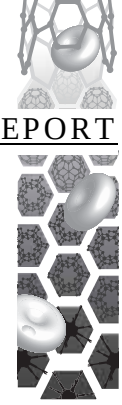

Patents and nanomedicine

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Big pharma's business model, which relies on a few blockbusters to generate profits, is clearly broken. Patent expiration on numerous blockbusters in recent years is already altering the drug landscape. Drug companies are also facing other challenges that necessitate development and implementation of novel R&D strategies, including those that focus on nanotechnology and miniaturization. Clearly, there is enormous excitement and expectation regarding nanomedicine's potential impact. However, securing valid and defensible patent protection will be critical. Although early forecasts for nanomedicine commercialization are encouraging, there are numerous bottlenecks as well. One of the major hurdles is an emerging thicket of patent claims, resulting primarily from patent proliferation as well as continued issuance of surprisingly broad patents by the US Patent and Trademark Office (PTO). Adding to this confusion is the fact that the US National Nanotechnology Initiative's widely cited definition of nanotechnology is inaccurate and irrelevant from a nanomedicine perspective. It is also the cause of the inadequate patent classification system that was recently unveiled by the PTO. All of this is creating a chaotic, tangled patent landscape in various sectors of nanomedicine where the competing players are unsure of the validity and enforceability of numerous issued patents. If this trend continues, it could stifle competition and limit access to some inventions. Therefore, reforms are urgently needed 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 nanomedicine products that can drastically improve a patient's quality of life and reduce healthcare costs.

New paradigms are shrinking our world and a technological revolution in medicine is unfolding. Nanomedicine [1,2], a newly emerging interdisciplinary field and part of the high-risk, high-payoff global nanotechnology phenomenon, has yet to establish itself fully, although there are a few nanomedicine products on the market and many more potential applications under consideration. Commercial nanomedicine is at a nascent stage of development and the full potential of nanomedicine is years or decades away. However, make no mistake, recent advances in nanotechnology-related drug delivery, diagnosis and drug development are beginning to alter the landscape of medicine. Towards this goal, significant technological advances across multiple scientific areas of nanomedicine will continue to be proposed, validated, patented and commercialized. Drug delivery is one area that will produce significant results here. For example, site-specific targeted drug-delivery systems (DDSs), with their potential to address unmet medical needs (made possible by the availability of unique nanomaterial delivery platforms, such as dendrimers, nanoshells, nanoparticles and nanoliposomes) and personalized medicine (a result of advances in pharmacogenetics and pharmacogenomics) are on the horizon. Other more futuristic targeted drug-delivery approaches involve 'nanofactories', in which biological molecules found *in vivo* can be converted into active biotherapeutics in response to a localized medical condition.

Early forecasts for nanomedicine commercialization are encouraging but there are formidable challenges as well. These include legal, environmental, safety, ethical and regulatory questions as well as emerging thickets of overlapping patent claims. Patent systems in general are under greater scrutiny and strain, with patent offices around the world continuing to struggle with evaluating the swarm of nanomedicine-related patent applications. There is great concern today over the inherent health risks and safety of some nanomedicines. Government regulatory agencies are grappling to formulate an appropriate set of guidelines, a difficult task given the current level

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future medicine part of fsg

of uncertainty regarding such health risks. However, I believe that current fears about self-replicating nanobots, the potential toxic effects of nanoparticles and the resultant calls for strict regulatory oversight or a nanotech moratorium will eventually give way to intelligent public dialog on the realistic impact of nanomedicine (and nanotechnology).

Given this backdrop, it is natural to question whether nanomedicine-related advances in the laboratory will result in viable commercial products that benefit society, or whether certain bottlenecks and unforeseen problems will prevent their introduction to the marketplace. One thing is clear: nanomedicine is here to stay and will generate both evolutionary as well as revolutionary products in the future, thereby improving all aspects of our lives.

Drug industry & nanomedicine: a need for miniaturization

The need for drug companies to focus on technologies that support miniaturization and high-throughput (which enables faster drug target discovery and drug development) is real and urgent. US 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 chemical entities (NCEs) while reducing R&D costs as well as cycle time for producing new drugs. This is especially true for new blockbusters. In fact, the cost of developing and launching a new drug to the market, although widely variable [3,4,101], may be upwards of US$800 million. Typically, the drug appears on the market some 10–15 years after discovery [5]. Furthermore, for every 8000 compounds screened for potential drug development, only one makes it to clinical use [6] and only one out of five lead compounds makes it to final clinical use [7]. Annual R&D investment by drug companies has risen from US$1 billion in 1975 to US$40 billion in 2003, while new approvals have essentially remained flat – 20–30 drugs per year [8]. In fact, for the past few years, NCEs accounted for only 25% of products approved, with the majority of approvals being reformulations or combinations of already approved agents [6]. While the cost of drug R&D continues to rise, only 30% of drugs are able to recover their R&D costs. The weakened product pipeline issue is a global problem; the decreasing numbers of new drugs approved by the US FDA and foreign drug agencies continues to haunt the drug industry. For example, FDA approvals have fallen by half since 1996, with only 20 approvals in 2005.

The drug industry is currently facing other related hurdles as well:

- Increased pressures to keep healthcare costs affordable and a demand by patients and healthcare providers for added value;
- An increase in the global generics' share of the prescription-drug market;
- International competition from low-cost centers, like India and China (especially with respect to generic competition, pricing pressures, clinical trials and manufacturing);
- Forced or voluntary withdrawal of several drugs in recent years (as highlighted by Merck's Vioxx and Scientific's Taxus);
- For the first time, expiration of patents on blockbusters is altering the drug landscape (According to Merrill Lynch [9], 23 of the top global pharmaceutical patents will expire by 2008, accounting for an annual revenue loss of more than US$46 billion. In fact, various reports project that drug revenues worth US$70–80 billion will be lost by 2011 as various drugs go off-patent);
- State and federal government's increased vigilance pertaining to hyperaggressive business practices, especially illegal drug marketing and improper drug pricing (~150 cases of alleged fraud by drug companies are currently on the Justice Department's docket [10]);
- Difficulty or inability in effectively formulating active agents due to the fact that 30–40% of all active agents identified via combinatorial screening programs have poor water solubility;
- Unique drug-development models are being successfully developed to circumvent some patented branded drugs [11];
- Difficulty in delivering promising compounds, such as peptides, proteins and other therapeutic biologicals (generated as a result of the rapid growth of the global biotechnology industry);
- Pricing pressures because of high industry profit margins;
- A gradual erosion of public confidence in the drug industry in recent years;
- Quality and performance problems at the FDA and the US Patent & Trademark Office (PTO).

Given all these critical issues and problems, it is evident that the current business models of drug companies (with their mammoth size and

excessive reliance on blockbusters) are broken and in need of a fix. 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 rapidly introduce them to new markets. Clearly, numerous factors are dictating that new drug discovery, development and delivery approaches be developed and implemented.

This is where nanomedicine can impact the industry and save the day. In other words, although the aforementioned trends are creating novel challenges for the drug industry, they also represent a great opportunity to focus on nanoenabled R&D technologies. At this stage, however, several obstacles beset nanoenabled R&D and nanomedicine commercialization efforts, including:

- High production costs;
- The public's general reluctance to embrace innovative medical technologies without real safety guidelines;
- Relative scarcity of venture funds;
- Few near-term commercially viable products;
- A general lack of knowledge regarding the interaction between nanomaterials and living cells (the issue of biocompatibility and toxicity of nanomaterials);
- Big pharma's reluctance to seriously invest in nanomedicine;
- Production issues, such as lack of quality control, reproducibility and scalability of most nanostructures of commercial interest;
- Confusion and delay at the PTO (with respect to the burgeoning number of nanomedicine-related patent applications) and the FDA (with respect to a lack of clear regulatory/safety guidelines);
- The media's continuing focus on the negative aspects of nanomaterials, especially nanoparticulate nanomedicines, often without proper scientific evidence (environmental, health and safety concerns are at the forefront).

Nevertheless, governments around the world are impressed by nanotechnology's potential and are staking their claims by doling out billions of Dollars, Euros and Yen for research. International rivalries are growing [12,13]. Political alliances are forming and battle lines are being drawn. Globally, governments, corporations and venture capitalists spent US$12.4 billion on nanotechnology R&D in 2006, up 13% from 2005 [14]. One market report noted that, in 2005, nanotechnology was incorporated into more than US$30 billion worth of manufactured goods [15]. This report predicts that by 2014, US$2.6 trillion in global manufactured goods may incorporate nanotechnology (~15% of total output) [15]. Global spending in 2006 on nanotech products (US$50 billion) far surpassed that spent on nanotech R&D (US$12 billion) [15]. A recent study claims that there are over 500 nanotechnology-based consumer products in the marketplace today [102]. It should be emphasized that most market reports or studies on nanotechnology rely on the US National Nanotechnology Initiative's (NNI) definition of nanotechnology (discussed later) to draw their conclusions. Also, the data reflected in these reports may sometimes be unreliable. Poor assumptions often underlie the analyses, rendering the results highly questionable or largely irrelevant. Therefore, these market reports should be taken as indicating general trends rather than reflecting solid figures.

Flawed patent classification: the result of an inaccurate definition

One of the problems facing nanotechnology is the confusion, hype and disagreement among experts about its definition [16]. Nanotechnology is an umbrella term used to define the products, processes and properties at the nano/micro scale that have resulted from the convergence of the physical, chemical and life sciences.

One of the most quoted definitions of nanotechnology is the definition used by the NNI [103]: '[n]anotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications.' However, some experts have cautioned against such a rigid definition of nanotechnology, emphasizing instead the continuum of scale from the nanoscale to the microscale [17–22,104]. Clearly, the NNI definition excludes numerous devices and materials of micrometer dimensions, a scale that is included within the definition of nanotechnology by many nanoscientists [19–19,21,22].

In fact, various federal agencies are also grappling with the definition of nanotechnology. Government agencies, such as the FDA and the PTO, use a definition based on a scale of less than 100 nm – a definition essentially copied from the NNI. This definition continues to present difficulties, not only for understanding nanopatent statistics [23], but also for the proper assessment of nanotechnology's scientific, legal, environmental, regulatory and ethical [24,25] implications.

