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Emerging Issues in Nanomedicine and Ethics

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1. Introduction

The high-risk, high-payoff global nanotechnology phenomenon is in full swing. Significant technologic advances intersecting engineering, biotechnology, medicine, physical sciences and information technology are spurring new directions in research, education, commercialization and technology transfer. Clearly, nanotechnology will continue along this interdisciplinary path.

There is enormous excitement and expectation regarding nanotechnology's potential impact on every aspect of society. Although early forecasts for commercialization efforts are encouraging, there are bottlenecks as well. Some formidable challenges include legal, environmental, safety, ethical and regulatory questions as well as emerging thickets of overlapping patent claims.[1,2] In fact, patent systems are under great scrutiny and strain, with patent offices around the world continuing to struggle with evaluating the swarm of nanotech-related patent applications. Adding to this confusion is the fact that the US National Nanotechnology Initiative's (NNI) widely-cited definition of nanotechnology is inaccurate and irrelevant, especially in reference to nanomedicine (see §2). 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.[3] International rivalries are growing.[4] Political alliances are forming and battle lines are being drawn.

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[1] The emerging thicket of patent claims has primarily resulted from patent proliferation but also because of the continued issuance of surprisingly broad patents by the US Patent and Trademark Office (PTO). This is creating a chaotic, tangled patent landscape in various sectors of nanotechnology where the competing players are unsure as to the validity and enforceability of numerous issued patents. If this trend continues, it could stifle competition, limit access to some inventions and cause commercialization efforts in certain sectors of nanotechnology to simply grind to a halt. Therefore, if the full potential of the nanotechnology "revolution" is to be fully realized, certain 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. All players involved in nanotechnology agree that a robust patent system is essential for stimulating the development of commercially viable products.

[2] Bawa R: Patents and nanomedicine. *Nanomedicine* 2(3), 351-374 (2007). Also refer to DL Harris and J Miller's essay in this volume.

[3] The passage of the 21st Century Nanotechnology Research and Development Act (Pub. L. No. 108-153) in 2003, which authorized 3.7 billion US dollars in federal funding from 2005 through 2008 for the support of nanotechnology R&D, is fueling the fervor over nanotechnology in the US. This legislation has resulted in the creation of R&D centers in academia and government. At present, there are over 50 institutes and centers dedicated to nanotechnology R&D. For example, the NSF has established the National Nanotechnology Infrastructure Network—composed of university sites that form an integrated, nationwide system of user facilities to support research and education in nanoscale science, engineering and technology. Similarly, there are currently numerous government agencies with R&D budgets dedicated to nanotechnology.

The 21st Century Nanotechnology Research and Development Act addresses nanoethics at length. As a result, the NNI strategic plan identifies ethics as a key research area and divides "the responsible development of

Some of the greatest impacts of nanotechnology are taking place in the context of biology, biotechnology and medicine. This arena of nanotechnology is generally referred to as nanomedicine, and sometimes broadly called bionanotechnology.[5] Already, there are a few nanomedicine-related products on the market[6] with numerous other potential applications under consideration and development.[7] But will nanomedicine provide valuable contributions to medicine and healthcare in the long run? It is hard to predict whether nanomedicine will deliver a variety of mostly incremental improvements of existing technologies or whether it will act as a catalyst for a vast technological and healthcare revolution. While exciting in its own right, clearly, the present day status of nanomedicine is only a milestone on the road to introducing truly innovative technologies. These will come about only over a period measured in decades, given the complexity of clinical trials and the hesitancy with which radical technologies are considered and adopted by the public.

However, there are a few bright spots where development is progressing more rapidly. In this essay we will emphasize one such area of nanomedicine that is already producing significant results – drug delivery.[8] Drug delivery accounts for 78% of global sales in nanomedicine and 58% of patent filings worldwide.[9] For example, site-specific targeted drug delivery systems, with their potential to address unmet medical needs and personalized medicine (a result of advances in pharmacogenetics and pharmacogenomics) are on the horizon. Other more futuristic targeted drug delivery approaches involve "nanofactories" where biological molecules found *in vivo* can be converted into active biotherapeutics in response to a localized medical condition.

Numerous nanotechnology market reports are available, each varying widely in their statistics and conclusions.[10] For example, the National Science Foundation (NSF) claims that by 2015 the annual global market for nano-related goods and services will top 1 trillion US dollars. On the other hand, Lux Research, Inc. predicts that by 2014, 2.6 trillion US dollars in global manufactured goods may incorporate nanotechnology (about 15% of total output).[11] It has been

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nanotechnology" into two classes, namely (i) environmental, health and safety (EHS) implications; and (ii) ethical, legal and other societal implications.

[4] Edwards SA: *The Nanotech Pioneers - Where Are They Taking US?* Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany (2006).

Van Lente MA: Building the new world of nanotechnology. *Case W. Res. J. Int. Law* 38(1), 173-215 (2006).

[5] Vo-Dinh T: *Nanotechnology in biology and medicine – methods, devices, and applications.* CRC Press, Boca Raton, Florida (2007).

