Toxicological and public good considerations for the regulation of nanomaterial-containing medical products

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Increasing research interest in the new and unusual properties of nanotechnology-related pharmaceuticals and medical devices has led to international and national reviews of safety regulation. Significant considerations emerging here are the relative paucity of metrological and toxicological data, as well as the absence of adequate funding and standardized approaches for its acquisition. Some areas are better researched, such as the toxicity of carbon nanotubes and use of engineered nanoparticle titanium and zinc oxides as broad-spectrum ultraviolet-blocking agents. Such in vitro studies do reveal concerns – for example, related to oxidative stress and granuloma formation – but their uncertain clinical ramifications may require more integration in preclinical drug discovery of research characterizing structure–toxicity relationships and limiting safety liabilities. Regulatory considerations for medically related nanoproducts should also involve improving cost-effectiveness systems and ensuring that industry involvement in standard-setting does not become a means of reducing competition. It is also important that nanotechnology policy and regulation encourages new models of safe drug discovery and development that are more systematically targeted at the global burden of disease.

Keywords: nanomedicine, nanotechnology, regulation, toxicology


1. Introduction

Nanotherapeutics can usefully, if not definitively, be defined as involving the manufacturing of medical products from ultra-small particles having at least one dimension less than ~100 nm (0.00001 cm) [1]. Twelve drugs involving nanotechnology as vectors and particle formulations have already been approved for human use. The nanotherapeutics field is rapidly growing, particularly in diagnostic imaging and devices, and is estimated to be worth US$3.7 billion in 2009 [2].

The physical and chemical properties of engineered nanoparticles (ENPs) differ considerably from their bulk equivalents. For example, they have considerably larger surface area per unit mass (increasing their potential for both reactivity and biopersistence), are very hydrophobic and electrophilic, and have quantum effects below 10 nm involving altered conductivity, catalytic properties, and wavelength of emitted light [3]. Some ENPs are the diameter or length of large proteins or viruses (100 – 300 nm) [4]. These factors create promising opportunities for diagnostic and therapeutic product development, but are also stimulating intense interest in the regulation of nanotechnology. The purpose of this editorial is to
highlight some of the most significant considerations currently involved in debates about the regulation of nanomedical products.

2. Nanotoxicity concerns

Significant regulatory, public and professional concerns have arisen about unforeseen and unique toxicities from ENPs. Such concerns are fueled not only by consideration of factors such as their unusual size, shape, surface chemistry and charge, high mobility in the body and reactivities, but by difficulties in determining reference materials and sizes [5]. Both in vivo and in vitro ENPs of various sizes and chemical compositions have been proven to generate reactive oxygen species (ROS) and preferentially accumulate in mitochondria [6]. Research on the human effects of ENPs comes principally from studies of ingestion or inhalation of nanoparticles [7,8]. Only a few specific ENPs have been investigated in a limited number of test systems, and blanket reassurances about human and ecosystem safety appear premature [9].

The Royal Society and the Royal Academy of Engineering issued a report in 2004 that urgently, but unsuccessfully, called for (among other things) increased investment in research into the environmental, health and safety (EHS) aspects of nanotechnology [3]. Particle Risk is one illustrative collaborative toxicological research project funded by the European Commission FP6-NEST program; it aims to assess, from in vitro experiments and animal models of healthy/susceptible individuals, the health risk from exposure to a bank of fullerene C60, carbon nanotubes, carbon black, CdTe quantum dot, and nano-sized gold [10].

Should such projects focus on which ENPs cause most oxidative injury within cells, or on those medical nanoproducts that will be most utilized, create the greater risk of public health problems, or are most important economically? How should such researchers systematically select and obtain reference nanomaterials, standardize and validate in vitro testing approaches, prior to developing toxicity screens? What benchmark exposures should be organized in which test cells, organisms and animals, and with what size and type and concentration of nanoparticles? One approach would be to fund and coordinate exploratory research into fundamental mechanisms of interactions between nanoparticles and biological materials to verify test protocols, while also encouraging systematic targeted research on the toxicity of nanomaterials close to market [3,10].

3. The nano-sunscreens example

The widespread use of titanium (TiO2) and zinc oxide (ZnO) nanoparticles in marketed sunscreens (e.g., in Australia) is a good example of such regulatory uncertainties. When TiO2 particles, for example, are incorporated into cells, mobilization of electrons by absorption of ultraviolet (UV) A light causes the generation of ROS with induction of DNA in human cells (strand breakage and base modification) and cell membrane damage [11]. The International Agency for Research on Cancer (IARC) and the US Toxicology Program rate TiO2 as an improbable human carcinogen [11]. Recent work, however, has shown that ultratine TiO2 (10 – 20 nm) induced oxidative DNA damage, lipid peroxidation, and micronuclei formation in a human bronchial epithelial cell line [12]. Inorganic zinc salts are known to be potent biocides, and zinc oxide nanoparticles (as well as manufacturing by-products containing zinc) manufactured for use in cosmetics and sunscreens are thus currently subject to disposal restrictions in most nations.

