many of the properties of nanomaterials are fundamentally different from those of their macroscopic/bulk analogues due to an increased surface area and quantum effects. As a particle's size decreases, a greater proportion of its atoms are located on the surface relative to the interior (core), often rendering it more reactive. In fact, these "quantum effects" coupled with these "surface area effects" can affect optical, electrical, chemical and magnetic properties of nanomaterials, which in turn can affect their *in vivo* behavior. Therefore, nanopartice-based therapeutics, often offer an advantage[14] as compared to their bulk counterparts due to one or more parameter or property.[15]

It is important to note that there are numerous engineered nanoparticles of varying architectures that can act as platforms for therapeutics. Since there is no universal convention or nomenclature that classifies nanoparticles as perfect spherical structures with nanoscale dimensions, various nanoscale structures are sometimes loosely classified as nanoparticles. In fact, some of the common shapes include spheres (hollow or solid), tubules, particles (solid or porous), and tree-like branched macromolecules.[16]

Nanoparticles are synthesized by various methods (self-assembly, vapor or electrostatic deposition, aggregation, nano-manipulation, imprinting, etc.) where the specific protocol is dictated by factors like the specific therapeutic used and the desired delivery route. The critical characteristics of a nanoparticle related to its function include size, surface charge, encapsulation efficiency and release properties.

2. Applications of Therapeutic Nanoparticles

Oral delivery of actives via polymeric delivery carriers and systems is the primary mode of therapeutic delivery. However, it is well established that traditional oral therapeutics are not necessarily the most efficient formulations for a given active.[17] In this regard, note that 8-10% of an oral therapeutic is either denatured by the stomach environment or eliminated via liver metabolism. Therefore, targeting therapeutics to the site of action by circumventing this metabolism will have numerous advantages, such as reduction of unwanted side effects, reduced toxicity due to lowered dose requirement, enhanced patient

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[13] *See* Paul R. Lockman et al., *Nanoparticle Technology for Drug Delivery Across the Blood-Brain Barrier*, 28 DRUG DEV. & INDUS. PHARMACY 1 (2002).

[14] Some of these parameters or properties include: solubility (high surface to bulk ratio), bioavailability, half-life/stability/shelf life, ability to penetrate biological barriers/membranes, toxicity/safety/patient compliance, patient fasted versus fed variability, delivery dose, catalytic properties, imaging, multifunctionality, site-specific delivery/targeting, pharmacokinetics/timed release/controlled release, surface structure/chemistry/modification, drug distribution, and physical properties (i.e., color, transparency, magnetism, and quantum effects).

[15] *See e.g.*, Raj Bawa & Mark Haymann, *Solid Biodegradable Nanoparticles for Drug Delivery*, INT'L J. OF NANOMED. (in press 2008); *See also* Masayuki Yokoyama, *Drug Targeting with Nano-Sized Carrier Systems*, 8 J. ARTIFICIAL ORGANS 77 (2005); Barrett E. Robinow, *Nanosuspensions in Drug Delivery*, 3 NATURE REV. DRUG DISCOVERY 785 (2004); Jean-Christophe Oliver, *Drug Transport to Brain with Targeted Nanoparticles*, 2 NEURORX 108 (2005); S. Moein Moghimi et al., *Nanomedicine: Current Status and Future Prospects*, 19 FASEB J. 311 (2005), *available at* http://www.fasebj.org/cgi/content/short/19/3/311; Celeste Roney et al., *Targeted Nanoparticles for Drug Delivery Through the Blood-Brain Barrier for Alzheimer's Disease*, 108 J. CONTROLLED RELEASE 193 (2005) ; *See also supra* note 10.

[16] Examples of nanoparticles of varying architectures that can act as platforms for therapeutics include: nanocrystals/colloidal dispersions, quantum dots, nanoshells, dendrimers, liposomes, micelles (polymeric micelles, cylindrical worm micelles), polymersomes, cyclodextrins, magnetic nanoparticles, nanosphere hydrogels, fullerenes, and nanocochleate delivery vehicles.

[17] *See* Dwaine F. Emerich & Christopher G. Thanos, *The Pinpoint Promise of Nanoparticle-Based Drug Delivery and Molecular Diagnosis*, 23 BIOMOLECULAR ENG'G 171 (2006).

compliance, greater therapeutic effectiveness, economic benefits, etc. This is the motivation for major research projects in recent years focusing on oral nanoparticles.

Nanoparticles are also better suited than their microparticle counterparts for intravenous (IV) delivery because the tiniest capillaries are in the 5-6 micron range, a size that impedes most microparticles (or aggregations thereof) from entering these capillaries. It is generally accepted that for systemic applications, nanoparticles should be in the range of 10-100 nanometers, with minimum surface charge.[18] Specifically, these properties permit systemic circulation and determine its biodistribution within the human body. It is this size regime that allows more effective systemic circulation than smaller molecules and access to places in the human body where larger particles cannot reach. For example, chemotherapeutic-tagged nanoparticles of specific size can penetrate tumors due to the "leaky" nature of their microvasculature. This classic effect, referred to as the "enhanced permeation and retention (EPR) effect", results in prolonged circulation and accumulation of a therapeutic within the tumor.

Nanoparticles can also be used for getting drugs into the brain. The blood-brain barrier (BBB) is a dynamic endothelial interface which has a unique structure due to the presence of tight junctions. In fact, 98% of drugs are unable to transverse the BBB.[19] However, nanoparticle drug delivery is particularly useful for disorders of the central nervous system (CNS) because some nanoparticles are able to cross this BBB.[20] Often, nanoparticle drugs can be delivered directly to the CNS without prior need for drug modification or functionalization (which can affect efficacy). Moreover, both hydrophilic and hydrophobic drugs may be delivered without first opening the BBB. Obviously, nanoparticles delivered systemically for non-CNS diseases are of general concern because they may cross the BBB and cause brain toxicity or psychoactive effects.

Nanoparticles can also permeate the tight epithelial junctions of the skin that normally impede delivery of drugs to the desired target.[21] Topical emulsion systems incorporating nanoparticles are being developed which rapidly permeate tissue to deliver actives or remove lethal toxins from the blood stream.

Generally, by controlling the size and architecture of nanoparticles, a particular pharmacokinetic release profile of the drug can be generated. Often, a near zero-order kinetic drug release profile is desired since it maintains a steady drug concentration at the site of delivery. Such a profile is more likely to be achieved by nanoparticles where a drug has been functionalized onto or encapsulated within a carrier polymer matrix. Various technologies employ just such an approach where polymeric nanoparticles serve as "Trojan horses" and have been functionalized via a variety of NMEs (see Tables 1-3). Furthermore, such surface-modifications of drug-loaded nanoparticles often prevent their rapid clearance by phagocytes following IV delivery. For oral applications of nanoparticles, research has focused on lymphatic uptake of nanoparticles by the Peyer's patches of the gut-associated lymphoid tissue (GALT). It has been shown that during oral drug delivery of drug loaded nanoparticles, the nanoparticles are disseminated systemically while their microparticle counterparts remain in the Peyer's patches.[22]

Particle size has an impact in another way also. The efficiency of drug distribution within various body cavities is influenced, in part, by the size of the drug particles. As the particle size of a drug

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[18] *See* Mark E. Davis, *Nanoparticles for Systemic Medicines and Imaging Agents*, 3 NANOTECH. L. & BUS. 255 (2006).