Niemeyer CM, Mirkin CA: *Nanobiotechnology – concepts, applications and perspectives.* Wiley-VCH Verlag Gmbh & Co. Weinheim, Germany (2004).

[6] The FDA has approved around a dozen nanotech-related products, both drugs (Rapamune, Doxil, Estrasorb, Amend, TriCor, Abraxane, Megase ES) and medical devices (NanOss, Vitoss, TiMesh).

[7] Vo-Dinh T (2007); Niemeyer CM, Mirkin CA (2004); Kubik T, Bogunia-Kubik K, Sugisaka M: Nanotechnology on duty in medical applications. *Curr Pharm Biotechnol* 6, 17–33 (2005).

[8] Thassu D, Deleers M, Pathak Y: *Nanoparticulate Drug Delivery Systems (2nd Edition).* Informa Healthcare USA, Inc., New York, NY, USA (2007)

[9] Wagner V, Dullaart A, Bock A, Zweck A: The emerging nanomedicine landscape. *Nature Biotechnology* 24, 1211–1217 (2006).

[10] In our view, the data reflected in these reports may not always be completely reliable. Poor assumptions often underlie the analyses, rendering the results highly questionable or largely irrelevant. Therefore, these reports should be taken as indicating general trends rather than reflecting solid figures.

[11] Report. *Sizing Nanotechnology's Value Chain,* Lux Research, Inc., New York (2004).

reported that governments, corporations and venture capitalists in 2006 spent 12.4 billion US dollars on nanotechnology R&D globally, up 13% from 2005.[12] In fact, in the past few years, global spending on nanotech products has far surpassed that spent on nanotechnology R&D. In 2006, global government spending grew to 6.4 billion US dollars, up 19% from 2005. One widely-cited market report noted that in 2005, nanotechnology was incorporated into more than 30 billion US dollars worth of manufactured goods.[13] A recent study claims that presently there are around 500 nanotech-based consumer products in the marketplace.[14] Once again, it should be emphasized that most such market reports rely on the flawed NNI definition of nanotechnology to draw their conclusions (See § 2).

Yet, despite all of this research and development in nanotechnology, federal funding (through the NNI) related to the research and educational programs on nanoethics have clearly lagged behind.[15] Some ethical issues pertaining to nanomedicine have been recently addressed by a few authors, including those who have articulated ways in which nanomedicine might change the health care system[16] and the needs in terms of policy, funding and scholarship that would ensure the ethical advance of nanomedicine.[17] It is critical that ethical, social and regulatory aspects of nanomedicine be proactively addressed so as to minimize public backlash similar to that seen with genetically-modified foods in Europe.[18] The public and other stakeholders should be properly educated regarding the benefits as well as the risks of nanomedicines. In this regard, taking an integrated approach to implications and commercial applications is essential for greater public acceptance and support.

This essay will outline many of the current trends, emerging issues and ethical questions related to nanomedicine. First, clarification about the definition of nanotechnology and nanomedicine will help set the stage for discussions about the nanomedicine industry, the ethical issues at stake with these technologies and an assessment of the future for nanomedicine.

2. Current Definitions of Nanotechnology and Nanomedicine

One of the problems facing nanotechnology is the confusion, hype and disagreement among experts about its definition.[19] 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.

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[12] Reisch MS: Nano goes big time. *Chemical & Engineering News* 85(4), 22-25 (2007).
[13] Report. *The Nanotech Report* (4th Edition). Lux Research, Inc., New York (2006).
[14] A nanotechnology consumer products inventory. http://www.nanotechproject.org/index.php?id=44
[15] Cameron NM de S: The NELSI imperative: nano ethics, legal and social issues, and federal policy development. *Nanotechnology Law & Business* 3(2), 159-166 (2006).
Berube D: *Nano-hype: The Truth behind the nanotechnology Buzz*, Prometheus Books (2006).
Also see, National Nanotechnology Initiative. Supplement to the President's FY 2007 budget www.nano.gov/NNI_07Budget.pdf
[16] Best R, Khushf G: The social conditions for nanomedicine: disruption, systems, and lock-in. *J. Law Med. Ethics* 34(4), 733-740 (2006).
[17] Johnson S, McGee G: Nanotechnologies in healthcare: a needs assessment regarding ethics and policy in nanomedicine. *Harvard Health Policy Review* (2007) *(in press)*
[18] Mills K, Fleddermann C: Getting the best from nanotechnology: approaching social and ethical issues openly and proactively. *IEEE Tech. Society Mag. Winter* 24(4), 18–26 (2005).
[19] Bawa R: (2007); Editors: Nanotechnology. *Nature Nanotechnology* 1(1), 8-10 (2006).

