Handling Worker and Third-Party Exposures to Nanotherapeutics During Clinical Trials

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Introduction

Nanomedicine is a rapidly growing field in the academic as well as commercial arena. While some had predicted nanomedicine sales to reach $20.1 billion in 2011,[1] the actual growth was much more rapid, with the global nanomedicine market being valued at $53 billion in 2009, and forecast to increase at an annual growth rate of 13.5% to reach more than $100 billion in 2014.[2] In 2006, more than 130 nanotechnology-based drugs and delivery systems had entered preclinical, clinical, or commercial development.[3] The European Medicines Agency (EMA) reviewed 18 marketing authorization applications for nanomedicines in 2010.[4] In 2011, 22 drugs that had been approved by the FDA, and 87 Phase I and Phase II clinical trials were listed in the U.S. National Institutes of Health (NIH) data base, www.clinicaltrials.gov.[5] Although the fastest growing areas of nanomedicine are applications in medical imaging and diagnosis using contrast-enhancing agents, most nanomedicine research and commercialization is in the area of cancer drug therapy, including nano gold shells.

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In the short and medium term, the main use of nanoparticle medicinal products is to provide vectors carrying active components or to deliver materials that can be activated and/or detected at the site of interest. This includes reformulation of existing therapeutics as small particles to aid delivery — a strategy used in several products already marketed like Doxil™ and Abraxane™. However, most current work is in the area of third-generation vectors that combine a biodegradable core and a polymer envelope (PEG) with a membrane recognition ligand.[6] While previous uses of nanomedicines have included using liposomes as passive vehicles for drug transport, active nanomaterials with complex properties and functions in drugs are not too far in the future. These include self-assembling peptide nanofibers, scaffolds for tissue regeneration, sensors of biomarkers, artificial retinas, and chip-based nanolabs.[7]

These developments hold the potential to provide immense benefits for disease treatment in the near future. At the same time, the novel technologies also raise safety and ethical concerns in human subjects research (HSR) that may challenge the existing system of oversight. One aspect of HSR that has not received robust attention are concerns about occupational exposures of researchers and lab workers, and exposures of bystanders such as health care workers, family members, and caretakers during HSR using nanomaterials ("third-party" exposures). In principle, exposures can occur during the handling and administering of the pharmaceutical by the health care workers or the family members (if they are involved in drug administration). The high nanoparticle content of biological wastes excreted by research subjects also has been cited as a concern for potential exposure to bystanders and the environment.[8] Laboratory containment and disposal practices, as well as excretion and shedding, can additionally release nanomaterials into the environment.

There are several stages that precede the clinical trial phase of nanomedicine research, including the production of the raw nanomaterials, synthesis of the pharmaceutical in a lab or manufacturing setting, and preclinical drug studies in animals and in vitro. Most of the somewhat limited exposure information that we have so far is associated with such production, synthesis, and preclinical studies in industrial settings. Less is known about occupational exposures in the clinical trial phases and the post-marketing phase — both in terms of the types and magnitudes of the nanomaterial exposures as well as the types of workers who may be exposed. This paper provides a description of the types of potential nanomedicine exposures, the existing oversight framework for handling worker and third-party exposures, the deficiencies of that framework in clinical and residential settings, and possible new approaches to oversight.

Defining Nanomedicine

Nanomedicine, nanotherapeutics, and nanodiagnostic techniques incorporate materials that are engineered at the nanometer scale to take advantage of novel and advantageous properties that become manifest at that scale. However, defining nanotechnology remains a matter of debate and controversy. Agencies and scientific bodies have defined nanotechnology in a variety of ways that reflect the different aims and perspectives of the respective organizations.