[19] *See* William M. Pardridge, *Brain Drug Targeting: The Future of Brain Drug Development*, 3 MOLECULAR INTERVENTIONS 90 (2003).

[20] *See* Giovanni Tosi et al., *Polymeric Nanoparticles for the Drug Delivery to the Central Nervous System*, 5 EXPERT OPIN. DRUG DELIVERY 155 (2008).

[21] *See supra* notes 10 and 11

[22] *See* M. D. Blanco & M. J. Alonso, *Development and Characterization of Protein-Loaded Poly (Lactide-Co-Glycolide) Nanosphers*, 43 EUR . J. PHARMACEUTICS & BIOPHARMACEUTICS 287 (1997).

decreases, its total surface area increases exponentially (see Figure 1). This reduction in particle size increases its dissolution rate and saturation solubility, which frequently correlates to improved *in vivo* drug performance.[23] In some cases, the pharmacokinetic behavior of nanoparticle drugs may help minimize peak plasma levels (which may be toxic) as well as prevent a drop below the targeted therapeutic range (which may reduce efficacy).

Finally, it should be noted that imaging or sensing agents may additionally be incorporated into a nanodelivery system to generate multifunctionality (e.g., drug-loaded quantum dots).

III. NANOPARTICLE-BASED THERAPEUTICS—A SURVEY

It is known that drugs with poor bioavailability often result in higher cost to the consumer, not to mention inefficient treatment and increased risk of toxicity. Ironically, as stated earlier (Section I), due to the high-throughput technologies available today, there has also been an increase in the number of potential NMEs that are poorly water soluble.[24] In recent years various nanoparticle technologies have been successfully employed to tackle drugs with low water and/or lipid solubility.[25] In fact, numerous pharmaceutical companies are revisiting shelved drugs that were "difficult" from a formulation point-of-view due to their solubility profiles. They are starting to rely more on nanotechnology companies to address their formulation challenges.

All nanoparticulate nanomedicines currently on the market have been approved by the FDA according to preexisting laws (see Tables 1-3). Although the FDA has not required any special testing of nanoparticle-based therapeutics (e.g., with respect to their pharmacokinetic profiles), there are not many marketed nanoparticle-based therapeutics (see Tables 1-3). This is an obvious consequence of the extremely complex and demanding requirements of clinical trials by the FDA. There are, however, numerous nanoparticle-based therapeutics under development.[26]

Below, I will highlight some nanoparticle-based therapeutics that are either approved for sale by the FDA (listed in Tables 1 and 3) or are presently in various phases of clinical trials (listed in Table 2):

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[23] *See* Robinow *supra* note 15; *See also* Vandana B. Patravale et al., *Nanosuspensions: A Promising Drug Delivery Strategy*, 56 J. PHARMACY & PHARMACOLOGY 827 (2004).

[24] *See e.g.*, Chris A. Lipinski, *Poor Aqueous Solubility: An Industry Wide Problem in Drug Discovery*, 5 AM. PHARMACY REV. 82 (2002); Magdalene Radtke, *Pure Drug Nanoparticles for the Formulation of Poorly Soluble Drugs*, 3 NEW DRUGS 62 (2001).

[25] *See e.g.*, Radtke *supra* note 24; *See also* RAINER H. MULLER & BERNHARD H. L. BOHM, NANOSUSPENSIONS 149 (Rainer H. Muller et al., eds., Medpharm Scientific Pubs. 1998); Elaine Marisko-Liversidge et al., *Nanosizing: A Formulation Approach for Poorly Water-Soluble Compounds*, 18 EUR. J. PHARMACEUTICAL SCI. 113 (2003); *See also* U.S. Patent No. 5,145,684 (issued Sep. 8, 1992).

[26] *See e.g.*, RAJ BAWA, PATENTING INVENTIONS IN BIONANOTECHNOLOGY: A PRIMER FOR SCIENTISTS AND LAWYERS 309 (David E. Reisner ed., CRC Press, 2008); *See* Bawa & Hayman *supra* note 15; *See also supra* notes 10 and 11; Op ed., *Top Ten Nanoparticle Drug Patents*, 5 NANOTECH. L. & BUS. 111 (2008); RAJ BAWA & S. R. BAWA, PROTECTING NEW INVENTIONS IN NANOMEDICINE 31 (Cynthia G. Wagner ed., World Future Society Press, 2005); Laura Mazzola, *Commercializing Nanotechnology*, 21 NATURE BIOTECH. 1137 (2003); Robert Paull et al., *Investing in Nanotechnology*, 21 NATURE BIOTECH. 1144 (2003); Robert A. Freitas Jr., *What is Nanomedicine?* 1 NANOMED. 2 (2005).

1. Elan Corporation—NanoCrystal Technology[27]

Because consumers prefer oral drugs over implantables or injectables, nano-engineering traditional or shelved compounds could greatly enhance oral bioavailability in some cases. A classic example of improving the bioavailability of poorly soluble drugs is Ireland-based Elan Corporation's NanoCrystal technology. This technology is: (a) an enabling technology for evaluating NMEs that exhibit poor water solubility and/or (b) a valuable tool for optimizing the performance of current drugs. According to Elan, NanoCrystal technology can be incorporated into both parenteral and oral dosage forms. The particles are produced by proprietary attrition-based wet-milling techniques that reduce the size of drug particles to less than 1,000 nanometers.[28] This reduction in size substantially increases the particle's surface area, hence, increasing the solubility (see Figure 1). The nanosized drug particles are then stabilized against agglomeration by surface adsorption of selected GRAS (Generally Regarded As Safe) stabilizers.[29] This results in a final product that behaves like a solution (a colloidal dispersion). Studies have shown that reformulating old drugs by this technology can enhance bioavailability compared to commercial products[30], reduce the time to achieve maximum concentration, as well as result in an increase in the "area under the curve" (AUC) during the first hour.[31] Elan's technology may enable an increase in drug loading, thereby enhancing the maximum tolerated dose compared to commercial products.[32] Typically speaking, drug nanocrystals imply a crystalline state of the discrete particles. Unlike polymeric nanoparticles, they lack any polymeric matrix material.

It should be pointed out that reformulation of an existing therapeutic into a nanoparticulate version generally results in a novel NME because it usually displays an altered pharmacokinetic profile (altered AUC and C_{max}) as compared to its parent (larger) counterpart. In other words, nanoparticulate therapeutics are generally not bioequivalent to their parent (larger) counterparts and hence, cannot apply for FDA approval via an Abbreviated New Drug Application (ANDA) route. But, if the nanoparticulate formulation is bioequivalent to its parent (larger) version, an ANDA can be filed to seek regulatory approval.