Yet most studies indicating lack of ENP dermal penetration below the dead cells of the stratum corneum have been done in non-human skin or on multiple sites in a single subject, taking little, if any, account of demonstrated wide interindividual variability [13]. Likewise, they appear not to have systematically considered cuts, abrasions, dermatological conditions, co-application of insect repellants, pre-existing UV damage, age or flexure of skin, despite the impact that these factors are likely to have on ENP sunscreen absorption in daily life [14]. In 2007, Rouse et al. found, for example, that flexing porcine skin for 90 min facilitated fullerene-substituted peptide ENP penetration of the dermis; ENP size is clearly of utmost importance [14]. Yet most researched preparations for which no dermal ENP penetration has been demonstrated have had effective particle sizes greater than those found in new ‘clear’ or ‘microfine’ sunscreens [15]. Vogt et al., examining ENPs to facilitate transcutaneous vaccination, have shown that, after cyanacrylate skin surface stripping (which removes 30% of the stratum corneum, including keratinized material, lipids and cell debris from the follicular openings), ENPs of ≤ 40 nm do penetrate the stratum corneum, both via follicular ducts and in perifollicular tissue, to enter perifollicular Langerhans cells (potent antigen-presenting cells) [15]. A review of the literature concluded that very small (5 – 20 nm) TiO2 ENPs penetrate into the dermis and can interact with the immune system [16]. Nonetheless, a recent paper involving two authors directly associated with the L’Oréal cosmetic company expresses the view that TiO2 and ZnO nanoparticles in sunscreens pose no additional health risks [17].

4. Conclusion and broader regulatory concerns

Apart from the need for coordination of metrological issues and accumulation of relevant basic data, the nature of existing public safety legislation has become an issue here. A scoping study by the UK Central Science Laboratory, for example, found major areas of existing product regulation that are inadequate to handle the various scales of risk from nanomaterials that blur physicochemical rules [18]. A report
of the influential Project on Emerging Nanotechnologies at the US Wilson Center went further and advocated regulatory technology that can tackle environmental and energy challenges, for example with new solar energy and water treatment technologies and to reduce the amount of energy, water and chemicals used in a whole range of nanotechnology manufacturing processes [19].

Safety and efficacy regulatory approval for nanotechnology-related medical products may create additional concerns for regulators. Nanodrugs, for example, will not fit into abbreviated generic (biosimilar type) abbreviated safety and efficacy approval pathways if they involve increased bioavailability, faster onset of action, dose uniformity, and smaller and more stable dosage forms. Nanotechnology, additionally, will blur the different regulatory pathways that exist for drugs, devices, biologics and combination products. Also relevant are likely to be conflict of interest problems in industry-funded regulatory agencies under corporate pressure to achieve ‘fast-track’ approval of innovative nanotherapeutic products, rather than full implementation of the ‘precautionary principle’ [4].

5. Expert opinion

It is unacceptable from a public health point of view that no health technology regulator internationally currently specifies distinct safety regulations/requirements that must be met by manufacturers in health products. Similarly, no regulatory agency internationally currently possesses effective methods to monitor ENP exposure risks [20]. The aim eventually should be to improve manufacturing methods so that nanoparticles of a standardized size with known low toxicity can be incorporated into medically related products. Nanotechnology drug development may not be well served by existing models where start-up and small biotech companies select profitable targets and carry out little preclinical safety assessment before acquisition or licensing by larger pharmaceutical multinationals [21,22]. Regulatory models promoting academic global cooperation, and developing world capacity-building in nanotechnology for infectious disease diagnosis and treatment, should become a funding priority for governments and major charities [23,24].

One often-overlooked regulatory consideration for nanomaterial-containing products relates to evidence-based assessment (at either national or international levels) of their comparative cost-effectiveness (or ‘health innovation’). Those mandatory reporting schemes or voluntary industry codes of conduct that are currently being debated for nanotechnology regulation should not become a de facto substitute for rigorously enforced public health and environmental protection standards. Similarly, industry involvement in standard-setting committees should not be allowed to become a vehicle for shaping the regulatory architecture so that it freezes out smaller players, inhibits public interest disclosures by employees, or is used to avoid legal responsibilities and penalties. In the interim, before toxicity testing protocols, data and standards are in place, regulatory authorities should consider packaging disclosures of the average size or size range of ENPs involved.

Declaration of interest

TA Faunce is director of an Australian Research Council (ARC) Discovery Grant DP0772231, ‘Regulating medical nanotechnology in Australia: Developing practical improvements in safety and cost-effectiveness analysis.’
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