This problem persists because nanotechnology represents a cluster of technologies, each of which has different characteristics and applications [17–19,21,22]. The sub-100-nm size range may be critical for a nanophotonic company in which quantum effects depend on particle size (e.g., quantum dot size dictates the color of light emitted therefrom). However, this size limitation is not critical to a drug company from a formulation, delivery or efficacy perspective because the desired property (e.g., improved bioavailability, reduced toxicity, lower dose or enhanced solubility) may be achieved in a size range greater than 100 nm. Several examples from the pharmaceutical industry highlight this important point (e.g., Abraxane's albumin–paclitaxel nanoparticles, Elan Pharma International's nanoparticles and Kereos's anticancer particles).

To further add to this confusion, experts point out that nanotechnology is nothing new. For example, protein vaccines predate the NNI, falling squarely within its definition of nanotechnology. In fact, the scale of many biological structures is similar to various 'nanocomponents'. For example, peptides are similar in size to quantum dots (~10 nm) and some viruses are the same size as some drug-delivery nanoparticles (~100 nm). Hence, most of molecular medicine and biotechnology can be classified as nanotechnology. I propose a practical definition of nanotechnology that is unconstrained by an arbitrary size limitation [22]:

'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.'

Naturally, disagreements over the definition of nanotechnology carry over to the definition of nanomedicine. At present, there is no uniform, internationally accepted definition for nanomedicine either. One definition, unconstrained by size while correctly emphasizing that controlled manipulation at the nanoscale, results in medical improvements and/or significant medical changes, comes from the European Science Foundation [26]:

'…the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.'

Hence, I propose that the size limitation imposed in the NNI's definition be dropped, especially when it is applied to nanomedicine. In fact, the phrase 'small technology' may be more appropriate here since it accurately encompasses both nanotechnologies and microtechnologies. I believe an internationally acceptable definition and nomenclature of nanotechnology should be promptly developed in this context.

Defining nanomedicine or nanotechnologies applied to medicine also has significant ethical implications. Definitions help determine the scope of ethical inquiry and define the common language with which to engage in ethical discourse. Definitional murkiness for both nanotechnology and nanomedicine begs the question from the ethical perspective as to whether nanomedicine presents any new challenges for ethicists or whether nanotechnologies applied to health and healthcare simply raise old issues in a new light [24,25].

Due to the burgeoning number of new patent applications filed at the PTO and continued pressure from industry, in November 2004, the PTO finally created a preliminary classification (a cross-reference digest or art collection) for nanotechnology (designated as Class 977). The purpose of this class was described by the PTO on its official website [105]: '[e]stablishing this nanotechnology cross-reference digest is the first step in a multi-phase nanotechnology classification project and will serve the following purposes, facilitate the searching of prior art related to nanotechnology, function as a collection of issued US patents and published pre-grant patent applications relating to nanotechnology across the technology centers and assist in the development of an expanded, more comprehensive, nanotechnology cross-reference art collection classification schedule.' It is important to note that this digest should not be construed as an exhaustive collection of all patent documents that pertain to nanotechnology.

The phrase 'prior art' refers to various sources of information that the PTO uses to reject a patent application. In other words, it is the 'knowledge' that exists at the time of the claimed invention that is used to establish whether or not it is novel. It can include documentary material, such as publications, patents, websites or other disclosures, that suggest that the invention is not new. It can also include evidence of actual uses or sales of the technology within the USA.

The PTO has recently expanded Class 977 into numerous subclasses [106]. As of December 2006, the PTO has placed approximately 4500

patents into Class 977. However, these figures should only be considered a rough underestimate of the total number of nanopatents. This is because the PTO has copied the NNI's narrow definition of nanotechnology for classification purposes, which has resulted in a skewed patent classification system, especially with respect to nanomedicine- and bionanotechnology-related inventions. Furthermore, this classification scheme is neither sufficiently descriptive enough to accommodate many of the unique properties that nanomedicine inventions exhibit nor does it address the interdisciplinary nature and range of technologies encompassed by nanomedicine. The PTO's efforts to provide a home for a few thousand US patents via a skewed classification system defeats the very purpose for the creation of Class 977, namely:

- To gauge the number of nanotechnology patent applications filed and patents issued;
- To assist patent practitioners as well as patent examiners (PTO employees who review patent applications and grant patents) in searching nanotechnology patent documents.

Searching nanomedicine prior art: issues & challenges

There are various issues pertaining to nanomedicine patent searching that are of concern. For example, some experts state that the PTO lacks effective automation tools to search nanomedicine prior art. Moreover, their databases may not be exhaustive. This problem may be particularly acute regarding nonpatent prior art. Although there has been a dramatic rise in nanomedicine patent activity, most of the prior art still exists in the form of journal publications and book articles. Websites and pregrant patent publications provide an additional resource. I believe that a large amount of this nonpatent scientific literature directed at nanomedicine predates many of the nanomedicine patents that have been issued and are currently being issued. It is possible that patent examiners lack access to some of this critical nonpatent information either because the PTO does not subscribe to the relevant commercial database or because not all patent examiners are experienced searchers. As a result, patent examiners may miss discovering prior art. The problem of access to nonpatent information may not be unique to nanomedicine patent examination; it is seen in most technology areas. Furthermore, the internet usage policies of the PTO may sometimes prevent patent examiners from accessing all relevant databases to retrieve information. The issue here may be one of security since prior art searching on the internet can run the risk of being tracked externally. Given these inferior search capabilities, I agree with the conclusion that 'the informational burdens on the examiner are clearly heavy – even before the examiner engages in the heavy lifting of interpreting the prior art' [27].

It seems that patent examiners are often basing decisions about the grant of nanomedicine patents on limited information. It is frightening to envision that their faulty decision-making will shape a nascent industry for years to come. It is possible that this information deficit has rendered examination unfocused and inefficient, resulting in the issuance of numerous unduly broad nanomedicine patents (discussed later).

Add to this confused state of affairs the general difficulty in searching nanotechnology (or nanomedicine) prior art. Because of its broad and often overlapping definition, searching and retrieving nanotechnology-related patents and publications is complicated relative to other technology areas. Different terms can refer to the same nanomaterial or nanostructure. For example, 'nanofibers', 'fibrils' and 'nanotubes' have been used to describe multiwalled carbon nanotubes, while 'single shell nanocylinders', 'buckytubes', 'nanowires' and 'nanotubes' have been used to describe single-walled carbon nanotubes. Because of this particular point, mapping the patent landscape accurately is also a real challenge. Patents or publications that are truly nanotechnology based may not use any specific nanorelated terminology. In fact, patents or publications are often written 'not to be found' in order to keep potential competitors at a knowledge disadvantage. On the other hand, there are business-savvy inventors and assignees who use key words incorporating a nano prefix into their patents or publications to better market their invention or concept. Therefore, part of the challenge to finding 'true' nanotechnology (or nanomedicine) prior art is the judicious use of key terms, patent classification codes and alternative phraseology when searching patent and commercial databases. Coupling this strategy with additional filtering by a technology expert is probably the most reliable method of uncovering prior art.

A patent law primer

Globally, industries that produce and manage 'knowledge' and 'creativity' have replaced capital, colonies and raw materials as the new wealth of nations. Property, which has always been the

essence of capitalism, is increasingly changing from tangible to intangible. In fact, intangible assets as a portion of corporate market capital are also rising steadily. Intellectual property (IP) rights are a class of assets that accountants call intangible assets. These assets play an ever-increasing role in the development of emerging technologies, such as biotechnology, drug development and nanotechnology. Modern IP consists of patents, trademarks, copyrights and trade secrets. Patents are the most complex, tightly regulated and expensive form of IP. They have the attributes of personal property – they may be assigned, bought, sold or licensed.

Patent law is a subtle and esoteric area of law that has evolved in response to technological change. It has been modified numerous times since 1790, the year the first US Patent Act was enacted. This is due to new interpretations of existing laws by the PTO or by the courts and via the creation of new laws by Congress, often in response to new technology. Patent law, arguably one of the most obscure legal disciplines, is now at the forefront of nanotechnology. In the new millennium, patent issues are making headlines on a daily basis. As the line between academia and industry becomes fuzzier, the axiom for success in science, 'publish or perish', is being replaced with 'patent or perish' or 'patent and prosper'. Universities are straying from their education mission by focusing increasingly on patents for potential license revenue. I believe that patents are as important, if not more so, as publications on *curriculum vitae* and have a major impact on hiring, tenure and promotion.

The PTO issues three types of patents as defined by the Statute:

- Utility patents for 'any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof';
- Plant patents for 'any distinct and new variety of plant' (i.e., asexually reproduced nontuber plant varieties);
- Design patents for 'any new, original and ornamental design for an article of manufacture.' (i.e., ornamental designs of an article of manufacture).

Patentable inventions need not be pioneering breakthroughs – improvements of existing inventions or unique combinations/arrangements of old formulations may also be patented. In fact, the majority of inventions are improvements on existing technologies. However, not every innovation is patentable. For example, abstract ideas, laws of nature, works of art, mathematical algorithms and unique symbols and writings cannot be patented. Works of art and writings, however, may be copyrighted and symbols may be trademarked. Laws of the universe or discoveries in the natural world, even if revolutionary, cannot be patented. For instance, Einstein's Law of Relativity cannot be considered anyone's IP.

A US patent provides protection only in the USA, its territories and its possessions for the term of the patent. It is estimated that 90% of the world's patents are issued through the three main patent offices: the USA, Europe and Japan. Legally speaking, a US patent is a document granted by the federal government (at the PTO), whereby the recipient (or 'patentee') is conferred the temporary right to exclude others from making, using, selling, offering for sale or importing the patented invention into the USA for up to 20 years from the filing date. Similarly, if the invention is a process, then the products made by that process cannot be imported into the USA. All patented inventions eventually move 'off' patent at the end of their patent term ('patent expiration'), at which time they are dedicated to the public domain. This is the basis for low-cost generic drugs that appear in the marketplace after expiration of the costlier versions of the patented branded drug.

A patent is not a 'hunting license'; it is merely a 'no trespassing fence' that clearly marks the boundaries of an invention. In other words, a patent grant is a negative grant – it prevents other parties from using the invention without prior permission of the patent holder (which can be in the form of a license). This does not imply that the patent holder can automatically publicly practice (i.e., commercialize) the invention. Often, appropriate government regulatory approval is required.

