NANOTECHNOLOGY AND NANOMEDICINE

Implications for Drug Safety, Pharmacovigilance and Risk Management

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The advent of nanotechnology is considered to be the biggest engineering innovation since the Industrial Revolution.[19] Study in nanotechnology began in the 1900s, expanded slowly, then reached extensive growth in the later 20th and early 21st century. Nanotechnology has expanded into many fields including, but not limited to, physics, chemistry, energy, agriculture, electronics, and medicine.[1] A full review of the complex and growing topic of nanotechnology and its implications is beyond the scope of this paper. Therefore, this discussion will be limited to a brief overview of engineered (deliberately created) nanotechnology and its implications for drug safety, pharmacovigilance, and risk management.

Because of the many facets of nanotechnology, there are several application-dependent definitions. A common definition is the manipulation of matter in the structural size range of 1 to 100 nanometers (nm). A nanometer is one-billionth of a meter or 1/100,000th of a millimeter.[8, 9, 11] Figures 1a and 1b provide a comparative perspective of nanomaterials.

Nanomedicine and nanomaterials used in medicine can take many forms within this structural range. Applications of nanomedicine include imaging and diagnosis, drug delivery and other applications (Table 1). Engineering materials on this scale allows for novel medical therapies, such as designing nanoparticle-based drugs that target cells with improved specificity, resulting in decreased side effects of the bio/pharma agent. Other advances are being made in medical devices and instrumentation for use in surgical procedures that are less invasive, leading to shorter recovery times and decreased risk of postoperative infections and/or other complications. Such innovations will improve patient quality of life, extend life expectancies, and could reduce the overall cost of health care.[5] The revolutionary nature this technology suggests an immense future market.[7, 18]

Because of their diminutive size, nanomaterials have an increased surface area. Their physical, chemical and biologic properties can change unpredictably and be different from their bulk counterparts. There are no product class distinctions with nanomaterials. A 10nm particle may have different properties from a 20nm particle of the same material.[5] Nanogold is being studied for cancer, antibiotic use and its other unique nanoproperties. Above 60nm in particle size gold retains its known properties. However, below that size nanogold's color changes from gold to red and its melting point and reactive properties change.[4] As particle size decreases, optical properties of nanomaterials change. Titanium dioxide, a common ingredient in sun protection products, is opaque (white) in its macro form. It becomes more transparent as the particle size decreases and ultimately becomes clear in appearance.[19] For drug delivery, not only engineered particles may be used as a carrier, but the drug itself may be formulated on a nanoscale, and then function as its own carrier.[15]

Safety Issues

Nanomaterials have safety and environmental issues involved in their manufacture and laboratory use. Nanomaterials that escape the laboratory or manufacturing site can enter the environment. Then they may deteriorate or become free to interact unpredictably with anything, potentially creating unknown environmental hazards. Because of the limited knowledge about nanomaterials, organ toxicity, tumor development and immune responses are possible concerns with exposures through the routes discussed below.[3, 18]

Inhalation Route

Inhaled nanomaterials can aggregate in the alveoli where their increased surface area places a burden on mucociliary and macrophage clearance. While in the lung, nanomaterials may translocate to

Figure 1a. Relative Size of Nanoparticles Compared with Familiar Items[17]