The U.S. National Nanotechnology Initiative (NNI) defines nanotechnology as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications,"[9] and this is often taken as the *de facto* definition. However, such a one-size-fits-all definition does not capture subtle yet significant features of nano-products. The nanocomponents in nanomedicines include a great variety of materials and structures, some of which are passive with fixed functionality and others that are active with functionalities that are triggered or changed by internal or environmental stimuli.[10] In many cases, advantageous as well as potentially harmful functionality is not sharply confined to the size region between 1 nm — 100 nm, leading to debate about the upper size limit of the nanoscale range. For instance, while some make the case for novel behavior becoming predominant below 30 nm,[11] others note that novel biological interactions enabled by nanotherapeutics may occur at scales larger than 100 nm.[12] The Food and Drug Administration's (FDA) Center for Drug Evaluation Research (CDER) defines nanomaterials in its Manual of Policies and Procedures (MAPP) as "any material with at least one dimension smaller than 1,000 nanometers."[13] More broadly, FDA has stated that the agency as a whole does not adhere to a specific definition of nanotechnology, but rather focuses on material behavior. At the same time, OSHA[14] and NIOSH[15] have used the 100 nm cutoff as the basis for defining nanomaterials.

The considerable uncertainty over how size alone affects biological behavior suggests that purely size-based definitions may be inappropriate for the oversight of nanomedicine, if indeed one can even properly identify a category of therapeutics by "nano" size. One of the authors of this article has argued that it might be more useful to have oversight triggered on the basis of an ensemble of relevant attributes of a product or material rather than a size-based defini-

tion.[16] This ongoing debate goes to the heart of what it means for a product to be labeled as "nano," and whether such labeling should spur oversight beyond what exists for other entities for which there is already an assessment of potency, ability to cross barriers (e.g., hydrophobicity and ability to cross the barrier provided by gloves), and the degree to which one is exposed. In other words, are the existing best practices for handling hazardous materials sufficient for nanomedicine products as well? We argue that while further research is needed to characterize the risks of exposure to nanomedicine products, a precautionary approach to managing exposures is warranted.

Risks from Potential Exposure for Workers and Third Parties

The typical model for commercial innovation in nanomedicine is one where discovery made in academic labs is transferred to small start-up companies that validate the concept and initiate the pre-clinical and Phase I clinical trials. Then large companies take over these start-ups for further development of the drugs or devices, Phase II and III clinical trials, and bringing the drugs or devices to market. There are several stages that precede the clinical trial phase of nanomedicine research, including the production of the raw nanomaterials and synthesis of the pharmaceutical in a lab or manufacturing setting. The issues surrounding oversight and management of exposure and risk in such standard occupational settings have been described at length in the literature [17] and are not the focus of this paper. Instead, we focus primarily on the clinical trial phases.

In the United States, an investigational new drug (IND) must progress through several phases of testing before approval can be granted for introducing the therapeutic into the market.[18] Preclinical studies can involve *in vitro* tissue or *in vivo* animal pharmacology and toxicity tests for initial safety screening of the drug. Results of this phase determine whether permission is granted for proceeding with a Phase I trial. This phase usually involves a small number of subjects (20-100) and is used to establish a safe dosage range and identify side effects of the IND in human beings. Based on the results from this phase, the IND is then approved for Phase II trials, where the drug is given to a larger group of people (100-500) to see if it is effective and to further evaluate its safety. Based on these results, approval is granted for Phase III trials in large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the IND to be used safely.[19] Based on the results from these three phases of clinical trials, the FDA approves the drug for marketing in the United States. Sometimes Phase IV trials or post-marketing studies are conducted to obtain additional information including the drug's risks, benefits, and optimal use.

In terms of risks not only to the patients undergoing an experimental treatment but also to the health care workers and third parties, the maximum risk during clinical trials is during Phase I. While preclinical studies *in vitro* and in animals do inform Phase I trials, they have significant limitations, especially in the context of nanomedicine. There are three broad reasons for this.

In terms of risks not only to the patients undergoing an experimental treatment but also to the health care workers and third parties, the maximum risk during clinical trials is during Phase I. While preclinical studies *in vitro* and in animals do inform Phase I trials, they have significant limitations, especially in the context of nanomedicine.