The solid-dosage tablet formulation of the immunosuppressant Rapamune (sirolimus, Wyeth Pharmaceuticals; FDA approval in 2000) is the first marketed drug developed with NanoCrystal technology and the first commercial launch of a nanoparticulate therapeutic. Some other examples of reformulated, FDA-approved drugs that employ this technology are TriCor (fenofibrate, Abbot Laboratories; FDA approval in 2004) and Emend (aprepitant, Merck & Co.; FDA approval in 2003). It is interesting to note that the variability observed in the fasted and fed patients upon administration of Abbot's micronized TriCor was not observed upon administration of the reformulated nanoparticulate formulation. Table 3 provides the complete listing of marketed nanoparticulate products developed via Elan's NanoCrystal technology.

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[27] *See* U.S. Patent No. 5,145,684 (issued Sep. 8, 1992); U.S. Patent No. 5,302,401 (issued April 12, 1994); U.S. Patent No. 5,399,363 (issued March 21, 1995); U.S. Patent No. 5,494,683 (issued Feb. 27, 1996); U.S. Patent No. 5,552,160 (issued Sep. 3, 1996); U.S. Patent No. 5,569,448 (issued Oct. 29, 1996).

[28] *See* Marisko-Liversidge *supra* note 25.

[29] *See id*.

[30] *See* Gary G. Liversidge & Kenneth C. Cundy, *Particle Size Reduction for Improvement of Oral Bioavailability of Hydrophobic Drugs: I. Absolute Oral Bioavailability of Nanocrystalline Danazol in Beagle Dogs*, 125 INT'L J. PHARMACEUTICS 91 (1995).

[31] *See id.*; *see also* Gary G. Liversidge & P. Conzentino, *Drug Particle Size Reduction for Decreasing Gastric Irritancy and Enhancing Absorption of Naproxen in Rats*, 125 INT'L J. PHARMACEUTICS 309 (1995).

[32] *See* Elaine Marisko-Liversidge et al., *Formulation and Antitumor Activity Evaluation of Nanocrystalline Suspensions of Poorly Soluble Anticancer Drugs*, 13 PHARMACEUTICAL RES. 272 (1996).

2. Abraxis BioScience, Inc.—Paclitaxel-Albumin Nanoparticles[33]

Abraxane is an albumin-bound nanoparticle formulation of the widely used anticancer drug, Paclitaxel (Taxol). It is the only albumin-bound solvent-free taxane nanoparticulate formulation (~130 nm) that takes advantage of albumin to transport Paclitaxel into tumor cells. It was approved by the FDA in 2005 for use in patients with metastatic breast cancer who have failed combination therapy (Table 1). Because Abraxane is free of toxic solvents typically associated with other approved Paclitaxel preparations, there is no need for pre-medication with steroids or antihistamines often needed to prevent these side effects. Another advantage is that it is administered in 30 minutes, as compared to three hours for solvent-based Paclitaxel. Note that albumin is a protein that acts as the body's natural carrier of molecules that are poorly water soluble. Two different proteins actively transport and concentrate albumin within tumors: gp60 found on the surface of the endothelial cells and SPARC found on the surface of many tumor cells.

At the molecular level, Paclitaxel induces abnormal arrays of cell microtubules by preventing depolymerization. The recommended dose for Abraxane is 260 mg/m^2 administered intravenously over 30 minutes, every three weeks. As of March 2008, Abraxane is approved for use in 33 countries and is under active review in Australia, Russia, Korea and China. Abraxane is marketed in the U.S. under a co-promotion agreement between Abraxis BioScience, Inc. and AstraZeneca Pharmaceuticals LP. Currently, Abraxane is being evaluated for other cancers, including advanced non-small-cell lung cancer[34] and ovarian cancer.[35]

3. Nanospectra Biosciences—AuroShell Particles[36]

AuroShell particles (previously known as Nanoshells) were developed by Drs. Naomi Halas and Jennifer West of Rice University in the 1990s which eventually led to the formation of Nanospectra Biosciences. Formal operations began in 2002 to commercialize applications using AuroShell particles (Table 2). Nanospectra has obtained FDA approval to commence human trial for the treatment of head and neck cancers. According to Nanospectra, AuroShell particles are a new type of optically tunable particles composed of a dielectric core coated with an ultra-thin metallic layer. For their oncology applications a silica core is surrounded by an ultra-thin gold shell (gold-coated glass nanoparticles).

The optical properties of AuroShell particles depend dramatically on the relative sizes of the core and the thickness of the metal shell. In fact, this core-shell structure can be smaller than a wavelength of

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[33] *See e.g.*, Neil Desai et al., *Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel*, 12 CLINICAL CANCER RES. 1317 (2006); William J. Gradishar et al., *Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared with Polyethylated Castor Oil-Based Paclitaxel in Women with Breast Cancer*, 23 J. CLINICAL ONCOLOGY 7794 (2005); PDR STAFF, DRUG INFORMATION FOR THE HEALTH CARE PROFESSIONAL, 25th ed. (Micromedex Thomson Healthcare 2005); Abraxis Oncology, *Package Insert: Abraxane for Injectable Suspension (Paclitaxel Protein-Bound Particles for Injectable Suspension)* (2005); U.S. Patent No. 6,096,331 (issued Aug. 1, 2000); U.S. Patent No. 5,362,478 (issued Nov. 8, 1994); U.S. Patent No. 5,439,686 (issued Aug. 5, 1995); U.S. Patent No. 5,498,421 (issued March 12, 1996); U.S. Patent No. 5,665,382 (issued Sep. 9, 1997); U.S. Patent No. 5,916,596 (issued June 29, 1999).

[34] *See* M. R. Green et al., *Abraxane, A Novel Cremophor-Free, Albumin-Bound Particle Form of Paclitaxel for the Treatment of Advanced Non-Small-Cell Lung Cancer*, 17 ANNALS OF ONCOLOGY 1263 (2006).

[35] John P. Micha et al., *Abraxane in the Treatment of Ovarian Cancer: The Absence of Hypersensitivity Reactions*, 100 GYNECOLOGIC ONCOLOGY 437 (2006).

[36] *See* D. Patrick O'Neal et al., *Photo-Thermal Tumor Ablation in Mice Using Near Infrared-Absorbing Nanoparticles*, 209 CANCER LETTERS, 171 (2004); Christopher Loo et al., *Nanoshell-Enabled Photonics-Based Imaging and Therapy of Cancer*, 3 TECH. CANCER RES. TREATMENT 33 (2004); S. J. Oldenburg et al., *Infrared Extinction Properties of Gold Nanoshells*, 75 APPLIED PHYS. LETTERS 2897 (1999); U.S. Patent No. 6,645,517 (issued Nov. 11, 2003); U.S. Patent No. 6,685,730 (issued Feb. 3, 2004).

light ("nano-scale" optics). The relative core size as well as the shell thicknesses can be varied, thereby altering the optical properties of AuroShell particles across a broad range of the electromagnetic spectrum (including the visible and the infrared regions). It is this ability to "tune" AuroShell particles to a desired wavelength that is critical to *in vivo* therapeutic applications. For example, gold particles generally absorb light in the green region of the visible spectra, but when used as the shell of an AuroShell particle they can be "engineered" to interact with near-infrared or other wavelengths—dramatically shifting the optical properties of the particle.