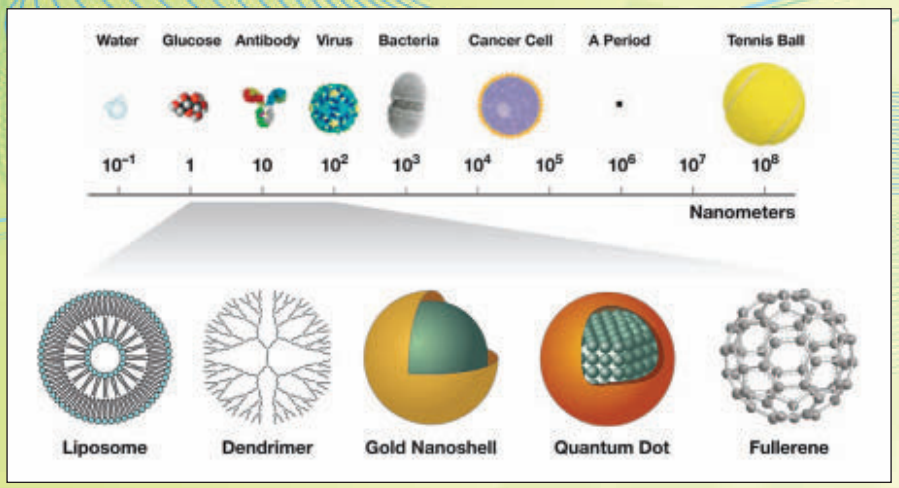


Figure 1b. The sizes and shapes of some nanomaterials as compared to more familiar materials. Shown for comparison are materials that are below, within, and above the nanoscale range, to put nanomaterial size in perspective.[18]

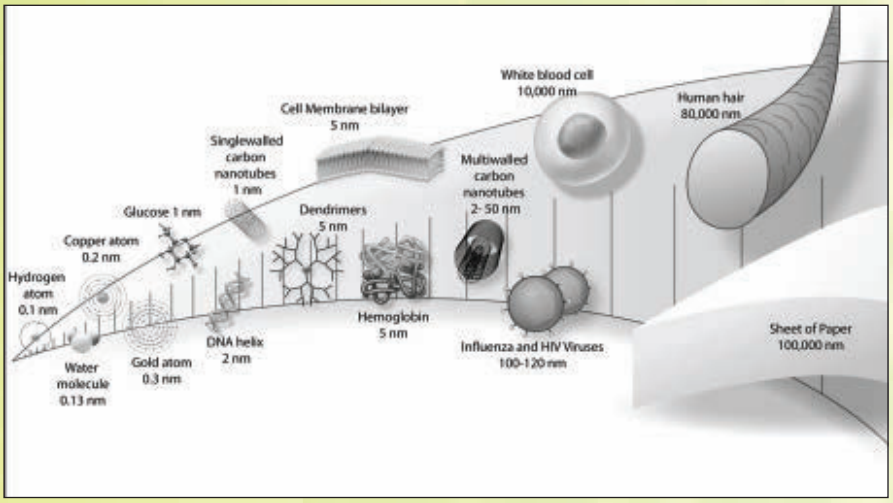
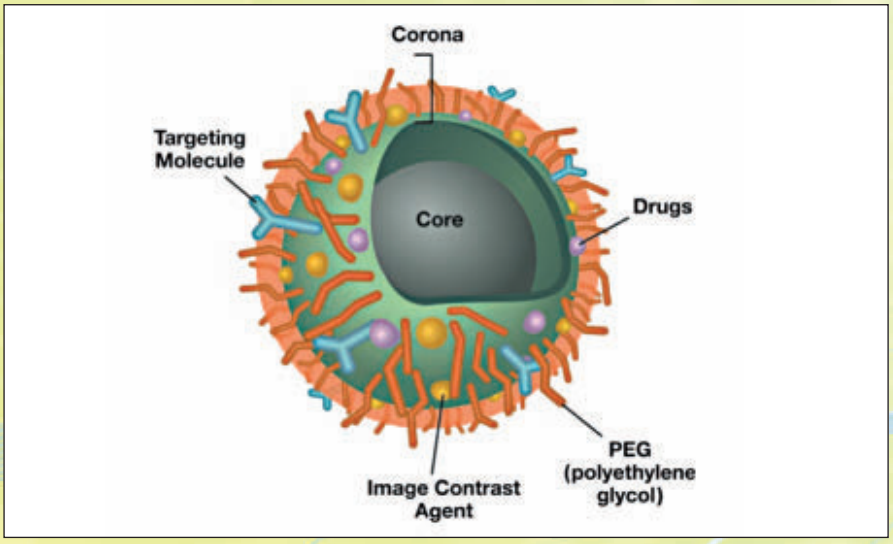


Figure 2. Multifunctional nanoparticle. The nanoparticle's "corona" can be functionalized with hydrophilic polymers, targeting molecules, therapeutic drugs, and image contrast agents. The interior core can be solid (e.g., quantum dots) or liquid (e.g., liposomes). Molecules are not shown to scale. PEG, Polyethylene glycol.[17]



the systemic circulation. Inhaled nanoparticles can also gain access to the CNS via olfactory nerves.[3]