The basic rationale underlying patent systems, both in the USA and abroad, is simple. An inventor is encouraged to apply for a patent by a grant from the government of a legal monopoly of limited duration for the invention. This limited monopoly or proprietary right justifies R&D costs by assuring inventors the ability to derive economic benefit from their work. In exchange for this grant, the inventor publicly discloses the new technology that might have otherwise remained secret (an 'immediate benefit' to the public) and allows the public to freely use, make, sell or import the invention once the patent expires (a 'delayed benefit' to the public). Hence,

the new technology that is brought to light in the form of valuable technical information provides a continuous incentive for future innovation. In this way, society obtains a *quid pro quo* from inventors in exchange for the temporary grant of exclusive rights. Such an advantageous exchange stimulates commerce (a 'long-term benefit' to the public). Patent protection is the engine that drives industry and the incentive for it to invest in R&D to innovate. Clearly, without such protection, most big companies would avoid costly R&D and society would be deprived of the many benefits thereof. However, it is critical that the scope or breadth of the patent issued by the PTO be just right; it should neither be unduly broad nor should it be too limiting. In other words, the invention that is granted a patent should just fit within the boundaries of that patent.

For a US patent to be granted, an invention must meet all of the following criteria set forth in Statutes:

- It must be novel (i.e., sufficiently new and unlike anything that has been patented, marketed, practiced, publicized or published previously);
- It must be nonobvious to a person with knowledge in the field related to the invention, meaning that the person would not automatically arrive at the present invention from a review of existing ones (i.e., trivial variations that are readily apparent to a person with knowledge in the field related to the invention cannot be patented);
- It must have utility (i.e., the invention has some use and actually works or accomplishes a useful task);
- It must be described adequately to the public in order to demonstrate 'possession' of the invention at the time of filing;
- It must enable a person with knowledge in the field related to the invention to make or carry out the invention without 'undue experimentation' (i.e., to make the claimed product or carry out the claimed process without undue trial and error);
- It must enable a person with knowledge in the field related to the invention to use the invention;
- It must be described in clear, unambiguous and definite terms;
- It must set forth the best mode of making and using the invention contemplated by the inventor at the time of filing the patent application;

Obtaining a patent for an invention is often a long, expensive and tedious process that generally involves the inventor, patent counsel or practitioner (i.e., patent agent or patent attorney) and PTO staff (especially a 'patent examiner'). Patent examiners are PTO personnel who review the filed patent application to ensure that it fulfils all pertinent requirements of the law listed above. This review process is commonly referred to as an 'examination'. The exchange of documents between the PTO and the patent counsel is broadly known as 'prosecution'. If the examiner believes that all requirements for a patent are met, then a 'notice of allowance' is issued to the applicant. Finally, a patent is issued once the applicant pays an 'issue fee'. Following this, the entire contents of the patent application ('the file wrapper' or 'prosecution history') along with a copy of the issued patent and all future documents pertaining to the patent are made available to the public. Since the granting of the first US patent in 1790, more than 7 million patents have been issued by the PTO. In fact, 1790 was the first year of operation for the PTO and it issued only three patents. On the other hand, in the 2006 fiscal year (October 1, 2005–September 30, 2006), 183,187 patents were issued. For the past few years, the PTO has received over 400,000 patent applications annually. In the 2006 fiscal year, the average patent pendency ranged from 25.4 to 44 months. The number of patent applications filed since 1996 has been increasing, on average, by over 10% per year.

As part of patent prosecution, all applications filed on or after November 29, 1999, are published 18 months after filing (up to that point they are kept confidential), unless the applicant opts out and foregoes foreign filing. This implies that, generally, a patent application as filed will eventually appear in the public domain (whether or not it is patented) and will be available to competitors. The entire patent examination process, starting with the filing of the patent application to its final allowance or final rejection, may take anywhere from 1 to 5 years or longer. This depends upon several variables, such as the specific technology area within the PTO where the patent is being reviewed by the patent examiner and the time to process the paper-work that accompanies the patent application by the PTO clerical staff.

Since the patent term commences from the date of filing and ends after 20 years, most commercially valuable nanomedicine inventions are, in reality, in the marketplace prior to the actual

patent grant date (unless regulatory approval is sought). Generally, it is impossible to predict the future commercial success or commercial viability of an issued patent. In part, this is owing to the fact that most patents are filed at the PTO without any clear idea of whether the invention is commercially valuable. For example, in nanomedicine, patent applications are continuously being filed on a large number of drugs, therapies and devices, even before it is known that they will be ruled safe and effective by the FDA. If litigation rates (which range from 1.5 to 2% of the issued patents) are any indicator of commercial value, then only a fraction of patents are commercially significant. Although obtaining a patent does not ensure commercial success, economists view patenting as an indicator of scientific activity. They argue that this is the basis for providing a nation with a competitive advantage, fueling its economy.

In recent years, however, patents have become the subject of much debate and controversy. In fact, there are plenty of antipatent players in the field who feel that patent laws (and most international treaties) are unfairly providing an economic advantage to some over others. It has even been suggested that patent laws and IP are the products of a new form of western colonialism designed to deny the developing world access to common goods. Issues such as biopiracy, IP theft and greed on the part of multinationals have been proffered as reasons for the unavailability of essential drugs to the poorest and neediest people in the world. Not surprisingly, those in the developing world support patent protection but prefer a regime that suits their own national interests. In this regard, they highlight the fact that, although western drug companies continue to cite the need to reward innovation as a justification for stronger patent laws or patent enforcement, the industry continues to spent more on reformulating pre-existing drugs and on expensive litigation to protect their current patent portfolios than to innovate [28]. Future struggles over patents on the international stage are almost certain to focus on drug patents where multinational drug patents are revoked or challenged [29]. In my view, a multinational drug company's patent rights and providing access to affordable drugs to the developing world are inter-related; they should never be considered mutually exclusive.

Note that the PTO does not police or monitor patent infringement nor does it enforce issued patents against potential infringers. It is solely up to the patentee to protect or enforce the patent, all at the patentee's cost. The patentee may enlist the US government's help via the court system to prevent patent infringement. PTO decisions are subject to review by the courts, including the Court of Appeals for the Federal Circuit (CAFC) and, rarely, the US Supreme Court. Sometimes Congress intervenes and changes or modifies some of the laws governing patents.

The CAFC was created by Congress in 1982 with the aim of creating uniformity in patent law, especially with respect to unpredictable, evolving technologies, such as biotechnology and nanotechnology. In reality, it has sometimes failed in this role by rendering inconsistent and contradictory patent decisions.

If a court deems a patent to be invalid, the patent holder is unable to enforce it against any party. However, suing an alleged infringer is a risky business. When a patent holder sues an alleged infringer, in certain technologies, there is a 50% risk that the patent holder's own patent will be found invalid.

Based on my review of seminal CAFC patent decisions from the past decade or so, it is my firm conclusion that the CAFC has fostered the following:

- Expanded what can be patented under the patent statutes
- Lowered the threshold to obtain a US patent
- Tilted its decisions in favor of patent holders

Clearly, this stance has resulted in stronger patent protections for patent holders. As a result, since the creation of the CAFC, the number of patents granted has increased at an annual rate of 5.7%, compared with less than 1% from 1930 to 1982 [30]. According to some experts, if this trend continues, it could stifle competition and limit access to some inventions. Moreover, this is contrary to the *quid pro quo* discussed earlier: it disturbs the delicate balance between the patent holder's limited-time monopoly on the invention on one hand and the public's interest in accessing the invention (from the public domain) on the other. Certainly, this could be the very reason why the Supreme Court is increasingly stepping in to hear more and more patent appeals of CAFC decisions. It is important to note that the Supreme Court, which has rarely reviewed patent decisions in the past, has heard seven important patent appeals of CAFC decisions in the past 4 years alone, reversing each one of them. One of these recent landmark rulings [31] broadly impacts nanomedicine. It allows drug companies to

infringe drug patents held by others as long as the infringement is during the R&D phase (i.e., preclinical phase) of drug development and generates data (on the compound being tested) that may (or may not) be ultimately submitted to the FDA as part of the drug-approval process. Another recent Supreme Court ruling may make patenting new inventions and defending existing patents much more difficult in all technologies [32].

By these and other recent decisions, the Supreme Court may be trying to re-establish the balance between the patent holder and the public's interest, a certain flexibility that it may have viewed as eroding under the CAFC. It is critical that the CAFC refocus its efforts to provide greater clarity to patent law and render patent decisions that are more consistent. After all, this is its true mission.

One highly controversial yet important statistic worth briefly discussing is the patent allowance or grant rate (percentage of applications reviewed by examiners that are approved). Several legal scholars have published studies to gauge this figure. One widely cited estimate places the average PTO grant rate at 77–95% of filed patent applications for the years 1981–2005 [33]. However, I agree with some legal scholars who consider this estimate to be artificially high, since it may be based on an inappropriate legal framework and somewhat flawed numbers [34]. In any case, the exact figures are immaterial; the crux of the matter is that the PTO grant rates are high and this may indirectly reflect a less rigorous review of patent applications compared with the other major patent offices. In other words, these high allowance rates may be partly to blame for the granting of poor-quality patents (other concerns are described later). In this context, it is interesting to note that the time taken for 1 million patents to be granted has greatly declined since the grant of US Patent No. 1 in 1836 (the first US patent was issued in 1790 while the numbering system was developed in 1836).

In light of this discussion about patent allowance rates and patent quality, it is rather interesting to note the PTO's recent announcement of a 54% allowance rate for the past fiscal year. In this regard, it is further worth noting that, although the number of patent applications has continued to increase, creating a steady backlog that threatens businesses (according to PTO's own estimate, at the end of 2006, there were more than 700,000 unexamined patent applications), the number of issued patents has declined in recent years. The most notable decline was in 2005, when a drop of 11% in the allowance rate was reported from the previous fiscal year. What does this mean? Do these figures imply a vast improvement in patent quality over the earlier years when allowance rates were much higher? Most experts would disagree. If this is not the case, then is it possible that numerous high-profile patent cases and blunders (like the recent BlackBerry case) have oversensitized PTO upper management, who are now actively engaged in artificially suppressing the high patent grant rate? Is the PTO trying to paint a rosy picture of improvement in patent quality? Some commentators are perplexed at this drastic dip in allowance rate, given that all indications are that 'inventive quality should be rising, not falling' [35]. Tinkering with the patent system can have disastrous consequences for the entire innovation process. Moreover, it is clearly counter to the basic tenet of the US patent system: '[t]o promote the Progress of Science and Useful Arts' [36].