AuroShell particles are injected intravenously and specifically collect in the tumor through the characteristically leaky vasculature via the classic EPR effect (see Section II, part 2). Generally, AuroShell particles of size ~150 nm are considered ideal for this application. Following accumulation of AuroShell particles in a tumor, the area is illuminated with a near-infrared laser at wavelengths chosen to allow the maximum penetration of light through tissue, converting the laser light into heat. The metal in AuroShell particles converts absorbed light into heat with high efficiency, thereby acting as "heat generators" and cooking or destroying a tumor from within. Human blood and tissue minimally absorb certain near-infrared wavelengths of light, enabling lasers to deliver light through human tissue to AuroShell particles that have selectively accumulated in a tumor. Theoretically, the technology could be useful for the eradication of any solid tumor, including cancers of the breast, prostate and lung. It is worth pointing out that the toxicity of gold remains to be fully investigated.

4. Calando Pharmaceuticals, Inc.—RONDEL Technology[37]

Calando Pharmaceuticals, Inc. is a privately held biopharmaceutical company funded by Arrowhead Research Corporation.[38] The company has developed proprietary therapeutic cyclodextrin-containing polymer RNA interference (RNAi) delivery technology and demonstrated the first clear *in vivo* sequence-specific gene inhibition in tumors. RNAi is a naturally occurring mechanism within cells for selectively silencing and regulating genes. Since many diseases are caused by malfunctioning genes, the ability to silence and regulate such genes selectively through RNAi could provide a means to treat a wide range of human diseases. According to the company, such systemic delivery through the bloodstream raises the prospect for broad application of RNAi therapeutics to treat a wide range of cancers and other systemic diseases.

Calando's technology for RNAi is called RONDEL. Specifically, it employs small interfering RNA (siRNA) as the therapeutic RNA. siRNAs are double-stranded RNAs that are targeted to a specific disease-associated gene because they are complementary to this gene. Calando's cyclodextrin-containing polymers are a two-part siRNA delivery system: a linear, cyclodextrin-containing polycation that binds to the anionic "backbone" of the siRNA. Following this, the polymer and siRNA self-assemble into nanoparticles (~50 nm). The cyclodextrin fully protects the siRNA from enzymatic degradation in serum. Furthermore, cyclodextrin enables the surface of the nanoparticles to be decorated via stabilizing agents and targeting ligands. According to the company, the surface-modifying agents have terminal adamantane groups that form inclusion complexes with the cyclodextrin and contain polyethylene glycol (PEG) to endow the particles with properties that prevent aggregation while increasing stability. Ligands

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[37] *See* Suzie Hwang Pun & Mark E. Davis, *Development of a Nonviral Gene Delivery Vehicle for Systemic Application*, 13 BIOCONJUGATE CHEM. 630 (2002); Derek W. Bartlett & Mark E. Davis, *Impact of Tumor-Specific Targeting and Dosing Schedule on Tumor Growth Inhibition After Intravenous Administration of siRNA-Containing Nanoparticles*, 99 BIOTECH. & BIOENG'G 975 (2008); U.S. Patent No. 6,509,323 (issued Jan. 31, 2003); U.S. Patent No. 7,270,808 (issued Sep. 18, 2007).

[38] Earlier this year, Arrowhead Research Corporation completed the merger between Insert Therapeutics, Inc. and Calando Pharmaceuticals, Inc. as part of a streamlining of the two companies in which Arrowhead assumed active management. The merged company is doing business under the name "Calando Pharmaceuticals, Inc."

to cell surface receptors can be covalently attached to the adamantane-PEG modifier, enabling the siRNA-containing nanoparticles to be targeted to specific tissues (see Figure 2).

Calando's nanoparticle delivery system is designed for IV injection. According to the company, upon delivery of the RNA-containing nanoparticles, the targeting ligand binds to membrane receptors on the targeted cell surface enabling the nanoparticles to be taken up into the cell via endocytosis. Once inside, the siRNA is released from its cyclodextrin delivery vehicle. It then binds to the disease-associated gene, preventing its replication and ability to cause disease. Importantly, Calando's delivery system does not produce an interferon-mediated immune response often associated with lipid delivery of siRNA, even if known immunostimulatory motifs are included in the siRNA.

In April 2008, the FDA approved Calando's application for an investigational new drug (IND) for its lead anti-cancer compound, CALAA-01 (see Table 2). This drug candidate is a targeted nanoparticle, comprising a non-chemically-modified siRNA against the M2 subunit of ribonucleotide reductase (a clinically-validated cancer target). This approval allows Calando to undertake a Phase I trial, the first clinical study using targeted, systemic delivery of siRNA in an oncology setting.

5. Starpharma Holdings, Ltd.—Dendrimer-based VivaGel[39]

Starpharma Holdings Limited,[40] a leader in the development of dendrimer nanotechnology products, is principally composed of two operating companies, Starpharma Pty. Ltd. and Dendritic Nanotechnologies, Inc. Products based on Starpharma's dendrimer technology are already on the market in the form of diagnostic elements and laboratory reagents. Starpharma's lead nanopharmaceutical development product is VivaGel (SPL7013 Gel) which is based on a dendrimer (Table 2). VivaGel is a topical vaginal microbicide for the prevention of HIV and genital herpes. It also has activity against clinically relevant human papillomavirus and also shows promise as a contraceptive agent. VivaGel has been successfully tested in a Phase I clinical trial, and phase II trials are currently underway. VivaGel has been granted Fast Track status by the FDA. In addition, in May 2008, the company reported positive results of a clinical trial that achieved all its objectives demonstrating that 3% VivaGel was safe and well-tolerated in sexually abstinent women when administered vaginally, twice daily for 14 days. In addition to the gel application, Starpharma has an agreement with SSL (the makers of Durex) to co-develop VivaGel-coated Durex condoms.

Dendrimers are precisely defined, synthetic nano-size tree-like macromolecules with branching emanating from a central core ("branched nanoparticles"). They were developed in the late 1970s by Drs. Fritz Vögtle (University of Bonn, Germany) and Donald Tomalia (then at Dow Chemical in Midland, Michigan). Dendrimers are synthesized around a central initiator core unit with each subsequent growth step representing a new layer of polymer resulting in a larger molecular diameter, twice the number of reactive surface sites, and approximately double the molecular weight of the preceding generation. Specifically, dendrimer synthesis begins with a central initiator core unit with the successive addition of new layers ("generations") to the branching groups. The selection of core, branching and surface molecules gives the dendrimer the desired properties and applications (see Figures 3(a) and 3(b)).