Dermal Exposure

Nanosized particles may penetrate more deeply into the skin than their larger counterparts. It has been hypothesized that nanoparticles of titanium dioxide (5-20nm) can penetrate the skin and enter the immune system or the systemic circulation. Quantum dots have been shown to penetrate porcine skin within 8 hours of application.[3]

Oral Route

Uptake of nanoparticles after oral exposure depends on particle size and surface chemistry (certain nanoparticles are combined with other materials). In rats, 50nm to 3 um particles were detected in the liver, spleen, blood and bone marrow after oral exposure. Particles >100nm did not reach the bone marrow and particles >300nm did not reach the blood, suggesting that nanoparticles of lesser size have been detected in bone marrow and blood. Nanomaterials can be used to enhance the GI absorption of a pharmacologically active compound.[3]

Pharmacokinetics

The pharmacokinetics of non-biodegradable nanomaterials has not been studied in detail and there are only a few studies focused on the removal of nanomaterials from organisms. Nanomaterials can potentially accumulate over a lifetime in an organism. Some nanomaterials may not be cleared by the reticulo-endothelial system and may accumulate in the liver. Larger nanomaterials may not pass through the glomerular filter. Nanodendrimers of 5nm were reportedly excreted in animal urine but also accumulated in the kidney.[3]

Genotoxicity and Carcinogenicity

Nanomaterials can enter the cell and, in some cases, the nucleus where it's

possible for them to interact with inter-nuclear processes where DNA damage may occur. While useful in concept to cancer treatments, the genotoxic effects on normal cells must be considered. Carbon nanotubes (CNTs) administered to mice demonstrated genotoxic results that were similar to those of asbestos. [3]

Development

Nanomaterials have been shown to cross the placenta in rats suggesting a risk to the developing fetus. Carbon nanotubes (CNT) have induced changes, in vitro, in the cell proliferation and other cellular activities suggesting in-vivo consequences in development.[3]

Immunological responses

Nanomaterials have demonstrated both positive and negative effects on the immune system that differ for inorganic and organic nanotypes. These effects may be desirable or undesirable. Therefore, nanomedicine testing should exclude undesirable immunological responses. In general, positively charged (cationic) particles are more likely to induce acute inflammatory reactions (innate reaction) than negatively charged (anionic) particles. Two parameters, size and surface charge, play a central role in these responses. The phagocytic activity of macrophages in the lung has also been linked to particle size. Although micrometre-sized particles stimulate phagocytosis, smaller nanometer sized materials often do not. Such particles may even reduce the capacity of the macrophages.[3]

With nanoparticles, the smaller they are, the greater their surface area to volume ratio and the higher their chemical reactivity and biological activity. The greater chemical reactivity of nanomaterials can result in increased production of reactive oxygen species (ROS) including free radicals. ROS production has been found in a diverse range of nanomaterials including carbon fullerenes, carbon nanotubes, and nanoparticle metal oxides. ROS and free radical production is one of the primary mechanisms of nanoparticle toxicity. It may also result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA. Size is not the only variable influencing the safety of a nanomaterial. Chemical composition, shape, surface structure, surface charge, aggregation, solubility, and the presence or absence of functional groups of other chemicals can also contribute.[6] Figure 2.

Products in Use Today

Nanotechnology and nanomedicines are in use today. Many cosmetics and sunscreens use nanosized ingredients (eg nanotitnium dioxide, nanozinc oxide).[12, 13] Currently, nanoenabled drugs have been approved by the FDA for the treatment of cancer. Examples include Abraxane®, which is used to treat breast cancer and Doxil® for ovarian cancer.[5]

Safety Challenges

Laboratory and manufacturing workers may be at risk for accidental exposures through dermal, nasal, ophthalmic and oral routes. Topically applied sunscreens and cosmetics that contain nanomaterials, when washed off, enter water ecology with unknown repercussions. Nanomedications and nanaomaterials may confound the safety evaluation of bio/pharma agents to which they are combined. Nanomedications and bio/pharma products combined with nanodelivery systems may present unique safety issues. The preliminary evaluation of many products is performed in normal animals and humans. However, sick individuals can be prone to unforeseen toxicities. Studies need to focus on therapeutic effect as well as nanoparticle disposition.[15, 18] Nanomedications need to be evaluated for their effects in clinical laboratory tests, drug interactions, dose, hepatic and renal impairment, special populations (eg pediatrics, elderly), interactions with other existing pathologies, interactions with foods and over-the counter-products. To the chagrin of consumer advocacy groups, at this time the FDA, EMEA, and MHRA do not believe that additional regulations are required to manage the licensure of nanomaterials/medications.[3, 5, 12, 13, 15] While unrelated to the clinical safety evaluation of nanomedicine, insurance providers may consider expensive nanotreatments as "experimental" or environmental hazards and outside the scope of coverage of certain health insurance policies.[20]