Significance of patents: the fuel for the 'nanomedicine revolution'

Patents are critical to the nanomedicine 'revolution'. When investors in nanomedicine or drug companies consider the merits of their investment, patent issues are one of the most important items they review. There is also ample evidence that companies, start-ups and universities are ascribing ever greater value and importance to patents. Increasingly, they are willing to risk a larger part of their budgets to acquire and defend patents. The process of converting basic research in nanomedicine into commercially viable products is proving to be long and difficult. The development of nanomedicine-related technologies is extremely research intensive and without the market exclusivity offered by a patent, development of these products and their commercial viability in the marketplace would be significantly hampered.

Patents are especially important for start-ups and smaller companies because they may help in negotiations over infringement during competitive posturing with larger corporations. Often large competitors employ frivolous suits to pressure a smaller company or start-up whose patent stands in their way, or which they wish to acquire. Patents may also protect the clients of a patent owner because they prevent a competitor from infringing or replicating the client's products made under license from the patentee. Moreover, patents provide inventors credibility

with their backers, shareholders or venture capitalists – groups who may not fully understand the science behind the technology. Generally, patents precede funding from a venture capital firm. For a start-up company, patents are not only a means of attracting investment but also serve to validate the company's foundational technology. Therefore, start-up companies aggressively seek patents as a source of significant revenue. They cite the potential for licensing patents and the power to control emerging sectors of nanotechnology as major reasons for seeking patents [23]. Moreover, venture capitalists are hesitant to support a start-up that relies on trade secrets alone. In summary, investors are unlikely to invest in a start-up that has failed to construct adequate defenses around its IP via valid, enforceable patents.

A company seeking a dominant position in a particular sector of nanomedicine may wish to review patent citations (i.e., patents cited in other patents). Patent citations can serve as a useful indictor of licensing potential: patents that are cited repeatedly are generally considered more commercially valuable. A quarter of all patents receive no citations at all, whereas a mere 0.01% earn greater than 100 citations [37]. According to one study, a patent cited 14 times on other patents is, on average, 100-times more valuable than a patent cited only eight times [37].

Millions of dollars may be lost if a company fails to take the necessary steps to protect its patent assets. Securing valid, defensible patent protection is vital to the long-term viability of virtually any drug or biotechnology company, whether or not nanotechnology is involved in the platform technology. Often, loss of these critical assets is a result of both the researcher's excitement with his or her research as well as general ignorance about IP. In fact, experts agree that 'patent awareness' (i.e., the knowledge that patents are intangible property that can be obtained and lost) is central to any business plan or strategy [38]. Furthermore, it is essential that managers and patent practitioners implement certain proactive measures to 'box out' the competition [18]. In other words, taking the correct preventive steps is critical to realizing the full commercial potential of an invention [18]. Because nanomedicine interfaces with fields, such as biology, physics, chemistry, engineering, medicine and computer science, filing a patent application (or conducting a patent search) in this field may require expertise in these diverse disciplines. Hence, employing a qualified patent counsel (a patent agent, a patent attorney or a multidisciplinary team of lawyers) who understands the legal and technical complexities is a critical step in obtaining quality patents. Additionally, issued patents and other prior art should be evaluated carefully and effective patent-drafting strategies devised accordingly.

The phrases 'patent value' and 'patent quality' are important, yet distinct concepts. But they are somewhat related and largely determine a patent's potential for commercialization, licensing opportunities, investor interest and enforceability. They are briefly discussed below.

The 'patent value' of an issued nanomedicine patent is often measured in terms of other factors ('valuation metrics'):

- The breadth and scope of the claims of the issued patent that affect competitors' freedom-to-operate (this correlates with the patent's originality);
- The number of potential competitors in that particular sector of nanomedicine;
- Government fees ('maintenance fees') paid to keep the patent enforceable;
- The patent's applicability to other fields;
- Licensing and litigation activity surrounding the patent;
- The frequency by which that patent is cited by others (discussed earlier);
- Other IP held by the patent-holder in that particular technology, including any blocking, pioneering or upstream patents.

'Patent quality' generally refers to the ability of a patent examiner to make proper, timely decisions about the validity and scope of protection during the examination process that is consistent with the legal ruling a court would make after comprehensive review of the same application.

Last year, the PTO proposed several changes in patent practice that could significantly alter the way in which nanomedicine companies file and prosecute patent applications [39,40]. Therefore, companies may need to rethink their patent strategies to maximize their patent rights, including taking appropriate proactive action on pending patent applications prior to the actual implementation of these new rules.

Patenting nanoformulations: the example of solid drug nanoparticles

Nanoformulating existing drugs

Nanomedicine is already impacting the drug-delivery arena. Drug companies now recognize that DDSs must be an integral part of their

R&D process at an early stage. According to one market report, nanotechnology-enabled DDSs will generate over US$1.7 billion in 2009 and over US$4.8 billion in 2012 [107]. This report projects that the global drug-delivery products and services market will surpass US$67 billion in 2009 [107]. Another report placed the nanotechnology-enabled drug-delivery market for 2005 at approximately US$1.25 billion, growing to US$5.25 billion by 2010 and US$14 billion by 2015 [41].

Current US patent laws allow the grant of patents on new drug formulations that have been created from old drugs (e.g., via novel DDSs). Nanotechnology could also allow reformulation of existing and/or orphaned compounds. These new reformulations may qualify as NCEs at the FDA and for patents at the PTO. In other words, 'nanoformulations' of older drugs may be patentable as long as they fulfill all the criteria for patentability mentioned earlier (see the 'A patent law primer' section). Furthermore, innovative DDSs or platforms may be patented on their own under current US patent statutes. Innovative DDSs could enable drug companies to devise novel drug 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 drug's life cycle. This is especially true if the reformulated drug 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 drug. This strategy, commonly referred to as 'product-line-extension' or 'patent evergreening', is broad in scope and includes any second-generation adaptation of an existing drug that offers improved safety, efficacy or patient compliance [42]. 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 DDSs or platforms can maintain market share even after generics appear in the marketplace.

There are a number of DDSs, platforms or polymer-carrier systems available that can be adapted to various drugs 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 drug itself to create a superior product (e.g., by creating poly[ethylene glycol] [PEG]-coated 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. Yet another strategy involves generating patent protection on a competitor's formulation (patented or off-patent) by analyzing the competitor's existing patent claims, then tweaking them and filing patents that circumvent the competitor's specific use or DDS.

All of these approaches could lead to potentially patentable drug versions with stable revenue streams. Obviously, it is important to have physicians and healthcare professionals switch to the new and improved (re)formulations so that market position is not lost to generic competition. Switching a branded drug, whenever feasible, to over-the-counter status (the so-called 'Rx-to-OTC switch') is another strategy that can extend the life of the branded formulation. Moreover, this approach almost always improves sales figures, especially if the FDA grants Hatch-Waxman 3-year exclusivity. According to one estimate, a single year of extended patent protection generates approximately 18% of the average product's sales volume [43]. Some experts estimate that, today, generics may take 80–90% of market share within the first few weeks of entering the marketplace [42]. The first generic to enter the market following patent expiration is generally priced 30–40% lower than brand names and this figure can further drop to 80% lower within 2 years of patent expiration [43].

Reformulations are generally considered to create a disproportionate amount of value given their cost [44]. According to a 2004 report, reformulations in the drug industry will grow from 62% of the total drug market in 2003 to 79% in 2008 [44]. However, it is worth mentioning here that branded drug patents, especially those directed to reformulations, are coming under relentless legal attack by proponents of generics who view them as stretching the limits of what deserves a new patent. Clearly, it is the multibillion dollar sales figures of these blockbusters that encourage generic and other drug companies to aggressively attack the validity of such patents.

Patenting solid nanoparticulate drugs

Solid nanoparticles are colloidal particles of size 1 to 1000 nm (1 µm) that are useful as drug-delivery platforms [45,46]. They have become an important area of research in DDSs owing to their

ability to deliver a variety of active pharmaceutical agents to different sites within the body for a prolonged period. Nanoparticle size and surface properties dictate their *in vivo* behavior. Specifically, these properties permit systemic circulation and determine nanoparticulate biodistribution within the human body. It is this size that imparts them with unique properties in contrast to larger particles. Their smaller size allows them access to places in the human body that larger particles cannot reach.

Particle size has an impact in another way too. 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 decreases, its total surface area increases exponentially [47]. This reduction in particle size increases its dissolution rate and saturation solubility, which frequently correlates with improved *in vivo* drug performance [48,49]. 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 lower efficacy). In fact, many drug companies are revisiting shelved drugs that were 'difficult' from a formulation point-of-view due to their solubility profiles. They are starting to rely on nanotechnology companies to address the formulation challenges of their drugs.

It should be pointed out that reformulation of an existing drug into a nanoparticulate version generally results in a novel NCE because it often displays an altered pharmacokinetic profile (altered AUC and C_{max}) compared with its parent (larger/bulk) counterpart. In other words, nanoparticulate drugs are generally not bioequivalent to their parent (larger/bulk) counterparts. Hence, drug companies cannot apply for FDA approval via an Abbreviated New Drug Application (ANDA) route reserved for generic drugs. However, if the nanoparticulate formulation is bioequivalent to its parent (larger/bulk) version (meaning the dissolution rate and absorption is similar), an ANDA can be filed to seek regulatory approval. Under the Hatch Waxman Act, the FDA approval process for NCEs benefits the innovator in two ways:

- The new drug enjoys a 3–5-year nonpatent exclusivity period that prevents generics from entering the marketplace;
- The patent owner can recover some of the patent term lost because of the delay caused by the FDA regulatory review process.

If the nanoparticulate drug is being tested on children, there is a FDA provision that extends patent protection by 6 months (known as the 'pediatric rule').

Although there are few widely marketed solid nanoparticle formulations, numerous nanomedicine-related products are either under development or nearing commercialization [1,11,18,19,21,46,47,50–52]. This is an obvious consequence of the extremely complex and demanding requirements of clinical trials by the FDA. However, based on their ability to reduce time to market, extend the economic life of proprietary drugs and create additional revenue streams, nanoparticle-based drugs will impact the drug commercialization landscape significantly in the near future. In the process, they will become an integral part of mainstream medicine, offering consumer-friendly products. As the drug industry increasingly begins to adopt them, nanoparticle-based DDSs are likely to be among the first products to generate serious patent battles and cross-licensing activity (which is an exchange of roughly symmetric patent positions between two or more parties) [53].