One of the most quoted definitions of nanotechnology is the definition used by the NNI[20]: "[n]anotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications." Clearly, this definition excludes numerous devices and materials of micrometer dimensions, a scale that is included within the definition of nanotechnology by many nanoscientists.[21]

Moreover, nanotechnology and nanoproducts are not new. For example, rubber tires have been reinforced for more than a century via incorporation of carbon nanoparticles ("high-tech soot nanoparticles"). Numerous nanoparticles exist in nature (e.g., volcanic ash, viruses, biomolecules, etc.) or are the result of human activity (e.g., diesel exhaust particles and smoke). Given this confusion, a more practical definition of nanotechnology that is unconstrained by any arbitrary size limitation has been recently proposed[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. Hence, the size limitation imposed in NNI's definition should be dropped, especially when it is applied to nanomedicine. Also, an internationally-acceptable definition and nomenclature of nanotechnology should be promptly developed.

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 about which persons can engage in ethical discourse. Definitional murkiness for both nanotechnology and nanomedicine, then, 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. If, for example, nanotechnologies applied to medicine really are not something new at all, it would seem reasonable to conclude that it would not present any new or unique ethical issues to be discussed. In fact, some do argue that there is nothing ethically novel about nanotechnology.[23] [24] [25] These observers dismiss that nanotechnology (and nanomedicine) will generate truly novel

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[20] What is Nanotechnology? The National Nanotechnology Initiative. http://www.nano.gov/html/facts/whatIsNano.html

[21] Bawa R: Nanotechnology patenting in the US. *Nanotechnology Law & Business* 1, 31-50 (2004).
Bawa R, Bawa SR, Maebius SB, Iyer C: Bionanotechnology patents: challenges and opportunities. *In: The Biomedical Engineering Handbook (3rd edition)*. Bronzino JD (Ed.), CRC Press, Boca Raton, Florida; 29-1 to 29-16 (2006).
Bawa R: (2007).

[22] Bawa R, Bawa SR, Maebius SB, Flynn T, Wei C. Protecting new ideas and inventions in nanomedicine with patents. *Nanomedicine: Nanotechnology, Biology and Medicine* 1(2), 150-158 (2005).

[23] Litton P: Nanoethics: what's new? *Hastings Center Report* 37, 22-25 (2007).

[24] Lewenstein BV: What counts as a 'social and ethical issue' in nanotechnology? *Hyle Int. J. for Philosophy Chem.* 5, 5-18 (2005).

[25] Grunwald A: Nanotechnology – a new field of ethical inquiry? *Sci. Eng. Ethics* 11, 187–201 (2005).

ethical and social issues. Instead, they feel that nanotechnologies simply raise the same standard issues of research ethics, privacy and confidentiality at stake in all other kinds of medical research and development. While this may be true to a large extent, nanoethics may be viewed as a convergence of many areas of ethics – it adds a new dimension to current ethical debates.[26]

It is our view that while many of the ethical issues in nanomedicine may be recurring themes in bioethics, there may be ways in which nanomedicine sheds new light on old issues or asks the old ethical questions in slightly new ways. For example, the highly interdisciplinary nature of nanomedicine means that engineers, biologists, physicists and others will be working on developing and implementing these technologies. The ethical codes and frameworks (and the emphases on certain ethical values such as efficiency or utility) differ slightly from profession to profession. This means that the ethics of nanomedicine may have a slightly different set of core moral values or considerations than traditional medical applications due to the influence of other ethical frameworks and perspectives on the research and development of these interventions.

3. The Pharmaceutical Industry's Role in Nanomedicine

The pharmaceutical industry depends upon innovation, both for profitability and for developing superior therapies. In today's global economy, the industry faces enormous pressure to deliver high-quality products to the consumer while maintaining profitability. US drug companies must constantly reassess how to improve the success rate of new chemicals entities (NCEs) while reducing research and development (R&D) costs as well as cycle time for producing new drugs, especially new blockbusters. In fact, the cost of developing and launching a new drug to the market, although widely variable[27], may be upwards of 800 million US dollars. Typically, the drug appears on the market some 10 to 15 years after discovery.[28] Furthermore, for every 8,000 compounds screened for potential drug development, only one makes it to final clinical use[29] and only one out of five lead compounds makes it to final clinical use.[30] Annual R&D investment by drug companies has risen from one billion US dollars in 1975 to 40 billion in 2003, while NCE approvals have essentially remained flat – between 20-30 drugs per year.[31] 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.[32] 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 an international problem as the decreasing numbers of new drugs approved by the US Food and Drug Administration (FDA) and foreign drug agencies continues to haunt the

[26] Allhoff F, Lin P: What's so special about nanotechnology and nanoethics? *Int. J. App. Philosolphy* 20(2), 179-190 (2006).
[27] DiMasi J, Hansen R, Grabowski H: The price of innovation: new estimates of drug development costs. *Journal of Health Econ*omics 22, 151–185 (2003).
Adams C, Brantner V: Estimating the cost of new drug development: is it really $802m? *Health Affairs* 25(2), 420–28 (2006).
[28] Anon R: Health Informatics into the 21st Century. *HealthCare Reports*. Reuters Business Insight February (1999).
[29] Breen P: It's all nano nano. *Pharma* 3(2), 22-25 (2007).
[30] Erickson J: Translation research and drug development. *Science* 312, 997 (2006).
[31] Sussman NL, Kelly JH: Saving time and money in drug discovery – a pre-emptive approach. In: *Business Briefings: Future Drug Discovery 2003*. Business Briefings Ltd, London, UK, 46–49 (2003).
[32] Breen P (2007)

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 and pressures as well. One of the most significant issues relates to an increase in the global generics' share of the prescription drug market. International competition from low-cost centers like India, China and Eastern Europe (especially generic competition, clinical trials and manufacturing), forced or voluntary withdrawal of several drugs, and expiration of patents on blockbusters are other issues that are impacting big pharma.