First, key mechanisms for exposure processes and toxic effects of engineered nanomaterials remain poorly understood. Uncertainties relate to questions such as: (a) How long do manufactured nanomaterials persist in the environment? (b) How stable are nanomaterials over time? (c) What is the effect of particle shape on their fate and transport? (d) What are likely routes of exposure (e.g., inhalation, dermal, ingestion, and ocular)? (e) What are the metrics by which exposure should be measured (e.g., particle mass, number of particles, or surface area concentration)? (f) What are key mechanisms of translocation to different parts of the body after nanomaterials enter the body? and (g) What are possible mechanisms of toxicity, including oxidative stress due to surface reactivity, presence of transition metals leading to intracellular calcium and gene activation, and intracellular transport of nanomaterials to the mitochondria?[20] The EHS hazards and risks associated with these different types of interventions and materials can further depend on the characteristics of the nanoparticles themselves (e.g., size, composition, and surface chemistry),[21] the behaviors of the nanoparticles in biological systems (e.g., protein adsorption,

barrier penetration, cellular uptake, aggregation, degradation, pathway signaling, and toxicity), and the route through which the nanoparticles are introduced into the body (e.g., oral ingestion, parenteral administration, topical application, and implantation).[22] For many types of nanomedicine applications the literature dealing with potential EHS risks is sparse. In assessing overall risk, both the exposure and hazard aspects of risk are poorly understood.

Second, *in vitro* tests are used to evaluate the generic toxicity of substances and are primarily used as a screening tool as well as a guide to the proper selection of an appropriate animal model for *in vivo* testing. Such *in vitro* tests are cost-effective and rapid in assessing toxicity end-points. However, studies to date have been somewhat contradictory in their assessment of the correlation between *in vitro* and *in vivo* tests.[23] While there is obviously a great need for relevant and accurate *in vitro* tests for nanotoxicity, some current methods for such testing have limitations. These tests were established to assess the toxicity of conventional chemicals, and in some cases over-estimate or underestimate the hazard of nanoparticles. Nanoparticle properties may cause interference with assay ingredients and detection systems, and cause artifacts in cytotoxicity studies. The properties causing interference include (a) high adsorption capacity that can cause the adsorption of nutrients and growth factors from culture media and is dependent on surface charge and hydrophobicity; (b) the light-absorptive nature of metallic properties that can affect cell viability readouts; (c) catalytic activity enhanced by the high surface area/mass ratios that can increase the production of reactive oxygen species and affect assays based on substrate oxidation; and (d) magnetic properties that can affect production of free radicals.[24] To ensure appropriate interpretation of assay results and comparison with other evaluations, *in vitro* testing requires a complete characterization of nanoparticle properties using reference materials and validation of assay techniques.

The health effects can also be extrapolated from studies performed on similar populations or due to exposure to similar agents to determine toxicity parameters that may not otherwise available. However, in the case of novel materials it may be difficult to find comparable populations or even comparable nanomaterials from which to estimate parameters, and uncertainty factors are typically required to account for the errors that are introduced during extrapolation.[25]) The clinical significance of the effects reported in the literature is unclear. Similarly, the long-term biological consequences of these particles in the body and the potential for unintended effects as well as immunological, inflammatory, or carcinogenic effects are also uncertain.[26]

Third, animal studies may not always be predictive of effects in humans due to differences in biology and the well-known problems of extrapolating from animals to humans. Animal and *in vitro* studies are typically short-term (typically ~100 days) acute toxicity tests and do not address toxicity resulting from longer-term or chronic exposure.[27]

The risk is somewhat decreased in Phase II trials because of the information gathered in Phase I. However, Phase I studies are also typically short-term in duration and do not address long-term effects that manifest over several years. Similarly, the risks to participants, health care workers, and third-parties are not minimized or eliminated in Phase III trials. Even Phase III studies do not have the large number of subjects needed to assess the risk of rare adverse events; it is recommended that Phase III trials should at least have 3000 subjects to be able to detect rare effects (defined as 1 case out of 1000) with some degree of confidence, and manufacturers should also conduct post-marketing (or Phase IV) studies.[28]

The above discussion indicates that the risk picture in clinical trials is that of a pyramid where the highest risk is at the top (i.e., Phase I). The lower tiers of the pyramid represent the decreasing risk in successive phases, but with increasing numbers of subjects.

