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Ethics in Nanomedicine

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Summary

As the science and technology of nanomedicine speed ahead, ethics, policy, and the law struggle to catch up. It is important to proactively address the ethical, social and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health and to avoid a public backlash. At present, the most significant concerns involve risk assessment, risk management of engineered nanomaterials (ENM), and risk communication in clinical trials. Though in vivo animal experiments and ex vivo laboratory analyses can increase our understanding of the interaction of ENM in biological systems, they cannot eliminate all of the uncertainty surrounding the exposure of a human subject to nanomedicine products in clinical trials. Significant risks can still materialize after a product has cleared the Phase I hurdle and is in Phase II or III clinical trial. Furthermore, as the use of ENM in nanomedicine increases, questions of social justice, access to health care and the use of nanotechnology for physical enhancement become increasingly important.

Keywords

nanomedicine; nanotechnology; ethics; risk; safety; clinical trials; social justice; enhancement

Background

In the next 10–15 years, nanotechnology is likely to revolutionize the practice of medicine and have a significant impact on human health.[1] Nanotechnology is already contributing to the development of new drugs, biologics, and medical devices and the augmentation of existing therapeutics. Over 200 companies are involved in nanomedicine research and development (R & D), thirty eight nanomedicine products are currently on the market and dozens of additional products are the pipeline.[2] Current total annual sales have reached $6.8 billion, and the market is expected to grow to $12 billion by 2012. The U.S. Food and Drug Administration (FDA) has approved nine different types of therapies that employ nanoscale materials, including products used for medical testing and imaging, drug delivery, wound healing, and bone and tissue repair.[3] To date, drug delivery has been the most popular application of nanotechnology to medicine, accounting for 78% of sales and 58% of patent filings worldwide.[2] Nanotechnology is expected to have a major impact on cancer treatment by making it possible to target chemotherapy to malignant tissues.[1] In neurology, products under development include nanoparticles to aid drug delivery and neurosurgery, nanowires for monitoring brain activity, nanofiber brain implants, and nanoscaffolds to repair neural tissues.[4]

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Discoveries and innovations in nanomedicine have occurred at a breathtaking pace: in just a short time, uses of nanotechnology in medicine have moved from laboratory testing, to clinical trials, to medical applications. As the science and technology of nanomedicine speed ahead, ethics, policy, and the law struggle to catch up.[5],[6],[7],[8],[9] Scholars, researchers, consumer advocates, and politicians have urged government agencies and private companies to proactively address the ethical, social and regulatory aspects of nanotechnology to minimize its adverse impacts on the environment and public health and to avoid a public backlash similar to the uproar in Europe concerning genetically modified foods.[6],[7],[9] Some governments have begun to follow this advice: the U.S. National Nanotechnology Initiative has included $82 million for research and educational programs on ethical, social, and legal issues related to nanotechnology.[10]

While most commentators agree that advances in nanotechnology will generate many different ethical, social, and legal issues, some argue that none of these are truly novel: nanotechnology simply reiterates perennial problems and dilemmas.[8] While we agree that nanotechnology has not raised any brand new ethical, social, or legal issues to date, we still believe it is important to carefully examine nanotechnology, to develop prudent policies and make wise decisions. In this essay, we will briefly discuss some of the ethical, social, and legal issues arising from the application of nanotechnology to medicine.

Ethics in Research and Development

Before nanomedicine products can be used in diagnosis, prevention, or treatment of disease, they must first undergo extensive pre-clinical and clinical testing. Researchers have only just begun to explore the toxicological, pharmacological, and immunological properties of different nanomaterials. The U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Science Foundation and the National Institute of Occupational Safety and Health have launched a variety of programs aimed at studying the risks of nanomaterials. Additionally, the National Cancer Institute has established a laboratory for characterizing the in vitro response to ENM that may be used in cancer diagnosis or treatment.[6] Most commentators agree that safety and risk issues must be thoroughly understood if society is to take advantage of the potential benefits of nanotechnology.[9],[11],[12]

Assessing the safety of nanomaterials can be a difficult undertaking because they have no common properties other than size (1–100 nm). Since nanomaterials are not a unified class of compounds, each type of material must be assessed on its own terms.[12] Moreover, variations in size and shape can have dramatic and unpredictable effects on the physical and chemical properties of nanomaterials: a substance that is non-toxic at 50 nm may be toxic at 1 nm or vice versa. Because they are heavily dependent on their microenviroment, nanomaterials may change in size or shape inside an organism. A 100 nm particle could disintegrate into 1 nm particles, or 1 nm particles could aggregate into a 100 nm particle. Nanoparticles could behave very differently in an organism than they do in cell culture.[12]