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[39] *See* Tom D. McCarthy et al., *Dendrimers as Drugs: Discovery and Preclinical and Clinical Development of Dendrimer-Based Microbicides for HIV and STI Prevention*, 2 MOLECULAR PHARMACEUTICS 312 (2005); U.S. Patent No. 5,714,166 (issued Feb. 3, 1998).

[40] In October 2006, Starpharma Holdings Ltd. acquired US-based Dendritic Nanotechnologies, Inc. expanding the company's potential product line. *See* Starpharma, Home Page, http://www.starpharma.com. In April 2008, Starpharma announced the first commercial product launch based on its Priostar dendrimer technology. *See* Starpharma, Press Release: April 22, 2008, http://www.starpharma.com/data/080422%20First%20commercial%20product%20launch%20DNT%20Priostar%20dendrimers.pdf. This product, developed under a license and supply agreement established in February 2007 between DNT and EMD Chemicals Inc., is a research reagent kit known as NanoJuice Transfection Kit and is for transporting DNA into cells. *Id*.

Furthermore, "polyvalency" can be introduced in a dendrimer by arranging multiple copies of an active group onto its surface. This is important because simultaneous presentation of an active group can result in new or enhanced activity as compared to single presentation of the same active group. This specialized chemistry used to make and modify dendrimers allows the chemist to control the physical and chemical properties of each dendrimer.

6. Mersana—Fleximer-Camptothecin Conjugate[41]

Mersana Therapeutics, Inc. (formerly Nanopharma Corp.) is a privately held, venture backed company that utilizes its proprietary nanotechnology platform to transform existing and experimental anti-cancer agents into new, patentable drugs with superior pharmaceutical properties. Mersana's key component of this platform is a "stealth" material derived from dextran called Fleximer. Fleximer is a biodegradable, hydrophilic and multivalent polymer that can be chemically linked to small molecules and biologics to enhance their pharmacokinetics and safety. It was developed by Dr. Mikhail Papisov of Massachusetts General Hospital.

Mersana's lead product candidate includes XMT-1001 (a Fleximer-camptothecin[42] conjugate where the polymer serves as a scaffold) is currently in Phase 1 clinical trials for cancer (see Table 2). XMT-1001 is a broad-spectrum cytotoxic that utilizes a novel, dual release mechanism to liberate the camptothecin prodrug, which is then converted within cells into camptothecin, a DNA topoisomerase I inhibitor. According to the company, in preclinical studies, XMT-1001 was better tolerated and more efficacious than either camptothecin or irinotecan in models of human cancer, showing extended plasma half-life and high concentrations in tumor tissue. It produced the same pharmacokinetic profile as seen in animals, gradually releasing the drug in a non-toxic form. Phase II trials in two solid tumor indications are planned for this year.

According to Mersana, its Fleximer platform has led to several collaborations in applications that are not suited to standard liposome or PEG approaches. These include a recombinant protein replacement therapy, an active tumor-targeting peptide, and a nucleic acid that inhibits a pathogenic protein.

IV. COMMERCIALIZATION POTENTIAL OF NANOPARTICLE-BASED THERAPEUTICS

Commercialization activities in nanomedicine are currently driven by startups and small and medium enterprises (SMEs). Universities are also pushing their basic nanoscience into real products.[43] However, it is imperative that most, if not all, of these organizations eventually partner and rely upon biotech or drug companies to make their enterprises a business success. They do, however, face the

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[41] *See* Alexander Yurkovetskiy et al., *XMT-1001, A Novel Polymeric Prodrug of Camptothecin, is A Potent Inhibitor of LS174 and A2780 Human Tumor Xenografts in a Mouse Model* (2007) (Abstract 781 on file at Mersana), *available at* http://www.mersana.com/library/user_files/XMT-1001__a_novel_polymeric_prodrug_of_camptothecin_071107.pdf; Claudette Bethune et al., Pharmacokinetics of A Novel Camptothecin Conjugate (XMT-1001) in the Rat and Dog (2007) (Abstract 4723 on file at Mersana), *available at* http://www.mersana.com/library/ user_files/ Pharmacokinetics_of_a_novel_camptothecin_conjugate_070907.pdf; Mikhail I. Papisov et al., *Semisynthetic Hydrophilic Polyals*, 6 BIOMACROMOLECULES 2659 (2005); Alexander Yurkovetskiy et al., *Fully Degradable Hydrophilic Polyals for Protein Modification*, 6 BIOMACROMOLECULES 2648 (2005).

[42] Camptothecins are a class of anticancer agents that inhibit DNA topoisomerase I but manifest cystitis and were not further developed. Camptothecin homologs such as Topotecan (Hycamtin, GSK) and Irinotecan (Camptosar, Pfizer) have more than one billion U.S. dollars in annual revenues combined.

[43] Ann M. Thayer, *Building Businesses*, 86(22) CHEM. & ENG'G NEWS 10 (2008), *available at* http://pubs.acs.org/cen/coverstory/86/8613cover.html.

daunting task of impressing and convincing biotech and drug companies to partner with them in light of the fact that few commercially viable products are around. Moreover, investors have also been cautious as to what route, if any, the FDA will take in regulating nanomedicines in the future.

So far, the process of converting basic research in nanomedicine into commercially viable products has been difficult. In the future, several variables will determine whether advances in the laboratory will translate into commercial products available in the clinic. Presently, multiple challenges and risks beset the commercialization of nanoparticle-based therapeutics.[44]

Moreover, securing valid and defensible patent protection will also be critical to any commercialization effort.[45] Sadly, the proliferation of nanoparticle patent applications filed at the U.S. Patent & Trademark Office (PTO), coupled with the continued issuance of surprisingly broad patents by the PTO, is creating a chaotic, tangled patent landscape where competing players are unsure as to the validity and enforceability of numerous issued patents.[46] If this trend continues, it could stifle competition and limit access to some patented inventions. On the other hand, a robust patent system will aid drug companies that are striving to develop commercially viable nanoparticle products because valid patents stimulate market growth and innovation, generate revenue, prevent unnecessary licensing and greatly reduce the need for infringement lawsuits. Therefore, it is hoped that desperately needed reforms to overhaul the PTO and the decades-old U.S. patent system,[47] along with clearer regulatory guidelines from the FDA regarding nanoparticle-based therapeutics, will be forthcoming.