Nanotechnology not only offers the potential to address some of these challenging issues but it can also provide significant value to pharma portfolios. Nanotechnology can enhance the drug discovery process via miniaturization, automation, speed and the reliability of assays. It will also result in reducing the cost of drug discovery, design and development and will result in the faster introduction of new cost-effective products to the market. For example, nanotechnology can be applied to current microarray technologies, exponentially increasing the hit rate for promising compounds that can be screened for each target in the pipeline. Inexpensive and higher throughput DNA sequencers based on nanotechnology can reduce the time for both drug discovery and diagnostics. It's clear that nanotechnology-related advances represent a great opportunity for the drug industry as a whole.

In fact, the nano-pharma market is expected to significantly grow in the coming years. Analysts project that by 2014, the market for pharmaceutical applications of nanotechnology will be around 18 billion US dollars per year.[33] According to a 2007 report, the US demand for nanotechnology-related medical products (nanomedicines, nanodiagnostics, nanodevices and nanotech-based medical supplies) will increase over 17% per year to 53 billion US dollars in 2011 and $110 billion in 2016.[34] This report predicts that the greatest short-term impact of nanomedicine will be in therapies and diagnostics for cancer[35] and central nervous system disorders.

In light of all this pressure for profitability, speed and efficacy, some raise the possibility of questionable ethical and safety practices among nanomedicine companies. They worry that the hype will obscure the ethical issues and larger social, legal and environmental implications of their research. Therefore, researchers, policymakers and businesses must take the time to consider the upstream and downstream ethical implications of their research agendas. The key time to think about ethical questions is not after the technology has been developed and adopted, but before R&D efforts even begin. Ethical considerations about priority setting and whether or not a technology should be used by society must take place before the technology is developed. Once the product is on the market, it is difficult to put the genie back in the bottle, particularly if market forces dictate otherwise.

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[33] Hunt W. Nanomaterials: nomenclature, novelty, and necessity. *Journal of Materials* October 2004. http://www.tms.org/pubs/journals/JOM/0410/Hunt-0410.html

[34] Report. *Nanotechnology in Healthcare.* The Freedonia Group, Inc. Cleveland, Ohio (2007).

[35] The National Cancer Institute (NCI) is funding a multi-million dollar cancer initiative to create centers of cancer nanotechnology. Several nanomedicine-based treatments for cancer are either approved or are pending approval by the FDA. Also see, Service R: Nanotechnology takes aim at cancer. *Science* 310, 1132–1134 (2005), and Gordon E, Hall F: Nanotechnology blooms, at last. *Oncol Rep* 13, 1003–1007 (2005).

The safety and risk issues of nanomedicine should be extensively assessed at the preclinical phase (*in vivo* animal experiments and *ex vivo* laboratory analyses) and clinical testing phase (human subject exposure). The risks of nanomaterials depends upon numerous factors, including size, shape, route of exposure and chemical reactivity of the components (See § 5). Since nanomaterials are a poorly-studied, chemically diverse class of compounds, they may behave differently or exhibit unpredictable toxicity in the host. Therefore, it is ethically essential that researchers inform potential research subjects in clinical trials of all details pertaining to the study (i.e., purpose, experiments, risks/benefits, alternatives, confidentiality protection, etc.).[36] Furthermore, when the clinical trials involve novel nanomaterials whose physiochemical properties are poorly studied, potential research subjects should be informed that unpredictable risks may arise during the trials.[37] It is critical that the research risks be clearly communicated to the subjects.[38] In fact, to gain and maintain public support for nanomedicine generally, an honest and open discussion with the public regarding the ethical and social issues surrounding nanomedicine should be promptly undertaken.[39]

4. The Promise of Nanomedicine

Nanotechnology promises to transform most industries and will have a particularly profound impact on health care and medicine. The future impact of nanomedicine on society could be huge. Specifically, nanomedicine will drastically improve the 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 improved clinical outcome for the patient. We expect that, in the coming years, significant research will be undertaken in various areas of nanomedicine – generating both evolutionary and revolutionary products.[40]

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 goal here. Advances in delivering nanotherapies, miniaturization of analytic tools, improved computational and memory capabilities and developments in remote communications will 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 – an enhanced quality of life.

Yet, nanomedicine is not a single class of medical interventions that easily can be analyzed from an ethical perspective. Nanomedicine will likely resurrect old questions about

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[36] Donaldson K: Resolving the nanoparticles paradox. *Nanomedicine* 1, 229–234 (2006).