Animal and tissue studies have shown that some types of anthropogenic and naturally occurring nanoscale materials, such as diesel exhaust particles, smoke, and viruses activate pathways that neutralize toxicity, such as oxidative stress, inflammation, and innate and adaptive immune responses.[12] Nanomaterials can translocate from the exposure site to other parts of the body. Like some other materials, they can also cross cell membranes and the blood-brain barrier.[13],[14] Inhaled nanomaterials can enter the capillaries, and once in the circulatory system, they may enter the liver, lymph nodes, spleen, and bone marrow.[12] Nanoscale materials may also accumulate in parts of the body and produce adverse effects.[15] The risks associated with exposure to nanoscale materials often vary according to the

route of exposure: a particle that is benign when ingested may be toxic when inhaled.[12], [13],[16] ENMs, such as fullerenes and C60 carbon shells, may pose more of a danger to human health than naturally occurring nanomaterial because human beings have evolved biological mechanisms for dealing with natural nanomaterials but not manufactured ones.[6]

Though in vivo animal experiments and ex vivo laboratory analyses can increase our understanding of different nanomaterials, they cannot eliminate all of the uncertainty surrounding the first exposure of a human subject to a particular type of nanomedicine product in a Phase I clinical trial. Ethical guidelines and regulations require that risks to human subjects be reasonable in relation to the potential benefits to the subjects and society and that risks be minimized, wherever possible.[17] Risk assessment, risk management, and risk communication are some of the most challenging issues for clinical research involving nanomedicine.[6] The research community recently learned some difficult lessons from a Phase I study conducted in the U.K. involving TGN1412, a monoclonal antibody. Six research subjects became critically ill in this study after receiving a dose of the antibody that produced no toxicity in animals at 500 times the dose.[18] One of those lessons is to be very careful with substances that can trigger an immune response, such as antibodies and antigens.[19] Another lesson is that it can be difficult to extrapolate from animal models to human beings.[20].[21] Substances that are safe in a particular animal species at a particular dose may be not be safe in human beings, and vice versa. While these lessons also apply to clinical trials involving other types of substances, it is still important for clinical researchers should keep them mind when they begin testing nanomedicine products on human subjects.

Significant risks can still develop after a product has cleared the Phase I hurdle and is in Phase II or III clinical trial. To minimize these risks, a clinical study must have a data and safety monitoring board (DSMB) to keep track of adverse events, adverse reactions, and other problems with the product under investigation. The DSMB should review the data frequently enough to spot any dangerous trends and control potential harm to human subjects.[22] Other strategies for minimizing research risks in nanomedicine clinical trials include careful review of the relevant literature, sound research design, appropriate inclusion and exclusion criteria, clinical monitoring, well-trained personnel, timely adverse event reporting, protection of confidentiality, and standard operating procedures, and follow-up with subjects after they complete the study.[23]

Since adverse reactions and unexpected side effects can also occur after a product has been approved and is on the market, it is important for physicians to report these problems to the relevant safety agency (such as the FDA), and for companies to conduct Phase IV (post-marketing) studies. Though the FDA does not require companies to conduct post-marketing studies, it should consider making this research mandatory for some nandomedicine products. Long-term studies (5–10 years in duration) may also be needed to monitor the safety of some nanomedicine products. Long-term follow-up and assessment is one of the weakest links in the drug safety system.[23],[24] Adverse consequences caused by new drugs often do not materialize until they have been on the market for several years, because clinical trials usually do not include enough subjects to detect rare side effects and some health problems require years of exposure to develop.[24] Since private companies are not legally required to conduct long-term studies of the effects of their medical products, government agencies should sponsor research on the long-term effects of exposure to nanomedicine products.[6]

Communicating the risks of nanotechnology to research subjects and other members of society also poses a difficult challenge. Ethical and legal rules require that an investigator inform a potential research subject (or his or her representative) about the purpose of the study, procedures, benefits, risks, alternatives, confidentiality protections, and other

information the subject would need to decide whether to participate.[16] Studies have shown that subjects often underestimate the risks of research participation and overestimate the benefits. Subjects also often fail to understand that the main goal of a clinical study is generate new knowledge that may help other patients, not to provide optimal medical care for the people who are participating in the study.[25] It is important for investigators to clearly explain the benefits and risks of participating in research involving nanomedicine during the consent process. If a nanomedicine clinical trial involves exposure to novel materials that have not been thoroughly studied, investigators should inform subjects that there may be some risks that cannot be anticipated.[6]

Risk communication with members of society is important so that nanomedicine may gain and maintain public support. The public may have a difficult time understanding some of the complex ideas pertaining to nanotechnology, such as the size-dependence of physical or chemical properties related to nanomaterials. Researchers should educate the public about how nanotechnology can be used in medicine, the benefits of nanomedicine, and the risks of nanomedicine. When people are not well informed about a new technology, they are likely to view it as dangerous or disruptive. Europe's reaction to genetically modified (GM) foods illustrates the importance of engaging the public in a dialogue concerning a new technology. One reason why Europe had such a negative reaction to GM foods is that manufacturers and industry representatives tried to force their agenda on Europeans and did not engage the public in open discussion of GM foods. Many Europeans resented this lack of respect for their opinions and lack of concern about safety. To avoid repeating these mistakes, nanomedicine manufacturers and researchers, and government agencies, should educate and inform the public about nanomedicine, develop an integrated program, perhaps partnering with museums, to engage in an honest and open discussion about the ethical, social, and legal issues it raises.[7]