In spite of all these challenges, the market impact of nanoparticle therapeutics on the pharmaceutical and biotech industries will be widely felt, ranging from new specialized treatments for exotic diseases to reengineered common over-the-counter drugs. Novel or reformulated nanoparticle delivery systems will even disrupt the generic drug market. Furthermore, based on their ability to reduce time-to-market, extend the economic life of proprietary drugs[48] and create additional revenue streams, nanoparticle-based

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[44] Some of the commercialization challenges for nanoparticle-based therapeutics are:
(a) lack of quality control; (b) nanoparticle separation from undesired nanostructures like byproducts, catalysts, and starting materials; (c) scalability issues; (d) enhancing the production rate; (e) reproducibility from batch to batch with respect to particle size distribution, charge, porosity, and mass; (f) high fabrication costs; (g) lack of knowledge regarding the interaction between therapeutic nanoparticles and living cells (the issue of biocompatibility and toxicity); (h) nanoparticle optimization for maximum therapeutic potential; (i) the public's general reluctance to embrace innovative medical technologies without government-sanctioned safety guidelines; (j) relative scarcity of venture funds; (k) few commercial products; (l) big pharma's reluctance to seriously invest in nanomedicine; (m) confusion and delay at the PTO (with respect to proliferation of nanoparticle-related applications filed and patents granted); (n) unpredictability at the FDA (with respect to a lack of clear regulatory or safety guidelines pertaining to nanoparticles); and (o) media's continuing focus on the negative aspects of nanoparticles, often without clear scientific evidence.

[45] *See* Raj Bawa, *Patenting Inventions in Nanomedicine: A Catalyst for Commercialization?* 5 SMALL TIMES 16 (2005); Raj Bawa, Op. Ed. *Will the Nanomedicine "Patent Land Grab" Thwart Commercialization?* 1 NANOMED., NANOTECH., BIO. & MED. 346 (2005).

[46] *See supra* note 26; Drew L. Harris & Raj Bawa, *The Carbon Nanotube Patent Landscape in Nanomedicine: an Expert Opinion*, 17(9) EXPERT OPIN. THER. PATENTS 1165 (2007); *see also* Bawa *supra* notes 6 and 7.

[47] *See* Glenn Hess, *Patent Reform Stalls in Senate*, 86(22) CHEM. & ENG'G NEWS 40 (2008).

[48] Current U.S. patent laws allow obtaining a patent on a new therapeutic formulation that has been created from an old formulation, for instance via novel carriers, novel formulation techniques or through improved DDS. In other words, "nanoformulations" of older therapeutics may be patentable. Innovative DDS could enable companies to devise novel reformulations of off-patent or soon-to-be off-patent compounds. This strategy could delay or discourage generic competition during the most profitable years of an innovator's life cycle. This is especially true if the reformulated therapeutic is superior to its off-patent or soon-to-be off-patent counterpart. In effect, this approach stretches the product lifecycle of an existing, branded, patented therapeutic. This strategy, commonly referred to as "product-line-extension" or "patent evergreening," is broad in scope and includes any second-

therapeutics should significantly impact the drug and biotechnology commercialization landscapes in the near future.

V. CONCLUSIONS AND FUTURE PROSPECTS

Novel or reformulated nanoparticle-based therapeutics currently account for a tiny niche of the total drug, biotech and device market. However, nanoparticle-based delivery holds enormous potential as an effective approach for targeted drug or gene delivery. Nanoparticulate therapeutics of varying compositions and properties have been formulated and characterized. The applications of this evolving technology will be further expanded in the near future as we increase our knowledge of how the human body transports, distributes and clears particles via the vascular and lymphatic systems (i.e., biodistribution of nanoparticles). This is likely to happen at a rapid pace once we develop imaging modalities that provide a better understanding of the precise molecular targets and metabolic fates following delivery of nanoparticles. Obviously, these advances will only come about if synthetic/ analytical technologies are coupled to *in vitro/in vivo* studies and undertaken prior to clinical trials. Computer modeling and simulation techniques will also need to be developed to further our understanding of drug nanoparticles. In addition, clinical trials will need to be conducted with well-characterized nanoparticles. In this regard, an international central "Nanoparticle Databank" should be created that characterizes nanoparticles and summarizes clinical trial data.

Clearly, nanoparticle-based "smart" therapeutics are here to stay and will generate both evolutionary as well as revolutionary products in the future, which will impact the healthcare landscape. But, if this is to happen, there are a few key biological requirements for such technologies to fulfill: (i) they must exhibit "stealth" qualities to evade macrophage attack and the immune response; (ii) be nontoxic, traceable and biodegradable following systemic administration through any route; (iii) display effective pharmacokinetic properties; (iv) the polymer must protect the embedded therapeutics; and (v) they must be selective in their targeting to specific tissue sites.

Finally, it is hoped that urgently needed reforms are undertaken at the PTO to address problems ranging from poor patent quality and questionable examination practices, to inadequate search capabilities, rising attrition, poor employee morale, and a skyrocketing patent application backlog. Only a robust patent system will stimulate the development of commercially viable products. Similarly, improvements are needed at the FDA. Additionally, the FDA must provide clear regulatory/safety guidelines for therapeutic nanoparticles. It is also imperative that we all pay attention to the environmental, health and societal implications of such nanoparticles.

Eventually, these undertakings will expand the burgeoning field of nanoparticle-based therapeutics. Pharma and biotech will embrace nanoparticle-based therapeutics, especially if they offer novel properties that meet medical needs and if the development costs and risks are low relative to commercializing new therapeutics and delivery systems. It is hoped that, in the end, nanoparticle-based therapeutics will become an integral part of mainstream medicine and a standard in the drug industry.

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generation adaptation of an existing therapeutic that offers improved safety, efficacy or patient compliance. In fact, reformulation strategies should focus on how to add value through added ease and convenience for the consumer. If this approach is successful, the innovator of the new reformulation can maintain market share even after generics appear in the marketplace. There are a number of DDS available that can be adapted to various therapeutic in an effort to reformulate them to generate improvements with respect to delivery method, dosage form or dosage strength. Improvements may also be created by conjugating, entrapping or modifying the active agent itself to create a superior product (e.g., by creating pegylated versions or reformulating it with a new salt or ester). Another often-employed approach is to develop and patent a novel polymorph of the innovator's drug compound prior to patent expiration.

APPENDIX

TABLE 1: SELECTED NANOPARTICLE-BASED THERAPEUTICS APPROVED BY THE FDA[49]

Product / Brand Name	Nanoparticle Drug Component / Active Ingredient(s)	Delivery Route	Company / Alliance	FDA Approved Indication(s)	FDA Approval Date[50]
Doxil Caelyx (outside the US)	pegylated doxorubicin (Adriamycin)HCl liposomes	IV	OrthoBiotech Schering-Plough	metastatic ovarian cancer and AIDS-related Kaposi's sarcoma	November 1995
Abraxane	paclitaxel (taxol) bound albumin nanoparticles (~130 nm)	IV	Abraxis BioScience AstraZeneca	metastatic breast cancer patients who have failed combination therapy	January 2005
AmBisome	amphotericin B liposomes (~45-80 nm)	IV	Gilead Sciences	fungal infections	August 1997
Diprivan	propofol liposomes	IV	Zeneca Pharma	anesthetic	October 1989
Renagel	cross-linked poly(allylamine) resin (sevelamer hydrochloride)	oral tablets (capsules discontinued)	Genzyme	control of serum phosphorus in patients with chronic kidney disease on dialysis	October 1998
Triglide	nanocrystalline fenofibrate	oral tablets	SkyePharma First Horizon	lipid disorders; markedly reduces elevated plasma concentrations of triglycerides, LDL and total cholesterol and raises abnormally low levels of HDL	May 2005
Myocet	liposome-encapsulated doxorubicin-citrate complex	IV	Zeneus Pharma Sopherion Therapeutics	cardio-protective formulation of doxorubicin used	Approved in Europe and

[49] The following abbreviations are used in the table: IV, intravenous; PEG-hGH, pegylated human growth hormone; PEG-G-CSF, pegylated granulocyte colony-stimulating factor; nm, nanometer; PEG, polyethylene glycol; VEGF, vascular endothelial growth factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AIDS, acquired immunodeficiency syndrome.