It is yet to be seen if nanoparticle patent applications will face the same patent hurdles that e-commerce and some biotechnology patent applications faced. These patent applications were initially held to be nonpatentable. In any case, nanoparticle-based drug formulations, as with other nanoscale inventions, are patentable so long as they satisfy the patent requirements discussed earlier (see the 'A patent law primer' section). Size alone is not a criterion for patentability in the USA; the mere fact that the device or process involves a change in scale does not allow for the granting of a patent. In fact, it is a well-established legal doctrine that limitations relating to the size of a claimed structure, device or process are not sufficient to distinguish over the prior art – the mere scaling up or down over the prior art does not by itself establish patentability [54,55]. The CAFC has held that when size is the only difference between the claimed device and the prior art device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device is not patentable [56]. However, a nanoscale invention may be patentable if it performs a new function, unless the function can be performed by other methods. Even this hurdle may be overcome by the inventor if he or she can demonstrate that the nanoscale invention's function involves an improvement over the prior art and is not obvious to a 'worker' in that particular scientific field or technology.

Typically, when patenting new formulations of previously known drugs, the biggest hurdle is establishing nonobviousness. The PTO often takes the initial position that new drug formulations are mere 'optimizations' and, hence, are not patentable. This particularly holds true where the ingredients in the formulation have been used previously in other formulations, especially with recognized effects or benefits. To establish that a particular formulation is nonobvious, it is often necessary for the applicant to convince the patent examiner that the formulation has some unexpected superior property or provides an improvement, such as reduced toxicity, enhanced bioavailability, altered drug stability, solubility or activity. Showing such an unexpected property often requires submission of experimental data during prosecution of the patent application, comparing the inventive formulation with the closest formulation previously known. In this manner, the applicant can rebut the initial position of the PTO and establish that his or her formulation is indeed inventive and therefore, entitled to a patent. Because the nanoparticulate drug prior art is still relatively immature and because nanoparticle properties are often unpredictable, it may be easier for an inventor to establish unexpected properties for nanoparticulate drugs over traditional drug formulations and obtain a patent. However, this patenting trend will eventually change as more and more nanoparticulate drug prior art accumulates and more judicial opinions on patents involving nanotechnology emerge.

Nanomedicine patent proliferation & PTO problems: a recipe for disaster

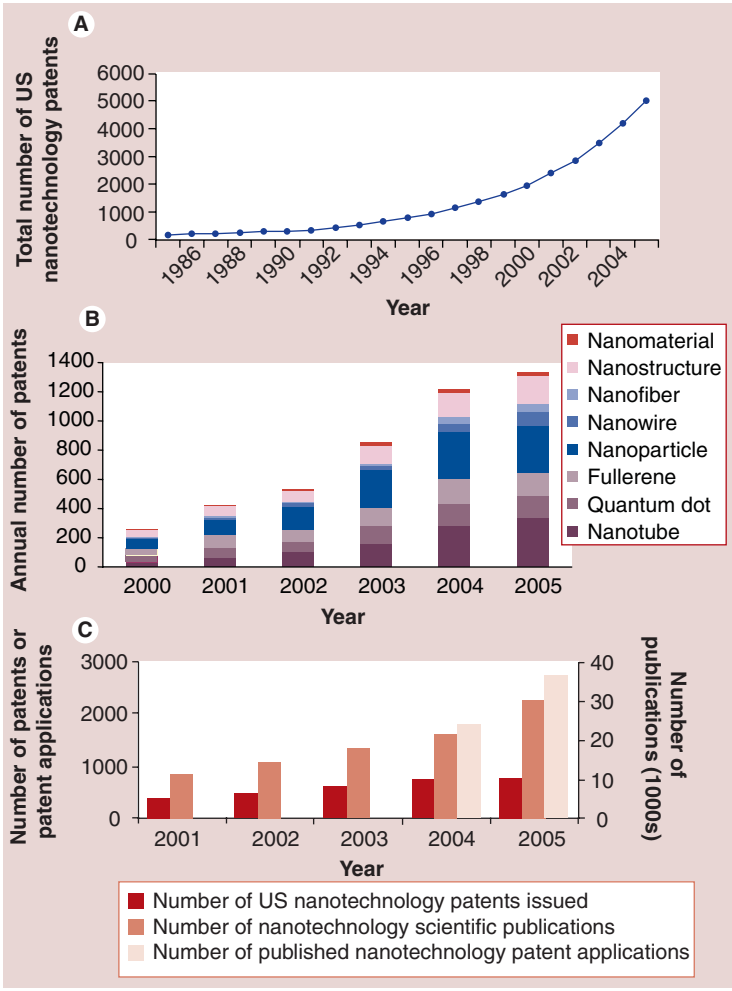
Federal agencies continue to grapple over nanotechnology issues. The PTO is no exception. In fact, for more than a decade, all of the world's major patent offices have faced an onslaught of nanomedicine-related patent applications [13,15,17,18,57–62,108]. The situation at the PTO is likely to worsen as more applications are filed and pendency rates further skyrocket. As companies develop products and processes and begin to seek commercial applications for their inventions, securing valid and defensible patent protection will be vital to their long-term survival. In the decades to come, with nanomedicine further maturing and promised breakthroughs accruing, patents will generate licensing revenue, provide leverage in deals and mergers and reduce the likelihood of infringement. The development of nanomedicine-related products, which is extremely research intensive, will be hampered significantly in the absence of the market exclusivity offered by a patent. Due to the PTO's dismal handling of critical problems such as poor examination quality, skyrocketing patent pendency, out-of-control examiner attrition, and poor work force morale I discuss below some of the more pressing issues with respect to 'patents and nanomedicine'.

A chaotic nanotech patent land grab continues

Because of the potential market value of nanomedicine products, every player in the international race for technological dominance – researchers, executives and patent practitioners – view the collection and exploitation of nanomedicine patents as critical. In fact, these players are making an effort to obtain the broadest protection possible for new nanoscale polymers, devices and systems that have applications in biotechnology and medicine. Therefore, a sort of 'patent land grab' (Figure 1A–C) is in full swing by 'patent prospectors' as start-ups and corporations compete to secure broad patents in nanomedicine during these critical early days [18,19,21,22,59–62]. This land grab mentality is further fueled by the relative lack of products and processes in the marketplace. Companies feel that, to demonstrate confidence and sway venture capitalists, they must generate or claim IP. Some companies also feel pushed into claiming as much IP as possible. They fear that if they lag behind in this effort, someone else will claim the broadest IP. Similarly, academic researchers feel compelled to file patents in order to bolster their reputation and *curriculum vitae*. Moreover, most inventors have quickly realized the opportunities available at a disorganized PTO during these early days of nanomedicine for securing broad patents on valuable upstream technologies with relative ease.

With nanotechnology maturing further, the number of claims in patent applications and the amount of scientific literature cited during patent prosecution is on the rise (Figure 2). The latter is significant because scientific publications are the most accurate indicator of scientific activity and productivity. Another trend observed is that nanotechnology patent owners are eyeing commercial potential and therefore maintaining more of their patents (Figure 3). All issued utility patents are subject to the payment of maintenance fees to the PTO to maintain them in force. Failure to pay a maintenance fee on time will result in the expiration of the patent.

Figure 1. Growth of the nanotechnology knowledge base.



(A) US nanotechnology patent explosion. **(B)** Annual nanomaterial-related US patents issued. **(C)** Rising patent applications and scientific publications in nanotechnology.
Data reflected in all figures are based on the National Nanotechnology Initiative's definition of nanotechnology. Therefore, they represent general trends and not exact numbers.

However, these patent prospectors have to deal with an overburdened PTO, which historically has been slow to react to emerging technologies, such as biotechnology and software. In fact, the entire US patent system is under enormous scrutiny and strain as the PTO continues to struggle with the evaluation of nanomedicine-related patent applications. Commentators are increasingly voicing their concerns regarding emerging nanotechnology patent thickets and their impact on global access to products [63]:

"Although industry analysts assert that nanotech is in its infancy, 'patent thickets' on fundamental nanoscale materials, building blocks and tools are already creating thorny barriers for would-be innovators. Industry analysts warn that IP roadblocks could severely retard the development of nanotechnology. Some insist that nanoscale technologies will address the most pressing needs of the [world's] marginalized peoples. But, in a world dominated by proprietary science, it is the patent owners and those who can pay license fees who will determine access and price … The world's largest transnationals, leading academic labs and nanotech start-ups are all racing in the patent gold rush. Increasingly, universities are licensing on an exclusive basis … Control and ownership of nanotechnology is a vital issue for all governments and civil society because nanomaterials and processes can be applied to virtually any manufactured good across all industry sectors … At stake is control over innovations that span multiple industry sectors … companies that hold pioneering patents could potentially put up tolls on entire industries."

In fact, some of the concerns highlighted above are borne out by US nanotechnology patent demographics from 2006 (Figure 4).

Problems plague the examination process

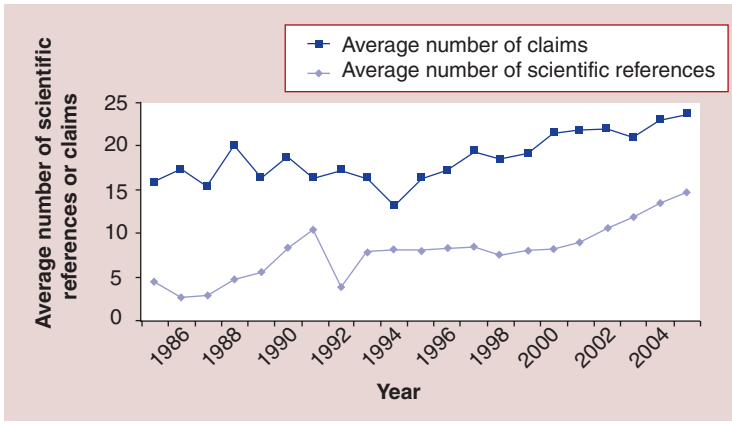
Although the PTO budget has bloated to it's current US$1.6 billion, various examination problems continue to haunt it. One patent expert recently summarized the current crisis at the PTO [64]:

"The US Patent and Trademark Office is under siege for issuing patents that should never have issued, and for excessive delays. Congress is considering changes such as a new opposition system for challenging patents when they emerge from examination…"