[37] Resnik D, Tinkle S: Ethical issues in clinical trials involving nanomedicine. *Contemporary Clinical Trials 28(4), 433-441* (2007).

[38] To be considered ethically sound, all biomedical research on human subjects must have scientific merit. Furthermore, certain cross-disciplinary guiding ethical principles must be followed: respect for free and informed consent; respect for individual privacy; respect for vulnerable persons; respect for justice; balancing the risks and benefits; minimizing harm; and maximizing benefit.

[39] Mills K, Fleddermann C (2005).

[40] Bawa R: The future of nanomedicine. In: *Hopes and Visions for the 21st Century.* Mack T (Ed.). World Future Society Press, Bethesda, MD, USA (2007) (In Press).

human enhancement, human dignity and justice that have been asked many times before in the context of pharmaceutics research, cloning or gene therapy. For example, nanomedicine raises fundamental questions like what it is to be human, how human disease is defined, and how treating disease is approached. Just as with genetics and biotechnology, physicians will have to reconceptualize how they think about the diseases they treat, the means they have to treat them, and the meaning of the phrase, 'do no harm.' Because it is difficult to exactly predict technology trends or innovations in nanomedicine, it is impractical for ethicists to envision or address all possible scenarios or issues that might arise out of nanomedicine in the future.[41] Yet, on the basis of other kinds of biomedical technologies that have affected health care, it is possible to conjecture what some of the perennial ethical issues and novel ethical problems for nanomedicine will be.

Broadly speaking, nanomedicine interventions fall into two major categories: therapeutic nanomedicine and diagnostic nanomedicine. Each of these technologies and their applications have particular, and in some cases, unique ethical implications for their development, use and accessibility. Two main types of nanomedicine products that are currently in clinical trials pertain to drug delivery and diagnostics. We will address ethical issues in these two broad categories of nanomedicine in § 5 and § 6 below.

5. Nanomedicine and Drug Delivery: Size Does Matter

(a) Market Trends: Nanomedicine is already impacting the drug delivery arena. Drug companies now recognize that drug delivery systems (DDS) need to be an integral part of their R&D operations at an early stage. According to one market report, nanotech-enabled drug delivery systems will generate over 1.7 billion US dollars in 2009 and over 4.8 billion US dollars in 2012.[42] This report projects that the global drug delivery products and services market will surpass 67 billion US dollars in 2009. Another report places the nanotechnology-enabled drug delivery market for 2005 at about 1.25 billion US dollars, growing to 5.25 billion US dollars by 2010 and 14 billion US dollars by 2015.[43]

(b) Formulating Nanomedicines: Nanodrugs are a heterogeneous group of drugs that generally offer unique properties because of their nanoscale dimensions (nanometer to micron) or due to enclosure/entrapment of therapeutic agents within their polymer matrices (nanoencapsulation). They are diverse both in their shape, size and chemical composition. Many of the properties of nanomaterials are fundamentally different from those of their macroscopic/bulk analogues. Therefore, nanodrugs, particularly, nanoparticulate drugs, *often* offer an advantage as compared to their bulk counterparts due to one or more of the following parameters or properties: solubility (high surface/bulk ratio); bioavailability; half life; stability/shelf life; ability to penetrate biological barriers/membranes; toxicity/side effects/safety/patience compliance; patient

[41] Bawa R, Johnson S. The ethical dimensions of nanomedicine. *Medical Clinics of North America,* (2007) *(in press).*

[42] NanoMarkets Report. Nano-enabled drug delivery market to pass $1.7 billion in 2009. http://www.nanotech-now.com/news.cgi?story_id=08590

[43] Jain KK, Jain V: Impact of nanotechnology on healthcare – applications in cell therapy and tissue engineering. *Nanotechnology Law & Business* 3(4), 411-418 (2006).

fasted/fed variability; delivery dose; catalytic properties; imaging; multifunctionality; site specific delivery/targeting; pharmacokinetics/timed release/controlled release; surface structure/chemistry/modification; drug distribution; and physical properties (color, transparency, magnetism, quantum effects).

There are numerous polymeric nanoscale materials (i.e., nanomaterials) of varying architectures that can act as platforms for active agents, including pharmaceuticals. It is important to note that these structures are sometimes loosely classified as nanoparticles. Furthermore, there is no universal convention or nomenclature that classifies nanoparticles as perfect spherical structures with nanoscale dimensions. Some of the common shapes include spheres (hollow, porous or solid), tubules, and tree-like branched macromolecules. They are synthesized by various methods, such as self-assembly, vapor or electrostatic deposition, aggregation, nano-manipulation, imprinting, etc. Similarly, the polymers that constitute nanomaterials are diverse; they are selected for properties such as biodegradability, biocompatibility, conjugation, complexation or encapsulation properties and their ability to be functionalized. The specific protocol for synthesis is dictated by the specific drug used and the desired delivery route.