[50] Note that therapeutic approval by FDA does not necessarily indicate that the therapeutic is available to consumers. Data presented herein is current as of June 1, 2008. Myocet and Epaxal have not been approved by the FDA. Marketed nanoparticulate products developed by Elan using NanoCrystal technology are shown separately in Table 3.

Product / Brand Name	Nanoparticle Drug Component / Active Ingredient(s)	Delivery Route	Company / Alliance	FDA Approved Indication(s)	FDA Approval Date[50]
				in late stage metastatic breast cancer	Canada
DepoCyt	sustained release cytarabine liposomes	IV	SkyePharma Enzon	lymphomatous meningitis	April 1999
DaunoXome	encapsulated-daunorubicin citrate liposomes	IV	Gilead Sciences	advanced HIV-related Kaposi's sarcoma	April 1996
Estrasorb	estradiol hemihydrate micellar nanoparticles (emulsion)	transdermal	Novavax	reduction of vasomotor symptoms, such as hot flushes and night sweats, in menopausal women	October 2003
Macugen	pegylated anti-VEGF aptamer	intravitreal	OSI Pharmaceuticals Pfizer	neovascular age-related macular degeneration	December 2004
Abelcet	amphotericin B phospholipid complex	IV	Enzon	invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy	November 1995
Adagen	pegylated adenosine deaminase	IV	Enzon	enzyme replacement therapy for patients with severe combined immunodeficiency disease	March 1990
Pegasys	peginterferon alfa-2a	subcutaneous	Nektar Hoffmann-La Roche	chronic hepatitis C virus infection	October 2002
Somavert	pegvisomant (PEG-hGH)	subcutaneous	Nektar Pfizer	acromegaly	March 2003
Neulasta	PEG-G-CSF or pegfilgrastim (covalent conjugate of recombinant methionyl human G-CSF	subcutaneous	Amgen	febrile neutropenia	January 2002

Product / Brand Name	Nanoparticle Drug Component / Active Ingredient(s)	Delivery Route	Company / Alliance	FDA Approved Indication(s)	FDA Approval Date[50]
	(Filgrastim) and monomethoxypolyethylene glycol)				
Copaxone	glatiramer acetate (copolymer of L-glutamic acid, L-alanine, L-tyrosine, and L-lysine)	subcutaneous	TEVA	relapsing-remitting multiple sclerosis	December 1996
Amphotec	colloidal suspension of lipid-based amphotericin B (~115 nm)	subcutaneous	Sequus	invasive aspergillosis patients who are refractory to or intolerant of conventional amphotericin B	November 1996
PEGIntron	peginterferon alfa-2b	subcutaneous	Enzon Schering-Plough	chronic hepatitis C virus infection in patients with compensated liver disease	January 2001
Oncaspar	pegasparginase	subcutaneous	Enzon	leukemia	February 1994
Epaxal	hepatitis A vaccine adjuvanted with immunopotentiating reconstituted influenza virosomes (IRIV)	Intramuscular (in the deltoid muscle)	Berna Biotech	active immunization against hepatitis A for adult and children >12 months (age may vary and depend upon the country)	available in Canada and elsewhere
Elestrin	estradiol gel (0.06%) incorporating calcium phosphate nanoparticles	transdermal	BioSanté	treatment of moderate to severe hot flashes in menopausal women	December 2006

TABLE 2: SELECTED NANOPARTICLE-BASED THERAPEUTICS IN CLINICAL TRIALS**

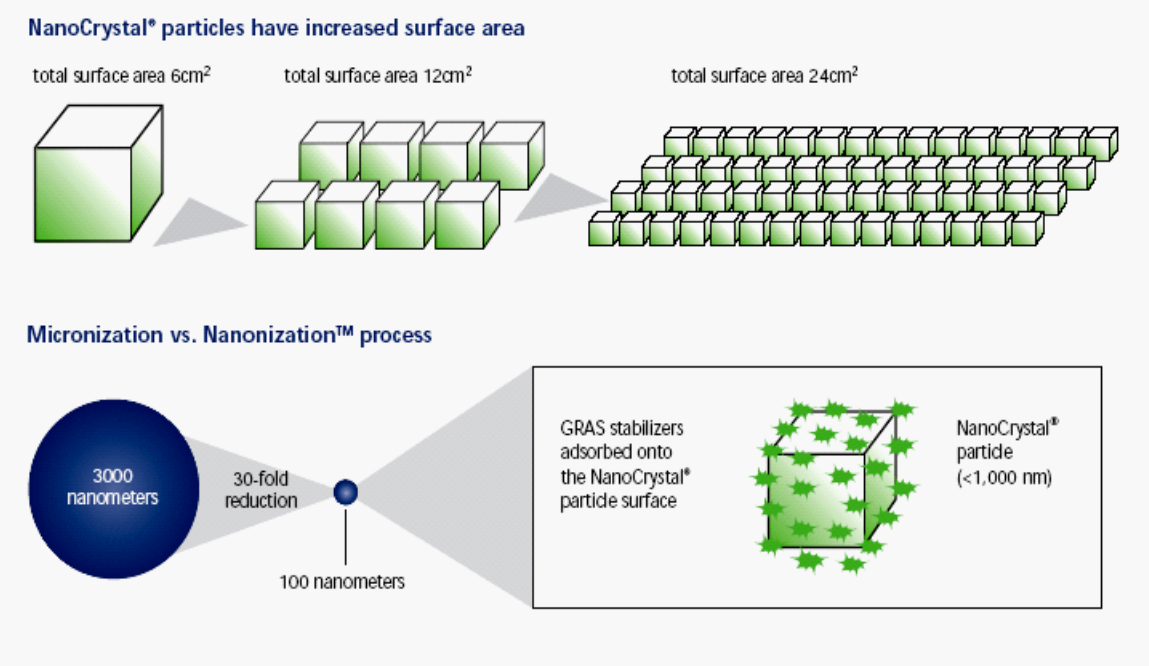
Product/ Brand Name	Nanoparticle Drug Component / Active Ingredient(s)	Delivery Route	Company	Indication(s)	Approval Status
VivaGel	dendrimer gel	topical	StarPharma Holdings	Vaginal microbicide for the prevention of HIV and genital herpes	Phase II; Fast Track
CALAA-01	cyclodextrin-containing siRNA delivery nanoparticles (~50 nm) based on Calando's RONDEL technology	intravenous	Calando Pharmaceuticals	various cancers	Phase I
INGN-401	liposome FUS-1	intravenous	Introgen Therapeutics	metastatic, non-small cell lung cancer	Phase I
Aurimmune (CYT-6091)	colloidal gold nanoparticles coupled to TNF and PEG-Thiol (~27 nm)	intravenous	CytImmune Sciences	solid tumors	Phase II
SGT-53	p-53 liposomes	intravenous	Synergene Therapeutics	solid tumors	Phase I
NB-00X	nanoemulsion droplets (~200 nm) based on NanoStat technology	topical	NanoBio	*herpes labialis* caused by herpes simplex I virus	Phase II
AuroShell	gold-coated silica nanoparticles (~150 nm)	intravenous	Nanospectra Biosciences	solid tumors	Phase I
XMT-1001	Fleximer-camptothecin prodrug conjugate	intravenous	Mersana Therapeutics	various cancers	Phase I