A law Professor is blunter in her criticism [109]: "The United States patent system is broken and desperately needs fixing … Why are so many bad patents being issued? … Under our current system, granting an application with little scrutiny takes less time than subjecting it to rigorous review … The examiners are unable to perform more than a cursory search of their own [due to time constraints] … Third parties – competitors and consumers – are generally excluded from the patent examination process, even though these parties have the greatest incentive to discover the prior art and disclose it to the Patent Office in order to prevent bad patents from being issued…"

Indeed, questionable patent examination practices at the PTO seem to extend across other technology areas. Although efforts are underway to improve the quality and efficiency

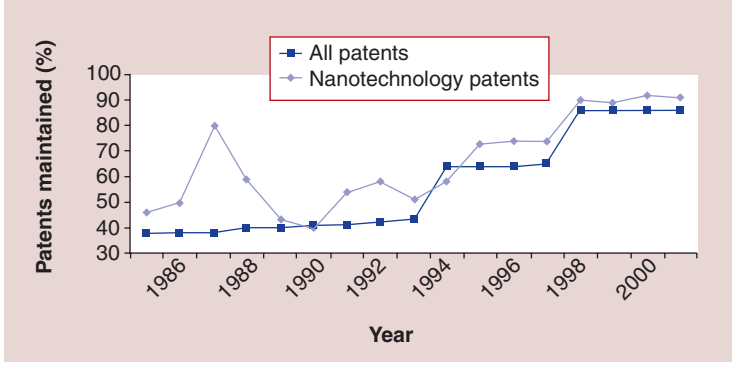
Figure 2. Trends in nanotechnology patent claims and cited references.



of the patent examination process generally, various shortcomings continue to beset patent examination. Some of the problems that impact nanomedicine are examined briefly below.

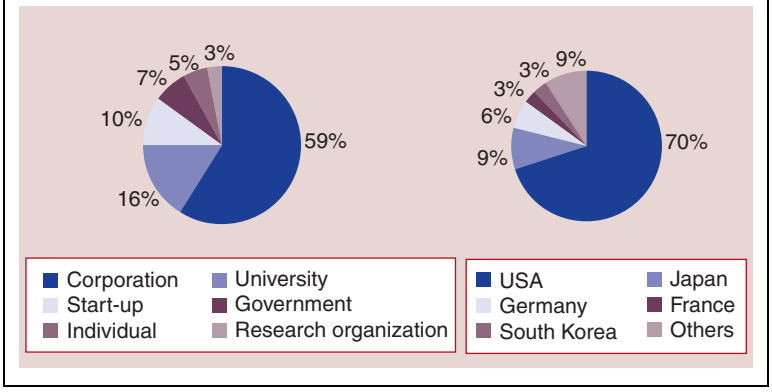
- At present, the agency lacks a dedicated examining group (so-called 'Technology Center' [TC]) to handle nanomedicine or nanotechnology applications. Although the formation of a separate TC may be premature, I suggest creating a working group or committee within each TC that identifies nanotechnology patent applications as they are filed, formulates examination guidelines, undertakes training of selected examiners and periodically meets with its counterparts from other TCs. This is especially critical because only a few examiners have experience in this rapidly evolving field. Because nanomedicine is interdisciplinary in nature, patent applications that are searched, examined and prosecuted in one TC could and should be examined more effectively via a coordinated review by more than one TC. In reality, there is no collective review and, as a result, applications continue to be examined differently within each TC. Obviously, such an approach does not provide a consistent and uniform examination of applications because examiners in different TCs may rely on case law, legal standards and prior art that may be somewhat unique to their own TC;

Figure 3. Maintaining US nanotechnology patents.



- Many nanomedicine patent applications may not receive adequate examination during prosecution because of the patent examiner's inability to locate applicable prior art, especially nonpatent prior art. Therefore, as discussed in detail earlier, it is accurate to conclude that patent examiners may sometimes be making decisions about the grant of a nanomedicine patent on limited information;
- The PTO continues to be understaffed in numerous TCs and it is plagued by high attrition. The agency's inability to attract and retain a talented pool of patent examiners is creating havoc. At hearings on Capitol Hill and in its annual reports, the PTO brass proudly touts hiring hundreds of new patent examiners each fiscal year to alleviate the backlog problem that is clogging the patent system. In fact, in this context, the Commissioner for Patents continues to highlight that the PTO will hire 1200 new patent examiners in the current fiscal year [65]. However, the PTO brass fails to focus on the critical issue of 'brain drain' resulting from an exodus of so many experienced patent examiners (and other senior-level executives). It would be wise for PTO upper management to focus on retaining more of its experienced employees and not putting all its efforts into hiring new ones. These attrition rates are likely to be further exacerbated by decreasing morale and generally poor work conditions. Moreover, many reports have highlighted the fact that the federal government is vulnerable to 'brain drain' both because baby boomers are retiring and because their potential replacements (most notably graduate students) do not view the government as their first choice of work [65]. According to many experts, patent examiners are underpaid (relative to US law firm salaries) and overworked (compared with their colleagues at the European Patent Office). They also have to review applications under unreasonable time pressures and skyrocketing patent pendency (discussed later). Arguably, the internal quality review process that monitors the quality of patents that have

Figure 4. Nanotechnology patent demographics.



been allowed by patent examiners is fraught with a general lack of legal and scientific expertise on the part of the reviewers;

- The PTO's funding problems are legendary. Congress's long-standing practice of 'diverting' PTO user fees collected from patent applicants to the general federal budget has always caused much consternation. Naturally, stopping this practice would alleviate some problems at the agency. In February 2007, a bill was signed by the President that allows the PTO to spend all its projected collected fees, thereby preventing funds from being diverted to other government programs. Hopefully, as a result of this law, the damaging drain on the agency's financial resources will finally come to an end. I also hope that the PTO will now temper its annual practice of hiking patent fees;
- Even today, with all the quality initiatives underway, examiners are still largely rewarded on the quantity of their work, not the quality. An antiquated quota system is in place. The patent examiner's production goals (quota) have not been adjusted in decades in spite of the increased complexity of patent applications filed, not to mention the substantial increase in the amount of prior art that the examiner has to search and analyze. Quality continues to take a back seat to quantity. Although, reading PTO annual reports or press releases would lead one to believe that all is perfectly well in this regard. According to recent PTO statistics, the allowance error rate has hovered around 4%. This could imply that the PTO's own conservative estimates indicate that thousands of US patents were 'wrongly' allowed [35];
- The PTO has failed to effectively engage outside legal or technology experts. Only a handful of experts from industry or academia have lectured on legal or technical issues unique to nanomedicine. This reluctance to use outside expertise has further added to the information deficit in nanomedicine. It is clear that the PTO lacks internal expertise in these matters and its isolationist policy only compounds the problem. Moreover, patent examiners are not required to have advanced degrees in science or engineering. Possessing advanced degrees or advanced training, by and large, goes unrecognized at the PTO;
- Few training modules or examination guidelines have been developed to educate patent examiners about the complexities and subtleties of nanomedicine. Similarly, no written guidelines specific to nanomedicine are available for patent practitioners.

Given all these challenges, it is hard to predict how these issues and challenges will play out with respect to nanomedicine patenting or commercialization. We will have to wait and see whether the nanomedicine industry thrives, like the information technology industry, or becomes burdened, like the radio patent deadlock [62].

Congress is continuing patent reform hearings in an effort to eliminate questionable patents as well as to provide adequate safeguards against abuses to the patent system. In fact, patent-reform bills are currently pending in both Houses of Congress. Similar measures in the past 2 years have failed as the information technology industry and big pharma battled over the finer points of the bills. However, it appears that the long-sought reform bill will finally be passed by Congress this year.

One of the proposals under serious consideration is a so-called 'post-grant review' of patent applications. However, I agree with some patent veterans that '[s]erious doubts exist whether a politically controlled PTO can guarantee the promise of the post-grant system that the patent community so desperately needs … [T]he patent community can hardly have confidence in a post-grant review system under the control of the PTO…' [110].

The nanotech patent onslaught tests the PTO

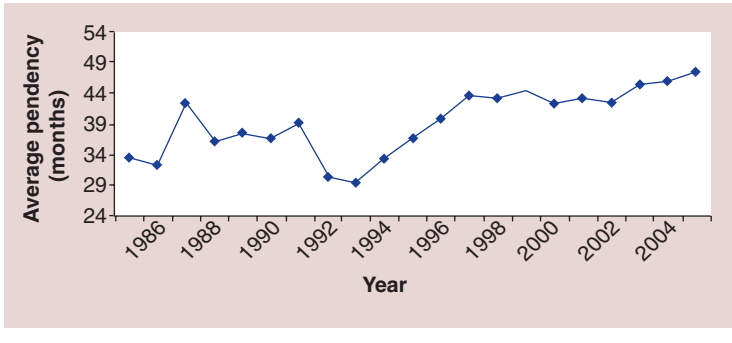
For the past decade or so, there has been a dramatic increase in the number of new nanotechnology patent applications filed and patents granted (Figures 1A & B), as well as an increase in published patent applications and scientific publications (Figure 1C). This information overload

has created numerous challenges for the PTO, an agency that traditionally struggles with this issue. Furthermore, this overburdened agency has yet to implement a solid plan to handle the enormous growth in nanotechnology patent applications filed. This has resulted in added time to review patent applications (i.e., an increase in patent pendency) and concerns about the validity and enforceability of numerous issued patents (reflects a decrease in patent quality).

The backlog of nanotechnology patent applications continues to build. A recent report puts the average nanotechnology patent pendency at 4 years (Figure 5) [15], a period that is simply too long for certain nanotechnologies that peak and are then obsolete in a few years. This excessive delay has serious business consequences, particularly for smaller companies and start-ups because these entities rely heavily on venture funds for their success. Therefore, it was no surprise that they recently confronted the Undersecretary of Commerce regarding the high patent pendency of their nanotechnology inventions. Surprisingly, the Undersecretary blamed the excessive delays on nanotechnology companies, accusing them of poaching nanotech-trained examiners *en masse* from the PTO [66]. I find the Undersecretary's argument an excuse for inefficiency and incompetence.

Furthermore, surprisingly broad patents in nanomedicine continue to be issued by the PTO [18,19,21,22,53,67]. Obviously, this is partly the result of court decisions in the past two decades that have made it easier to secure broad patents. During this period, laws have also tilted the table in favor of patent holders, no matter how broad or tenuous their claims. As a result, the PTO faces an uphill task as it attempts to handle the enormous backlog of applications filed. It also faces a torrent of improperly granted patents, many of which are likely to be 're-examined'.