The different tiers of clinical trials have different exposure potentials because they may most likely be conducted in different settings with varying degrees of exposure control and regulatory oversight: Phase I and II trials are most likely to be conducted in hospital or clinical settings with well-designed administrative and engineering controls. For example, the acute side effects of existing nanoparticulate agents such as Doxil™ (e.g., complement activation) have been characterized and dealt with through the usual preclinical and clinical trial evaluation methodologies. The exposure risk exists at the points of delivery or handling where conventional exposure controls would likely suffice in hospital settings, although further studies need to be conducted.

However, clinical trials are increasingly being conducted at the residence of the patients for reasons of cost. Phase III and post-marketing studies, in particular, may be conducted in quasi-clinical as well as residential settings where exposure controls may be minimal to non-existent. Exposures (e.g., in chemotherapy done at home by home health care nurses) would occur in settings that can be very variable and uncontrolled. While this may be true of exposures to nanomedicines, it is also true more generally of exposures to all types of therapies. Exposures in these settings have not been

studied in any depth and thus are poorly characterized. This is a frontier area in occupational health that requires further research. At the same, while the testing of therapeutics in such settings has become more frequent, there is a need for precaution and diligence in managing exposures effectively.

Oversight Regime

Health care is delivered in public and private hospitals; nursing and residential care facilities; offices of physicians, dentists, and other health care practitioners; home health care services; outpatient care centers and other ambulatory health care services; and medical and diagnostic laboratories. In all of these work settings, exposure to pharmaceuticals may occur. Health care is the largest sector in the American economy, employing nearly 12% of the total employed labor force in 2010, and has a high incidence of occupational injury and illness.[29] In 2004, the incidence of occupational injury and illness in hospitals was 8.7 cases per 100 full-time workers, and in nursing care facilities was 10.1 cases per 100 full-time workers, compared with the average of 5.0 for private industry overall.[30] Health care workers are exposed to a greater range of significant workplace hazards than workers in any other sector,[31] including potential exposure to airborne and bloodborne infectious disease, sharps injuries, and other dangers. The occupational risks faced by this category of workers have not been well characterized for all kinds of hazards, including those relating to nanomedicine.

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The plethora of settings in which nanomedicine research and clinical and post-marketing trials occur fall under several oversight and regulatory regimes.

Research and Clinical Laboratories

The occupational safety of laboratory workers and scientists falls under the purview of OSHA. Under this framework, research and academic institutions have laboratory safety committees responsible for ensuring the adequacy of safety training and the compliance of lab procedures with OSHA (29 C.F.R. part 1910). However, OSHA has no nanotechnology-specific standards; instead, only general OSHA standards are applicable. These include the standards for personal protective equipment (§1910.132), eye and face protection (§1910.133), respiratory protection (§1910.134), hand protection (§1910.138), sanitation (§1910.141), hazard communication (§1910.1200), occupational exposure to hazardous chemicals in laboratories (§1910.1450), and some substance-specific standards (e.g., §1910.1027, Cadmium). However, these generic standards are applicable to a wide range of chemical hazards and do not address nano-specific hazards.

Additional oversight is provided by the Centers for Disease Control and Prevention (CDC) and NIH through their joint Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual that provides guidance on laboratory practices, safety equipment, and facility design, as well as information on specific microbiological agents of concern to lab worker safety.[32] While this oversight applies to research with microbiological agents, the manual's standards may not be adequate in the case of active nanotherapeutics that straddle the boundary between chemical and biological agents. If the medications were administered to the patient by IV, injection or mouth the OSHA Blood Borne Pathogens standard would apply and would address issues such as PPE, and training.

NIOSH is already involved in nanotechnology-related occupational risk and safety assessment. This agency has produced a number of guidance documents on safe handling and monitoring of nanomaterials in the workplace,[33] some of which are specific to the use of nanomaterials in laboratories.