**Data present herein is current as of June 1, 2008. List excludes compounds or formulations where human clinical trials are being planned or are expected to be initiated.
The following abbreviations are used in the table: PEG, polyethylene glycol; nm, nanometer; siRNA, small interfering ribonucleic acid; HIV, human immunodeficiency virus; TNF, tumor necrosis factor.

TABLE 3: MARKETED NANOPARTICULATE PRODUCTS DEVELOPED BY ELAN USING NANOCRYSTAL TECHNOLOGY

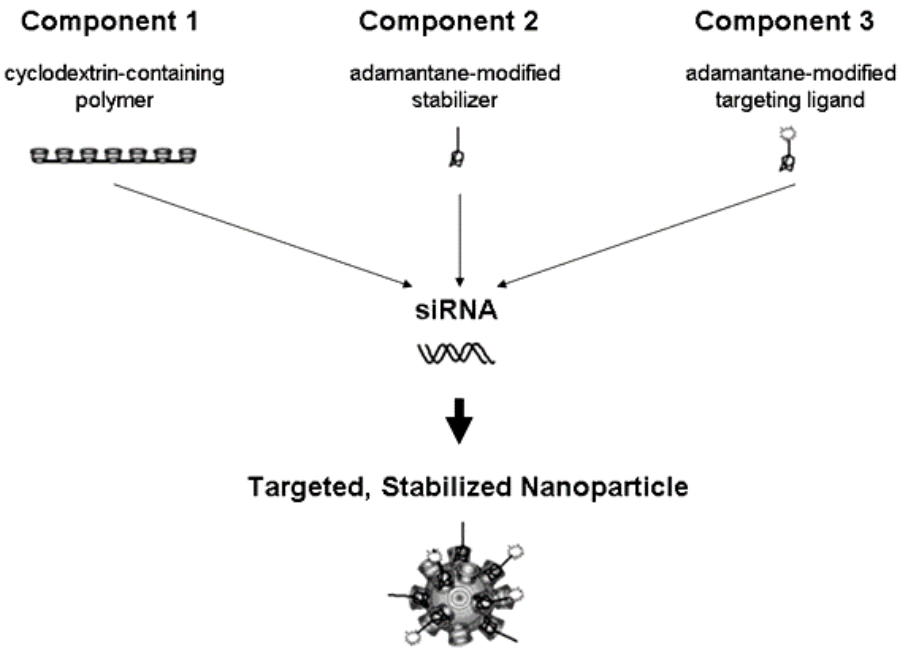
Avinza Once-daily, novel dual-release morphine sulphate formulation; marketed in the US	**Megace ES** Concentrated oral suspension; marketed in the US	**TriCor** new formulation of fenofibrate, which can be taken without regard to food; launched in the US by Abbott
Emend Oral capsule form of aprepitant, a poorly water-soluble compound; marketed in the US and other territories	**Naprelan** Once-daily, sustained-release naproxen sodium; marketed in the US	**Theodur** Twice-daily, sustained-release theophylline for the Japanese market
Focalin XR Once-daily extended release dexmethylphenidate hydrochloride	**Rapamume** Oral tablet of the poorly water-soluble immunosuppressant, sirolimus; marketed in the US	**Verelan** Once-daily, sustained-release verapamil; marketed worldwide
Herbesser Once-daily, high-potency, sustained-release diltiazem for Japanese and other Asian markets	**Ritalin** LA Once-daily, pulsatile release of methylphenidate; marketed in the US and other territories	**Verelan** PM Modified-release, chronotherapeutic verapamil; marketed in the US

FIGURE 1: NANOCRYSTAL PARTICLES ADSORBED WITH SURFACE STABILIZERS



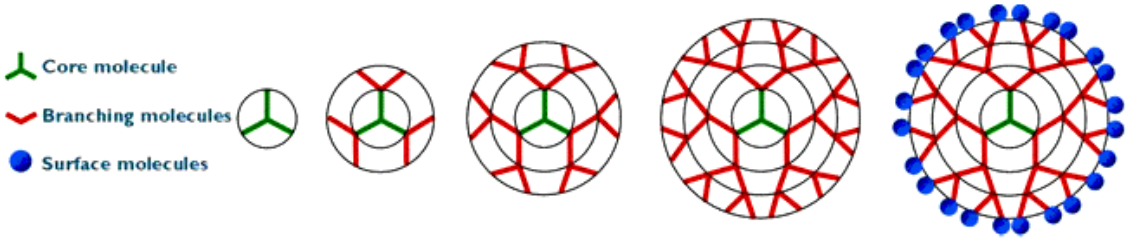
Courtesy of Elan Corporation

FIGURE 2: RNAI/OLIGONUCLEOTIDE NANOPARTICLE DELIVERY (RONDEL) TECHNOLOGY



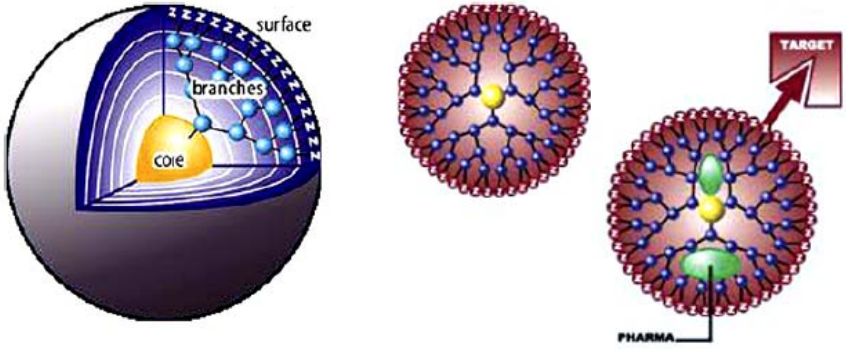
Courtesy of Calando Pharmaceuticals, Inc.

FIGURE 3(A): GROWTH OF A DENDRIMER NANOPARTICULATE



Courtesy of Starpharma Holdings Limited

FIGURE 3(B): STRUCTURE OF DENDRITIC DRUG-DELIVERY VEHICLES



Courtesy of Starpharma Holdings Limited