Figure 5. Pendency of US nanotechnology patents.



In this climate of patent proliferation, it is inevitable that, in the near future, there will be an increase in litigation. Most patent practitioners regularly highlight one or more of the following problems while discussing nanomedicine patents:

- An improper rejection of a patent application due to an examiner's erroneous conclusion that the subject matter is not novel;
- Issuance of an 'overly broad' patent that infringes on previously issued patents and gives far too much control over a particular swath of basic technology, allowing the patentee to exclude competition unfairly. This result runs the risk of impeding future downstream innovations;
- Issuance of a patent in spite of existing prior art that was overlooked or not uncovered by the examiner during patent examination.

Naturally, any of the above results is unacceptable. Issuance of patents of poor quality, or too many invalid patents on early-stage research, is likely to cause enormous damage to commercialization efforts because it can result in one or more of the following:

- Suppressing market growth and innovation;
- Causing a loss of revenue, resources and time;
- Discouraging industry from conducting R&D and manufacturing;
- Inducing unnecessary licensing;
- Increasing the possibility of patent appeals and infringement lawsuits;
- Stifling high-quality inventions (introducing noise into investment, valuation and contracting decisions) and undermining the patent system itself;
- Eroding public trust vis-à-vis nanomedicine;

One patent expert summarizes the impact of poor-quality patents in economic terms [68]: "Questionable patents can harm competition and hinder innovation by forcing market participants to pay licensing royalties, incur substantial legal expense to defend against infringement claims, engage in design-around efforts that raise costs and/or hinder product performance … [A] patent holder can have real power even without being a true inventor because the systems for patent issuance and patent litigation are tilted in favor of patent applicants and patent holders. The result is that the patent system, while intended to promote innovation, instead places sand in the gears of our innovation engine."

Emerging nanomedicine patent thickets

Currently, there are too many players holding too many nanomedicine patents. This has created the current fragmented, messy patent landscape. Most experts agree that this patent landscape is already producing 'patent thickets' that have the potential of causing protracted legal battles. This is obviously an undesirable result and could easily freeze nanomedicine development in its tracks. Patent thickets pose the biggest threat to commercialization efforts in nanomedicine.

Patent thickets are defined broadly in academic discourse as 'a dense web of overlapping IP rights that a company must hack its way through in order to actually commercialize new technology' [69]. Such patent thickets, a result of multiple blocking patents, naturally discourage and stifle innovation [69]. Claims in such patent thickets have been characterized as broad, overlapping and conflicting. Therefore, business planners and patent practitioners should steer company researchers away from such potential patent thickets. They may also need to analyze the patent landscape to gauge 'white space' opportunities (i.e., no overlapping patents) prior to R&D efforts, patent filing or commercialization activities (Figure 6). Classically, such an analysis into the number and quality of patents issued in a particular sector of nanomedicine can highlight a particular technology trend, areas of high/low commercialization potential and areas that indicate a high risk of market entry.

According to a widely circulated market study published in 2005 [111], nanoscience researchers around the world are steadily filing patents with the hope of creating 'toll booths' that could slow down future product development. Because there has been an explosion of overlapping and broad patent filing on nanomaterials, it is probable that the companies that want to use these building blocks in products will be forced to license patents from many different players to implement their inventions. The report focused on five fundamental nanomaterials that are platforms for numerous current and future nanomedicine applications: carbon nanotubes, dendrimers, fullerenes, nanowires and quantum dots. The study identified carbon nanotubes and quantum dots as of particular concern. The study noted that, although fullerenes and nanowires are relatively free of overlapping patent claims, the other categories are attracting patent applications quickly. For example, the study found that a large number of patent claims for dendrimers have been assigned to recently acquired Dendritic NanoTechnologies, Inc. (Mount Pleasant, MI, USA). It also noted that quantum dot patent claims tend to cover the materials themselves rather than specific applications and that the patent situation for using carbon nanotubes in electronics looks 'messy'. Although some dominant or pioneering patents on carbon nanotubes will expire in the near future, a classic patent thicket seems to be developing in the area of single-walled carbon nanotubes [13], where companies such as IBM (White Plains, NY, USA), NEC Corporation (Tokyo, Japan) and Carbon Nanotechnologies, Inc. (Houston, TX, USA) are likely to stake out their claims aggressively.

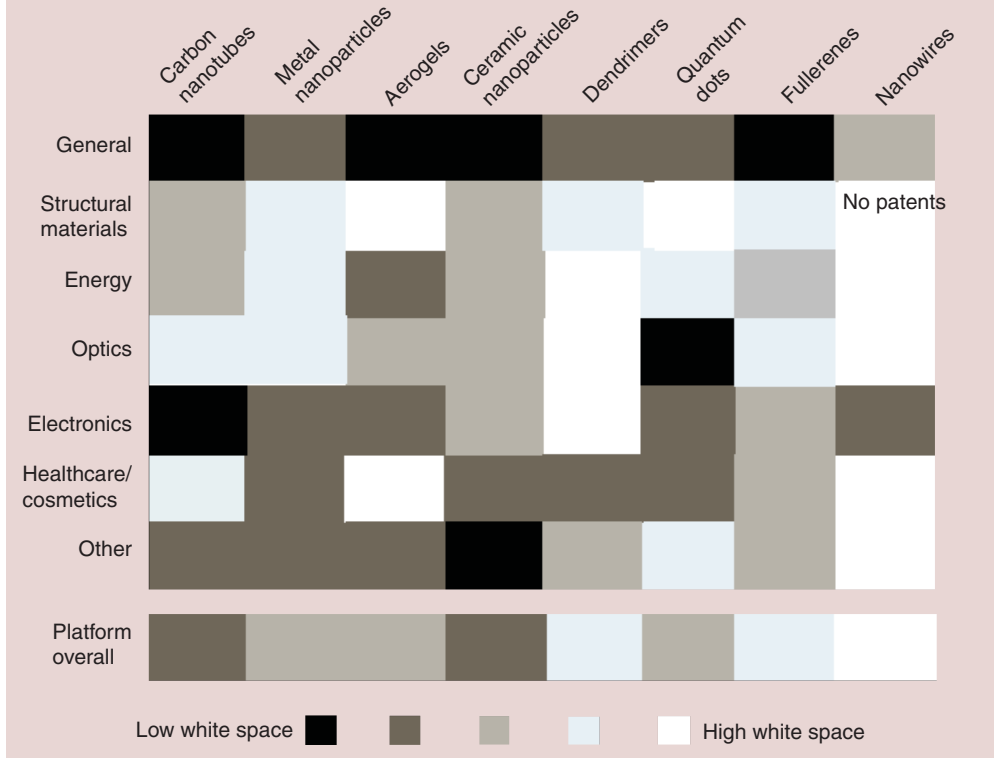
To analyze the perceived patent thicket in any nanomedicine-related technology, a detailed legal review of the claim set from the patents in the thicket may be necessary before decisions regarding patent filings or substantial investment on commercialization are undertaken.

Upcoming nanomedicine patent battles

At least in the US, patent grants in nanotechnology and nanomedicine-related inventions are likely to continue at a pace that is almost synchronous with funding. The aggressive mentality described above has not only produced overlapping patents, but a race to patent anything 'nano' has resulted in a flood of exceedingly broad upstream nanopatents. Although broad patents are generally awarded for pioneering inventions, they should never be allowed if prior art exists. Experts fear that nanomedicine's constantly growing patent estate may actually retard innovation because of uncertainty over who is infringing on whose patent. The PTO is often directly blamed for awarding numerous erroneous nanotechnology patents.

Clearly, this proliferation of unduly broad patents and the resulting patent thickets will require litigation to sort out, especially if sectors of nanomedicine become financially lucrative [67]. At the present time, it seems that nanomedicine companies are avoiding costly court battles. In fact, there is hardly any nanomedicine (or nanotechnology) patent litigation underway in the USA. Companies sometimes avoid costly litigation to prevent exposing their own patents, some of which may be based on a cursory review at the PTO whose validity may be questionable. In any case, I believe that expensive litigation is as inevitable as it was with the biotechnology industry, in which extensive patent litigation resulted once products became commercially successful. The reason for this is simple: at this stage, royalties may be collected from potential infringers.

Figure 6. US patent landscape analysis according to nanomaterial platform.



When this comes about, in most patent battles, the larger entity with the deeper pockets will prevail, even if the brightest innovative stars are on the other side. This situation is all too familiar to business leaders. It leads to higher costs to consumers (if and when products are commercialized), while impeding the innovation process itself [60].

Ultimately, companies introducing new products to the market will face considerable uncertainty regarding the validity of broad and potentially overlapping patents held by others. The ongoing land grab will definitely worsen the problem for companies striving to develop commercially viable products. In fact, nanomedicine start-ups may soon find themselves in patent disputes with large, established companies, as well as among themselves. Start-ups may also become attractive acquisitions for larger companies because takeover is generally a cost-effective alternative to litigation.

It is possible that companies may need to acquire costly licenses for patents from other companies in order to establish themselves. It is also possible that companies may use their patents to exclude rather than license out. Furthermore, those who do license may do so at an unreasonably high cost. However, I hope that none of these scenarios will come about. Instead, I hope that a more harmonious atmosphere will prevail where cross-licensing agreements by start-ups and large corporations alike will become the norm. In my view, liberal patent licensing is another particularly effective strategy to maneuver through the patent thicket at this stage in the development of nanomedicine, especially because the enforceability of so many patents is questionable. It should be noted, however, that when the total number of owners of conflicting IP is relatively small, cross-licensing has been the answer. But when the number of owners of conflicting IP is relatively large, the transaction costs of cross-licensing may be too great for it to be effective. Also, critics consider cross-licensing as a settlement of a patent dispute that may not serve the public interest since cross-licensing (as compared with litigation) limits competition when it is between competitors.

Navigating the nanopatent thicket

Following are additional proposals that may cut through the nanomedicine patent gridlock and prevent widespread and wasteful litigation.

Formation of patent pools

The multiple-party patent thicket problem may be solved by the cooperative formation of 'patent pools' by technologically competing entities. Patent pools are defined as legally permissible cooperative agreements whereby the members of the pool have access to the patents of the entire pool in exchange for a set price. However, it is uncertain at this stage whether patent pools will be a lawful, desirable or beneficial answer to the patent thicket problem.