Ethics in Medical Applications

A whole different set of issues emerges once a nanomedicine product has moved from the R & D stage and enters the market. A new medical product is often very expensive when it first goes on the market because the manufacturer's patents give it a temporary monopoly. The price of the new product begins to decline when other firms develop competing products and the manufacturer's patents expire. The price continues to decline as generic products enter the market and economies of scale improve the efficiency of production. While it may take a long time for the price of nanomedicine products to decline, due to its complexity and uniqueness, nanomedicine should also become less expensive. In the long run, the intellectual property system promotes human health and reduces health inequalities by providing incentives for investment in biomedical research and development. In the short term, however, intellectual property can exacerbate health inequalities, because economically disadvantaged people may not be able to afford new and expensive medical innovations.[26] It is likely that nanomedince products will also be very expensive when they first enter the market, and that nanomedicine may temporarily make health national and international inequalities worse. This problem could be a significant concern in countries that do not have guaranteed health care coverage, such as the U.S.

To promote national and international justice concerning access to nanomedicine, countries should ensure that intellectual property laws and policies do not give manufacturers excessive control over the market, develop health care financing systems that help poor people receive nanomedicine, participate in international efforts to assist developing nations obtain access to nanomedicine, negotiate fair trade agreements, and encourage companies to institute stratified pricing programs or other policies that make nanomedicine affordable.[27]

Another ethical issue related to social justice concerns the use of nanomedicine for physical enhancement rather than therapy. The medical enhancement problem is by no means unique to nanomedicine, since almost any new medical technology that can be used to diagnose, prevent, or treat diseases can also be used to enhance the function or appearance of the human body or the human mind.[28] For example, doctors can prescribe anabolic steroids to help patients recover from traumatic injuries, but athletes may also take these drugs to improve their performance. It is likely that nanomedicine will have a major impact on the tension between therapy and enhancement in medicine. Applications of nanotechnology to neurology that help to reduce or replace memory loss could also be used to enhance human memory. Nanomedicine therapies designed to help people with learning disabilities could also allow healthy people to become super-intelligent.

There are a number of different reasons why some people find medical enhancement to be morally troubling. First, enhancement can produce unfair competition. A person with an enhanced body or mind has an unfair advantage over someone with a normal body or mind. Enhancements can help people acquire a competitive edge in athletics, school, the job market, and other aspects of life. Second, enhancement can also exacerbate existing socioeconomic inequalities if only the rich people can afford enhancements, and they are able to convey their advantages to the next generation. The rich will get richer. Third, enhancement can lead to discrimination or bias against people who are not enhanced and to social inequality.[29]

Although there are good reasons for society to anticipate and respond to the use of nanomedicine for enhancement purposes, this may not be easy to do. First, the distinction between enhancement and therapy is not clear-cut and well-defined, because both of these concepts depend on the fuzzy concept of “normality.” Therapeutic interventions attempt to restore people to normal functioning, while enhancements attempt to make people “better than” normal. What is considered “normal” or “beyond normal” can be hard to define. Consider the use of human growth hormone (hGH) to treat abnormally short children.[30] How short must a child’s expected height be to qualify for growth hormone? Ten inches below normal American adult height? Eight inches? Would prescribing hGH be therapy to at ten inches below normal but enhancement at eight inches below normal? The therapy/enhancement distinction can create difficult line-drawing problems. Moreover, normality may vary among different societies or cultures. For example, an adult male who is 5′ tall would be considered abnormally short in the U.S., but abnormally tall in a pygmy society. Dyslexia is considered a disease in countries where reading is essential to participating in society, but it is not considered a disease in countries that have only an oral tradition.

Second, it may be difficult to enforce any laws or policies pertaining to the use of nanomedicine for enhancement. Enforcement of a rule can only be effective when society has a method for reliably detecting violation of the rule. It can be very difficult to determine whether an athlete has taken performance-enhancing drugs, because athletes can use drugs for a period of time and then stop, can take drugs that are difficult to detect, or ingest substances that mask drugs. It can also be difficult to enforce a rule if almost everyone is breaking the rule. For example, most drivers on interstate highways drive at a rate well above the posted speed. Highway patrol officers only have enough time to catch a few speeders: must speeders get away with it. Both of these problems are likely to undermine the enforcement of any rules pertaining to the use of nanomedicine for enhancement, assuming that society develops any.[31]

Executive Summary

- It is important to proactively address the ethical, social and regulatory aspects of nanomedicine to minimize its adverse impacts on the environment and public health and to avoid a public backlash.
- At present, the most significant ethical issues relating to nanomedicine involve risk assessment, risk management, and risk communication in clinical trials.
- Educating members of society about the benefits and risks of nanomedicine is important to gain and maintain public support.
- In the future, nanomedicine is likely to raise questions of physical enhancement, social justice and access to health care.

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