(c) Ethical Issues: One of the first areas where ethical considerations in nanodrug delivery and therapy arise is in the actual selection of the nanomaterial itself. As discussed above, a wide range of materials exist that can be used to deliver active agents to various parts of the human body. However, the nature of these materials (e.g., whether they are natural or synthetic, soluble or insoluble, hydrophobic or hydrophilic) has significant implications for the risks associated with using them for delivery of active agents to affected cells or tissues. In fact, assessing the safety of nanomaterials is particularly difficult, given their diverse chemical make-up. The only common property of nanomaterials is their nanoscale size; they are not a class of compounds. The size, surface charge, shape and chemistry of nanomaterials generally dictate their chemical and physical properties. These properties are what make them highly effective and desirable, but they can also make them particularly risky. For example, the ability of nanoparticles to unintentionally cross the blood-brain barrier, trigger a severe immune response, accumulate in certain tissues and cause toxicity, or enter cell nuclei and trigger an undesirable gene response raises significant questions about risk assessment that may not always be observed with conventional pharmaceuticals. Also, nanoparticle behavior is often unpredictable; they may behave differently *in vivo* as compared to *in vitro*.[44] For example, within an organism nanoparticles (or nanomaterials) may disintegrate into smaller particles that are toxic. Conversely, they may aggregate *in vivo* into larger clusters that are hazardous. Unpredictability is the underlying issue here. This makes the risk-benefit calculus of nanomedicines (compared to conventional pharmaceuticals) particularly challenging. Therefore, it is ethically desirable that extensive short- and long-term studies be undertaken to determine whether nanomedicines will be more effective and safe for humans when compared to conventional drugs.

As we rapidly move forward into the era of nano-based therapies, nanomedicines will have to be tested in clinical trials (Also see § 3). As with any clinical trial, there are concerns about the risk versus the benefit for human research subjects during the trial. However, it is the

[44] Oberdörster G, Oberdörster E, Oberdörster J: Nanotoxicity: an emerging discipline evolving from studies of ultrafine particles. *Environ. Health Persp.* 113, 823–839 (2005).

novel nature of most nanomaterial-based therapies and their unpredictability in clinical trials that is especially alarming to some. First, the complexity of nanotechnologies may make informed consent for human subjects' research increasingly complicated and may cause problems with comprehension and understanding for those wishing to participate in such trials. Second, the long-term effects of using nanomedicines and nanotherapies are largely unknown. This will continue to be the case for many years. If it is suspected that this may be the case, there is a moral responsibility on the part of R&D scientists conducting the clinical trial to allow for long-term follow-up (see next paragraph) with patients receiving a nanomedicine. More importantly, these patients must be informed at the onset of the clinical trial that there may be potential and unpredictable long-term risks or consequences.

Furthermore, the FDA must review its preexisting authority (regulatory and enforcement) with respect to nanotechnology and ensure that new drugs and new medical devices that incorporate nanomaterials provide adequate protection to the public. Comprehensive changes may indeed be necessary at the FDA to address the novel health and safety risks that numerous nanomaterials pose. For example, if needed, the FDA should mandate certain nanomedicine companies to conduct long-term studies on their products following their introduction into the marketplace. Currently, such long-term follow-up assessment of drugs (i.e., post-marketing surveillance or Phase IV studies) is poorly practiced because it is not legally required under current laws. It is clearly the weakest link in the entire US drug safety system.[45] However, introducing new regulations should be done with care. Like with any regulation relating to drugs and the FDA, the public and political interest for regulations needs to be carefully balanced with the interests of scientists and businesses for uninhibited science and technological efforts. Over-regulating nanomedicine will have a chilling effect on R&D, commercialization efforts and fair access of nanomedicines to the public.

The development of novel nano-based therapies also raises many of the perennial issues related to justice and fair access. It is likely that in the short-term, nano-based therapies will be quite expensive when they are first introduced into the market because they will be protected via patents. Obviously, the prices of these novel therapies will gradually decline as competitors develop products, or when the original patents on the novel technologies expire and generics arrive in the market. However, in the short term, due to patent monopolies, most of these therapies may be out of reach for many people of lower socioeconomic status or those who reside in developing countries. Nano-based therapies also have the potential to further marginalize those individuals in society that are perceived as disabled. In the future, a possible scenario could exist where only the rich have access to treatments while the poor are denied even the knowledge of their diseases. Nanomedicine could exacerbate these problems. For these people, the benefits of nanomedicine may be largely out of reach. National and international inequalities could also worsen. Therefore, the question of how to fairly distribute the benefits of nanomedicine to all segments of society – including thinking about ways to make these interventions more affordable, more easily produced and as safe as possible for all – are of great ethical consideration.