Summary

The current safety track record for nanomedicines is without clinical problems so far. However, because of rapid expansion in the area, much remains to be discovered. Nanomaterials bio/pharma properties are different from their macro counterparts. Currently, there are no nanomaterial class distinctions. The use of nanomaterials in the laboratory and manufacturing process may require "nanoproof" protective equipment to prevent inadvertent exposures. Environmental implications regarding nanomaterials need to be reviewed and updated, especially waste water testing standards. The environmental impact of nanomaterials and metabolites is largely unknown.

The implications for drug safety, pharmacovigilance, and risk management are as limitless as the possible applications of the technology. Nanomaterials and nanomedicines will require specific safety evaluations on a case-by-case basis for their use in humans. Clinical research will need to focus not only on therapeutic safety

and effectiveness, but also on nanomaterial impact and disposition. Pharmacokinetics for active moieties, nanomaterials, and metabolism of both will need to be studied. Present concepts of risk detection may not apply to nanomedications, especially in long-term exposures and effects or use in individuals with impaired health.[15] Current regulations may or may not be adequate in managing nanomaterials' licensing process for commercial use. Current US labeling requirements do not stipulate that nanomaterials are used in a product.[3, 5, 10, 11] However, health authorities should always be notified early in the development process if nanotechnology is involved with a medical use. Regulators do not want to see nanomaterials turn into the 21st century's "asbestos".[18] The US EPA is taking a new path forward in the regulation of manufactured nanomaterials under the Toxic Substances Control Act ("TSCA"). Revised regulations are expected in the near future.[14] Nanotechnology, nanomaterials, and nanomedicines currently under development represent a revolution in the visualization, diagnosis and treatment of many diseases. While current commercial and medical applications of nanotechnology appear to be "safe", in this rapidly growing and promising area, much remains to be revealed regarding their environmental and clinical safety profiles.

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FDA recognizes the role of nanotechnology. In June of 2011, the FDA issued a draft *Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*. This publication is open for comment through August 2011. (http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm, accessed 12Aug2011)

Table 1. Classes of nanomaterials for use in medicine[2]

Type of nanomaterial/ Basic description	Potential Medical Use	Disease state
Liposomes Spherical nanoparticle, lipid bilayer membrane, hollow interior	Drug delivery system	Cancer
Nanopores 20nM pores	Permits nutrients but limits immune penetrations	Transplanted tissue, genetics
Fullerenes, "Soccer ball" framework	Encapsulates radioactive material, transport antibiotic, antiviral, anticancer products	Imaging procedures, antibiotic with light stimulation, infection, HIV, Cancer
Nanotubes 1-25nm tubes with and without "caps"	Drug delivery, Amphoteracin B, DNA transport, increasing immune response	Can penetrate the cell wall, Fungal, Cancer therapy, vaccines
Quantum dots 2-10nm nanocrystal	Drug delivery by conjugation,	Diagnosis and treatments, Prostate cancer, Melanoma, Breast Cancer
Nanoshells Silaca core and thin metallic shell	Immunologic manipulation	Cancer, Immunoglobulin determinations
Nanobubbles Nano scalled bubble	Drug transport, combined with heat or ultrasound	Cancer, increased uptake by target cells. Vascular clearing
Paramagnetic nanoparticles (e.g. iron	Diagnostics, Imaging, rapid cell uptake	MRI imaging, Cancer
Nanosomes Silaca coated iron oxide nano particles with targeted antibody and contrast elements	Targeted diagnosis and treatment, combined with laser	Brain cancer
Dendrimers Nanomolecule with branching structures	Drug transportation within the branch "cavities"	Gene therapy, Anti-retroviral, Type 1 Diabetes, Potential for intra-nuclear cancer applications
Respirocytes Nano device Hypothetical RBC	Deliver up to 236x more oxygen than RBC	Cardiac arrest

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