Except for a very few substances, there are no established exposure limits for many nanomaterials. Even the few materials with exposure limits are not really relevant to nanomedicine applications. This, by itself, is not a cause for undue concern in terms of exposure management. There are many "hazardous drugs"[34] without exposure limits that have effective exposure management in the pharmaceutical industry. In the absence of exposure limits (which can also serve as performance standards for evaluating the adequacy

of exposure controls), we may need to rely on process standards (i.e., directives to implement specific control measures in specific situations). However, such process standards have not been validated for nanomedicines, so we cannot be sure whether the controls actually protect workers to the extent necessary to safeguard health. Many institutions have developed in-house guidelines for handling nanomaterials and for exposure management. For example, university Environmental Health and Safety departments typically have procedures for record-keeping and inventory, labeling and packaging, storage, engineering controls, work practices, engineering controls, use of personal protective equipment, clean-up procedures, and waste disposal. These guidelines tend to be generic with a presumption of conservatism, i.e., implementation of such procedures will ensure that exposures are *de minimis* and below acceptable levels. However, efforts at validation of these guidelines are in their infancy. For example, the degree of clean-up after a chemical spill is generally unspecified; in the case of a spill involving nanomaterials, there are further difficulties with difficulties detecting small quantities of nanomaterials.

NIOSH has developed a series of publications that provide guidelines and universal precautions for safe handling of antineoplastic and hazardous drugs. These documents make no attempt to perform drug risk assessments or propose exposure limits. Instead, the recommendations focus on the need to implement necessary administrative and engineering controls, assure that workers use sound procedures for handling hazardous drugs and proper protective equipment, and perform medical surveillance.[35]

The pharmaceutical industry has developed performance-based exposure-control methods based on performance-based exposure-control limits.[36] These methods are routinely validated using air and surface monitoring.[37] The level of control depends on the hazard PB-ECL category, and so does the degree of monitoring. Such approaches based on hazard bands can be adapted for application to the case of nanotherapeutics in the manufacturing environment. In health care environments, one approach would be to characterize nanotherapeutics as "hazardous drugs"[38] that require special monitoring and control. Inhalation and surface sampling techniques can be used to characterize exposures of health care workers along with medical surveillance and biomonitoring.[39] One of the main bottlenecks to such approaches in manufacturing and health care settings is the dearth of validated analytical methods for detection and quantification of nanomaterials, especially in small quantities. Secondly, as mentioned in previous sections, both the hazard and the proper metric for quantifying many nanomaterial exposures are poorly understood.

Home Health Care Settings

Both short-term and longer-term clinical trials increasingly occur in residential settings.[40] It is likely that Phase III clinical trials and post-marketing studies for nanomedicines, as well as regular treatment especially for cancer may occur in residential environments using home health care providers and family members of patients to administer the pharmaceuticals.

Home health care is the fastest growing sector of the health care industry.[41] This is partly due to economic forces that are reducing hospital stays and partly due to the kinds of chronic care that patients require in the home. Increasingly, sophisticated medical devices and treatments are being introduced into the home. The workers in this sector include registered nurses, home health aides, attendants, and personal care workers. Home health aides provide basic nursing services under medical direction, although without direct supervision. These services include checking patients' vital signs, changing dressings, administering medications, and assisting with use of medical equipment, in addition to bathing and grooming, dressing and feeding. Thus, the scope of home care includes everything from assisting with daily activities to more complex care required by chronically ill or post-surgical patients such as dialysis, chemotherapy, and respiratory and infusion procedures.[42]

Despite the increasing importance of this sector, the health hazards faced by this population of workers are poorly characterized. Since the home is not designed as a health care workplace, a number of hazards emerge in such environments for the health care workers. They face an increased incidence of injury compared to other health care workers.[43] Common household hazards reported in the few extant studies include unsanitary conditions and inadequate disinfection, mismanagement of medical wastes including biomedical wastes, sharps and needlesticks, and infections during home infusion therapies.[44] These are significant concerns in relation to potential exposure of home health care workers and family members to nanotherapeutics being administered in uncontrolled home settings. However, this is true of exposures to other types of therapeutics as well. There is poor oversight for such workers. OSHA's oversight of such workplaces requires improvement. Much more attention needs to be paid to the hazards faced by this group of workers.