In recent years, patents have become the subject of much debate and controversy. In fact, there are plenty of anti-patent players in the field who feel that patent laws (and most

[45] Strom B: How the U.S. drug safety system should be changed. *JAMA* 295, 2072–2075 (2006).

international treaties) are unfairly providing an economic advantage to some over others. It has even been suggested that patent laws and intellectual property (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 spend more on reformulating pre-existing drugs and on expensive litigation to protect their current patent portfolios than to innovate.[46] Future struggles over patents on the international stage are almost certain to focus on drug patents where multinational drug patents are revoked or challenged.[47] In our 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. Therefore, in order to promote global justice concerning access to novel nano-based therapies, national and international patent laws and intellectual property policies (especially those established by the industrialized nations) should ensure that manufacturers do not have excessive control over the market, and that fair trade agreements and fair pricing schemes (e.g., a stratified pricing program) are developed and practiced.[48]

The use of certain kinds of nanomaterials, nanomedicines or nanodevices also raises fundamental questions about human enhancement and human nature.[49] Although many of these questions about human enhancement engage in futuristic scenarios, it is important to consider the fundamental philosophical questions about how many implantable nanodevices it would take for a person to no longer be considered a human being. Some biomedical applications of nanotechnology will also blur the conventional boundary between "living" and "non-living." In this context, issues relating to unfair competition, socio-economic inequality, discrimination, and bias will certainly arise and need to be addressed. Moreover, is it morally acceptable to us as a society that athletes or military personnel have significant parts of their bodies altered to enhance performance in competitive or combat situations? In these instances, the use of such "technologies" is likely to have strong moral justification. However, when we start moving closer to personalized medicine, treatments for the healthy or intervention for those without disease, the moral justification for using such "enhancements" becomes much less clear.

In view of this, a broader question pertaining to enhancement arises: when is a medical procedure/intervention/treatment regarded as a therapy and when is it considered an enhancement? A little analysis, however, reveals these distinctions to be unavailing because both enhancement and therapy are based on the relative concept of "normal." In fact, most novel medical technologies that are employed for diagnosis, prevention or treatment of diseases can also be used to enhance the function of the human body or mind.

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[46] Saini A: Making the poor pay. *NewScientist* 193(2597), 20 (2007).
[47] Tremblay JF: Drug patent struggles in Asia. *Chem. Eng. News* 85(6), 11 (2007).
[48] Resnik D: Fair drug prices and the patent system. *Health Care Anal.* 12, 91–115 (2004).
[49] Beyond Therapy: Biotechnology and the Pursuit of Happiness. President's Council on Bioethics (2003). http://www.bioethics.gov/reports/beyondtherapy/

6. Nanodiagnostics and Ethical Implications

Many of the interventions, technologies, DDS and nanomaterials described above also have applications for the early detection and diagnosis of disease. For example, quantum dots have been used as an alternative to conventional dyes as contrast agents due to their high excitability and ability to emit light more brightly and over longer periods of time.[50] *In vivo* disease detection and monitoring using micro-electromechanical systems (MEMS) also appears to be promising applications for creating "lab-on-a-chip" devices to detect cells, fluids or even molecules that predict or indicate disease states.[51] Lab-on-a-chip devices involve a combination of nanotechnology and microfluidics where multiple sample mixing, transport, integration, detection and data processing are all conducted on a single chip.

The use of MEMS chips and other devices for the purpose of diagnosing or monitoring healthy or diseased states is likely to raise important questions about health information systems, privacy and confidentiality in our healthcare system. Currently, the use of devices that could provide real-time monitoring of blood glucose levels or other biometrics sound plausible and potentially beneficial to those with chronic illnesses like diabetes. In a nanoworld, where diagnostics assays and devices of much higher selectivity and sensitivity will be fabricated, we might have to reconsider as to what it means to be a ''healthy person'' versus a ''person who has a disease.'' Does disease imply the ability to detect an individual defective cell, subtle molecular alterations in genes or even minor "abnormal" changes in blood chemistry? What is "abnormal" and what is "normal" in this context? The answers to these questions are difficult to answer at this stage because at this point no one knows exactly how to define, diagnose or detect diseases at ultrahigh levels of sensitivity. It is important to remember that the development of such diagnostic technologies may also require reconceptualizing our understanding of certain diseases. All of this will have a significant impact on health care professionals and patients.

It has been postulated that by 2016 the clinician or healthcare worker will be capable of scanning one's entire genome within minutes.[52] Many ethical dilemmas are posed by knowledge of risk factors that are known only in probabilistic terms. Also, how will individuals be able to afford vastly expensive new medical procedures predicated on nanomedicine's diagnostic and therapeutic potentials? It is difficult to make predictions, especially about the future of technological innovations. Therefore, nanomedicine diagnostics should not move into the market place without extensive clinical evaluation, risk assessment and long-term monitoring. This long lag time will provide the critical breathing room necessary for society to sort out the complex social and political issues flowing from the potentially "disruptive" features of nanomedicine diagnostics.

Some have further warned that the volume of data pouring out of the nanomedicine diagnostic spigot may eventually overwhelm the ability of health information systems to evaluate

[50] Alivisatos AP: Less is more in medicine. In: *Understanding Nanotechnology*. Warner Books, New York (2002).
[51] Craighead H: Future lab-on-a-chip technologies for interrogating individual molecules. *Natur*e 442, 387-393 (2006).
[52] Goldstein AH. Nanomedicine's brave new world.
http://www.salon.com/tech/feature/2005/11/28/nanomedicine/print.html

it – making effective treatment impossible.[53] This situation could certainly arise if the amount of clinical information generated is too vast and no method of triaging exists. In this scenario, physicians would be forced to wade through haystacks of irrelevancies in search of a few precious needles of clinical wisdom. Yet today, although physicians are often overwhelmed by clinical data (the vast amount of which are of marginal significance) they are nonetheless able to put aside unsupportive data and make accurate diagnoses. Clearly, incisive diagnostics could eliminate fruitless treatments and save the healthcare system vast resources.