Government actions to encourage nonexclusive licensing

Some patent practitioners have also suggested that the government must step in and use its existing authority under the Bayh–Dole Act to encourage non-exclusive licensing of foundational nanotechnology patents [62]. Under the Bayh–Dole Act of 1980, universities and small business entities may retain patent ownership rights if the research was funded by the US government. The government retains a royalty-free license to any patented technology that is generated as a result of such funding. Naturally, the Bayh–Dole Act will assist nanomedicine-related companies in the same way it helped biotechnology start-ups – by promoting the transfer of university-owned patents funded by government grants to the private sector, especially since academia has become increasingly aggressive in patenting its nanomedicine-related research.

Other government action

Government action, such as the imposition of compulsory licensing of upstream and/or foundational patents that have been financed by public funds, may assist in breaking up dominant patent monopolies [62]. Enforcement of antitrust and unfair competition laws by the government may encourage more cooperation between the various players and stimulate active cross-licensing and patent pooling.

There are, of course, other strategies available to prevent or navigate patent entanglements, both before and after a nanomedicine patent issues [18,53]. Companies could also focus on trade secrets as a supplement to nanomedicine patents. Finally, a greater willingness on the part of the patent applicant to provide relevant prior art, particularly nonpatent prior art, would be helpful to the patent examiner during examination.

Conclusion

Securing valid and defensible patent protection is critical to nanomedicine commercialization efforts. Although early forecasts for commercialization are promising, the emerging patent thicket in this arena of nanotech could be a major stumbling block. Therefore, it is almost certain that the enforceability of numerous US nanomedicine patents (similar to e-commerce patents previously) will be a major problem in the future. Furthermore, due to the substantial annual increase in costs associated with maintaining and enforcing issued patents, enforceability may be a problem when the patent holder lacks the resources to maintain the patent, or enforce the patent against potential infringers.

The PTO continues to be under enormous strain and scrutiny. Reforms are urgently needed to address issues ranging from poor patent quality and questionable examination practices to inadequate search capabilities, rising attrition and an enormous patent backlog. Numerous government and nongovernment entities have recently become more vocal in their criticism of the PTO [70–73]. They have produced authoritative reports with detailed recommendations regarding overhauling the PTO and the US patent system [70–73].

Reforms are urgently needed at the PTO in order to restore the delicate balance between innovation and competition. Without these reforms, the cursory patent examination that is currently in place, coupled with patent proliferation and patent pendency that is fast approaching one million, will result in the issuance of too many invalid and unenforceable nanomedicine patents. This will continue to generate a crowded, entangled patent landscape with few open-space opportunities for commercialization. For many companies, navigating this minefield will be an unattractive option.

Ownership of technology in the form of patents is one thing, deriving sufficient economic value therefrom is another. Obtaining undeserving patents and profiting by threatening litigation, rather than providing beneficial nanomedicine products, runs counter to the foundations of our patent system. Therefore, if the current dense patent landscape becomes more entangled and the patent thicket problem worsens, it will be the major bottleneck to viable commercialization [74,75], negatively impacting the entire nanomedicine 'revolution'. For investors, competing in this high-stakes patent game may prove too costly.

Future perspective: the promise of nanomedicine

The potential future impact of nanomedicine on society could be huge. Nanomedicine could drastically improve a patient's quality of life, reduce societal and economic costs associated with healthcare, offer early detection of pathological conditions, reduce the severity of therapy and result in an improved clinical outcome for the patient. Nanomedicine is, in a broad sense, the application of nanoscale technologies to the practice of medicine, namely, for diagnosis, prevention and treatment of disease and to gain an increased understanding of complex underlying disease mechanisms. The creation of nanodevices such as nanobots capable of performing real-time therapeutic functions *in vivo* is one eventual long-term goal here. Advances in delivering nanotherapies, miniaturization of analytic tools, improved computational and memory capabilities and developments in remote communications are likely to be integrated. These efforts will cross new frontiers to the understanding and practice of medicine. The ultimate goal is obviously comprehensive monitoring, repair and improvement of all human biologic systems – basically, an enhanced quality of life.

In fact, the nanopharma market is expected to significantly grow in the coming years. Analysts project that by next year, the market for nanobiotechnology will exceed US$3 billion, reflecting an annual growth rate of 28% [76]. According to another recent report, the US demand for nanotechnology-related medical products (nanomedicines, nanodiagnostics, nanodevices and nanotech-based medical supplies) will increase over 17% per year to US$53 billion in 2011 and US$110 billion in 2016 [77]. This report predicts that the greatest short-term impact of nanomedicine will be in therapies and diagnostics for cancer and CNS disorders.

I predict that in the coming years, significant research will be undertaken in the following areas of nanomedicine, generating both evolutionary as well as revolutionary products [78]:

- Synthesis and use of novel nanomaterials and nanostructures (e.g., less antigenic);
- Biomimetic nanostructures (synthetic products developed from an understanding of natural or biological systems);
- Nanoanalytic tools, methods and instruments for studying single or multisubunit biomolecules or individual diseased cells (e.g., combining biochemical techniques with advanced imaging and spectroscopy to provide insights into the behavior of single diseased cells and their surrounding micro-environment, leading to personalized therapy);
- Devices and nanosensors for early point-of-care detection of diseases and pathogens (e.g., *in vitro* diagnostics such as molecular pathology or reading highly-integrated ultrasensitive biochips via devices that rely upon the polymerase chain reaction coupled with micro/nano fluidics);
- Identification and quantification of novel or disease-related biologic biomarkers/targets/receptors/ligands for imaging, diagnosis and therapy (e.g., for advising patients of the increased risks of certain cancers, neurodegenerative diseases and cardiovascular diseases, thereby providing an avenue for personalized prevention regimens);
- Construction of smart multifunctional biologic nanostructures, devices, implants and systems that combine/integrate diagnosis, targeted site-specific drug delivery and imaging (combined imaging and biochemical assays will allow tracing the drug path, following therapy progress after activation at a specific site as well as follow-up monitoring of the tissue site/patient after the acute therapy is completed);
- Nanotechnology for tissue engineering (nanostructured scaffolds) and regenerative medicine;
- Nano-imaging or molecular imaging via fabrication of noninvasive *in vivo* analytic nanotools with improved sensitivity and resolution for molecular imaging and for studying pathologic processes *in vivo* (main benefits include early detection of disease as well as monitoring of various disease stages);
- Nanodevices that will be able to cross biological barriers (e.g., to deliver active agents to the brain cancer cells by crossing the generally impenetrable blood–brain barrier);
- Miniaturizing of devices for reduced invasiveness, coupled with surface modification or 'fictionalization' to render the device more 'biologic', offers enhanced accuracy and therapeutic potential;
- *In vivo* nanosensors incorporated into stimuli-sensitive devices (e.g., in catheters) could provide data on physiological status and identify pathology/defects that could enhance patient outcome.

Drug delivery is one sector of nanomedicine where development is progressing more rapidly [41,45–49,76]. In fact, this arena of nanomedicine is already producing significant results. I list below

some examples of innovative products that I envision in the drug-delivery arena that cleverly integrate biological, information and material sciences. Some of these products could be available in the next 5–7 years, while others lie on the distant horizon. Nanotech-based drug delivery may involve:

- Miniaturized nanofluidic devices and systems that more efficiently transport fluids to the site of delivery, preventing turbulence and mixing (because fluids move with laminar flow through micro/nanochannels);
- More efficient site-specific or precision targeting via nanomedicines (functionalized nanoparticles or nanoencapusulated/nanocoated drugs) with reduced systemic side effects and better patient compliance;
- Close-looped drug-delivery nanodevices and implants (also known as 'smart pills') containing sensors (to monitor biomolecules) and drug reservoirs (for precise delivery) located on the same chip;
- Microsurgical devices, molecular motors or nanobots (could be manmade or be engineered microbes) that are capable of navigating throughout the body to carry out targeted healing, such as repairing damaged tissues, destroying tumors or viruses and even performing gene therapy or vaccination.

Funding & disclosure

There is no conflict of interest reported by the author of this manuscript. This report reflects the current views of the author, which are likely to evolve. Furthermore, they should not be attributed, in whole or in part, to the organizations with which he is affiliated, nor should they be considered as expressing an opinion with regard to the merits of any particular company or product discussed herein. Nothing contained herein is to be considered as the rendering of legal advice. This paper primarily focuses on US patents and the US patent system.

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Executive summary

- Big pharma's business model, which relies on a few blockbusters to generate enormous profits, is clearly broken. Patent expiration on several blockbusters in recent years is already altering the drug landscape. Additionally, numerous market forces are dictating that new R&D approaches be developed and implemented so that drug companies can continue to discover and fill the pipeline with novel compounds (or develop reformulations of older compounds). Some of these strategies revolve around nanotechnology and miniaturization. In fact, nanomedicine is already having an enormous impact in this regard.
- Securing valid and defensible patent protection is critical to the nanomedicine 'revolution'. Although early forecasts for nanomedicine commercialization are encouraging, there are bottlenecks, including emerging thickets of patent claims.
- The US National Nanotechnology Initiative's widely-cited definition of nanotechnology is irrelevant and confusing from a nanomedicine perspective. It is also the cause of the inadequate patent classification system that was recently developed by the US Patent and Trademark Office (PTO).
- The burgeoning number of new nanomedicine patent applications filed at the PTO, coupled with the continued issuance of surprisingly broad patents, is creating a chaotic, tangled patent landscape where competing players are unsure as to the validity and enforceability of numerous issued patents. If this trend continues, it could stifle competition and limit access to some inventions.
- The PTO continues to be under enormous strain and scrutiny. Reforms are urgently needed to address issues ranging from poor patent quality and questionable examination practices to inadequate search capabilities, rising patent examiner attrition and a soaring patent backlog.
- Many critical patent issues and scenarios will take center stage in the near future and impact nanomedicine commercialization: formation of patent pools, cross-licensing activity, patent litigation, Congress's effort at reforming the US patent system, the Bayh-Dole Act of 1980 and the Supreme Court's increased scrutiny and interest in patent law.
- A robust patent system will aid nanomedicine companies that are striving to develop commercially viable products. Valid patents stimulate market growth and innovation, generate revenue, prevent unnecessary licensing and greatly reduce infringement lawsuits.
- Nanomedicine is here to stay and will generate both evolutionary as well as revolutionary products in the future. Currently, there are a few innovative nanomedicine products on the market that cleverly integrate biological, information and material sciences. Many more potential applications are under consideration.

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