The employers of home care workers are mostly free-standing proprietary agencies, hospital-based

agencies, non-profit public health agencies, or private agencies.[45] In addition, there is an informal, unlicensed home care network whose extent is not well known. In theory, if the home health worker administering the drugs is employed by a company or hospital then she/he is covered under OSHA regulations. If the medications were administered to the patient by IV, injection, or mouth the OSHA Blood Borne Pathogens standard (29 CFR* 1910.1030) would apply and would address issues such as PPE, and training. While the employer of the workers may be responsible for the health and safety of the workers, they may not have complete control over exposures in the home.

However, they can provide training to their workers (e.g., for compliance with the bloodborne pathogens standard) in safe practices. NIOSH has conducted a review of occupational hazards faced by home health care workers that recommends management and prevention strategies to reduce illnesses from such hazards. The training of home care workers is variable and often inadequate.[46] Increased funding for the agencies employing these workers for training purposes, reimbursement for training time, and funding for appropriate safety equipment and supplies are necessary steps.[47]

Workers facing illnesses due to exposure to nanomedicine hazards would be eligible for worker's compensation. However, worker's compensation insurance requirements for employers vary from state to state. Thus, while Minnesota and Michigan require all employers to provide insurance coverage to all employees without exemptions, Alabama does not regulate worker's compensation requirements for employers, and other states provide employers with varying exemptions.[48]

Oversight that applies to family members who may be exposed to nanotherapeutics during home care is beyond the scope of this article. However, illnesses resulting from such exposures might be redressed through home owners insurance covering injury at the residence, product liability lawsuits, and tort suits claiming hospital negligence.

Conclusions

The rapid developments in nanomedicine research raise significant questions relating to the protection of researchers, lab workers, and health care workers engaged in clinical trials involving nanotherapeutics. The hazards from such exposures are poorly understood, as is true in the case of nanomaterial exposures more generally. There are several challenges to managing such exposures.

First, the very definition of what products need to be regulated varies among agencies such as the FDA, OSHA, and NIOSH; this may result in some nanotherapeutics falling through the regulatory cracks. At the same time, commentary has suggested that "nano" not be defined in terms of size and instead be replaced with definitions based on an ensemble of relevant attributes of a product or material. The effects of any such definitional changes on oversight and exposure management need to be studied thoroughly. Second, the diverse sites in which clinical trials can occur can potentially lead to varying oversight bodies at federal, state, and local levels. While laboratory and clinical settings may come under OSHA purview for chemical hazards, this agency's nanotechnology-related standards are generic. CDC/NIH oversight for microbiological hazards by means of the BMBL manual will pose challenges for nanomedicine, as active nanopharmaceuticals blur the distinction between biological and chemical agents. The pharmaceutical industry has been proactive in developing performance-based exposure controls and limits, and such approaches will most likely be applied for nanotherapeutics as well. However, just as in the case for conventional "hazardous drugs," such exposure controls for nanomedicines will need to be validated.

It may turn out that nanomedicine therapies do not represent fundamentally different categories of hazards to third parties. However, given the current state of knowledge regarding health risks from such exposures, a more precautionary approach seems advisable. Even if we assume that the health risks posed by nanomedicines are not very different, nanomedicines pose new challenges for monitoring, and therefore, for the validation of control measures. Further research is needed to determine whether the exposure controls for nanomedicines need to be different than those for conventional therapies or drugs that are defined as "hazardous."

Home health care workers are a sector of the health workforce raising particularly acute concerns. These employees are typically inadequately trained in safety procedures and work in residences that usually have few or no exposure controls, with employers having little control over workplace conditions. There is inadequate oversight of occupational hazards in general for such workers, and this will most likely be true for nano-drugs as well. This sector of the workforce requires more extensive study and health surveillance as they face novel technologies with unknown hazards.

Acknowledgements

Preparation of this article was supported by National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) American Recovery & Reinvestment Act (ARRA) Challenge grant #1-RC1-HG005338-01 on "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight" (S. M. Wolf, PI; J. McCullough, R. Hall, J. P. Kahn, Co-Is). The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of NIH or NHGRI.

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