However, currently, most countries do not have a healthcare information system ready to handle the significant amounts of data that would be generated by nanomedicine diagnostic devices described above. Moreover, such devices would have to ensure that the information could not be intercepted by third parties. If we are going to begin collecting significant amounts of real-time health information using nanotechnologies, we must ensure that such information does not wind up being used (or misused) by health insurance companies or employers. Obviously, without specific safeguards in place, it could be highly detrimental to individuals with nanodevices (e.g., implanted nanosensors) – the harm of such devices will outweigh their potential benefits.

A larger, more philosophical question raised by these nanomedicine diagnostics is the effect of real-time monitoring and/or early disease diagnosis on perceptions and understanding of health states. The ability to detect a single cancerous cell or only slightly elevated biometrics could have profound effects upon how individuals think about the status of their health and bodies. A heightened awareness of one's health status could result in increased anxiety and fear about illness and actually cause psychosocial harms. Such information could also have profound effects upon behaviors affecting health (e.g., information about precisely what effect eating a 12-ounce steak has on blood cholesterol levels). Such an implication might be beneficial for some but could result in increased anxiety for others. This example raises a larger question: how much medical information is really beneficial to human health and well being? Nanomedicine will allow us to understand down to the atomic and single-cell level how our bodies are performing at any given moment. For some, this information could be helpful, empowering or enlightening and may enhance human health. For others, it is likely that such information could result in fear, anxiety and other mental health issues. Therefore, a delicate balance may need to be established here between the information processed/disseminated versus the benefit to society and individual health. This issue is likely to be a significant consideration for ethicists when assessing nanodiagnostics.

7. Concluding Remarks and the Future of Nanomedicine

Nanomedicine is a global business enterprise impacting universities, startups and boardrooms of big pharma alike. Industry and governments are clearly beginning to envision nanomedicine's enormous potential. As long as government expenditure encourages facile technology transfer to the private sector, nanomedicine will eventually blossom as a source for corporate investment and revenue.

[53] Goldstein AH.

Will nanomedicine transform our industrial base and have a dramatic impact on healthcare and our long-term quality of life? As envisioned here, applications of nanomedicine hold out a wealth of promise, given the many applications in drug delivery, diagnostics, detection, discovery, sensing and imaging. However, nanomedicine has been so enthusiastically promoted that the hype and expectations may far exceed reality, especially given the immense lag time between R&D and the appearance of commercially-viable products in the marketplace. Therefore, for nanomedicine to truly become a global megatrend, this hype must be separated from reality.

It is also important to ensure that advances in medical care due to nanotechnology do not come at the expense of fairness, safety or basic understanding of what it means to be a healthy human being. The changes that nanomedicine is likely to bring about should be addressed and managed through strategic planning and ethical analysis. As scientific advances occur, the responsible development of nanomedicine requires that societal and ethical concerns be addressed. Even if many of these issues are not new or unique, it will still be essential to address these questions and arrive upon justifiable answers for them. Initially, some of the important ethical concerns will continue to focus on risk assessment and environmental management. Later on, classic ethical questions regarding social justice, privacy, confidentiality, long-term risks versus benefits and human enhancement are certain to arise. Eventually, novel ethical issues and unforeseen dilemmas will emerge as the field advances further and intercepts other areas of biomedical research, including genomics, personalized medicine, bioinformatics and neurobiology.

There is also great concern today over the environmental issues, health risks and safety of many nanotechnologies and nanomedicines. There have been dire warnings concerning the risks inherent in some of these technologies. Regulatory agencies like the FDA are struggling to formulate an appropriate set of guidelines, a difficult task given the current level of uncertainty. We argue that time to consolidate these discoveries is essential. The history of science is replete with technological innovations that moved from the laboratory to the marketplace, only to precipitate grievous consequences once they were widely disseminated. Classic examples include pesticides, atmospheric CO_2, atmospheric fluorocarbons, radioisotopes and thalidomide. Today, the stakes are much higher. Repercussions (real and imagined) may be rapidly forthcoming and blame will be assigned through the courts, which is generally not the most effective route to the truth. However, current fears about self-replicating nanobots, the potential toxic effects of nanoparticles and the calls for strict regulatory oversight or a nanotech moratorium, will eventually give way to intelligent public dialogue on the realistic impact of nanotechnology and nanomedicine.

Government and industry must pay greater attention to emerging public concerns of nanomedicine (environmental, ethical, societal and health issues) in order to prevent any public backlash. In the end, acceptance of nanomedicine will largely depend upon trust in government oversight of ethically sound R&D and commercialization. Only then will the public be more engaged in and aware of nanomedicine, leading to its wider adoption in society.