Expert Opinion

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

Thomas A Faunce
Australian National University Medical School and College of Law, Canberra, Australia

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 nanoparicle 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

Expert Opin. Drug Saf. (2008) 7(2):103-106

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

informa
healthcare

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 nano-products 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 (TiO_2) and zinc oxide (ZnO) nanoparticles in marketed sunscreens (e.g., in Australia) is a good example of such regulatory uncertainties. When TiO_2 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 TiO_2 as an improbable human carcinogen [11]. Recent work, however, has shown that ultrafine TiO_2 (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 the 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 $\leq$ 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) TiO_2 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 TiO_2 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 bio-availability, faster onset of action, dose uniformity, and smaller and more stable dosage forms. Nantoechnology, 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.'

Bibliography

1. US FDA. Regulation of nanotechnology. US Food and Drugs Administration. Available from: http://www.fda.gov/nanotechnology/regulation.html [Last accessed 19 August 2006]
2. Grainger SW. Implementing nanotechnology in near-term medical device markets. Proceedings of the NanoEurope Conference (13 September). St Galen, Switzerland; 2007, p 1-12
3. The Royal Society. Nanoscience and nanotechnologies: opportunities and uncertainties. Policy Doc 19/04; and Report of dialogue between academia and OECD, WPNM policy doc 13/07. London: Royal Society; 2004
4. Faunce TA. Nanotherapeutics: new challenges for safety and cost-effectiveness regulation in Australia. Med J Aust 2007;186:189-91
5. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. Science 2006;311:622-7
6. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 2005;113:823-39
7. Oberdorster G, Maynard A, Donaldson K, et al. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Particle Fibre Toxicol 2005;2:8
8. Borm PJA. Particle toxicology: from coal mining to nanotechnology. Inhal Toxicol 2002;14:311-24
9. Borm PJ, Robbins D, Haubold S, et al. The potential risks of nanomaterials: a review carried out for ECETOC. Particle Fibre Toxicol 2006;3:11
10. IOM Solutions. Risk assessment of exposure to particles. Available from: www.iom-world.org/research/particle_risk.php [Last accessed 1 November 2007]
11. US NIOSH. Evaluation of health hazard and recommendations for occupational exposure to titanium dioxide. CDC. Available from: www.cdc.gov/niosh/review/public/TIo2/pdfs/TIO2Draft.pdf [Last accessed 1 November 2007]
12. Gurr JR, Wang AS, Chen CH, Jan KY. Ultrafine titanium dioxide particles in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Toxicology 2005;213:66-73
13. Flinders Consulting Pty Ltd. A review of the potential occupational health and safety implications of nanotechnology. Australian Safety and Compensation Council. Available from: www.ascc.gov.au/NR/rdonlyres/AC17BA49-8BA1-43B8-BC08219DE53781E6/0ASCCReviewOHSImplicationsNanotechnology2006.pdf [Last accessed 1 November 2007]
14. Rouse JG, Yang J, Ryman-Rusmussen JP, et al. Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin. Nano Lett 2007;7:155-60
15. Vogt A, Combadiere B, Hadam S, et al. 40 nm, but not 750 or 1,500 nm, nanoparticles enter epidermal CD1a+ cells after transcutaneous application on human skin. J Invest Dermatol 2006;126:1316-22
16. Gamer AO, Leibold E, van Ravenzwaay B. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicol In Vitro 2006;20:301-7
17. Nohynek GJ, Lademann J, Ribaud C, Roberts MA. Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. Crit Rev Toxicol 2007;37:251-77
18. DEFRA and Central Science Laboratory (UK). A regulatory gaps study for the products and applications of nanotechnologies (CB01075). Available from: www2.defra.gov.uk/research/project_data/More.asp?I=CB01075&M=KWS&V=Nanotech&SUBMIT1=Search&SCOPE=0 [Last accessed 1 November 2007]
19. Woodrow Wilson International Center for Scholars. Green nanotechnology: it's easier than you think. Available from: www.nanotechproject.org/116 [Last accessed 1 November 2007]
20. OECD. Current developments/activities on the safety of manufactured nanomaterials. Environment, Health and Safety Publications: Series on the Safety of Manufactured Nanomaterials, No. 3. Paris: OECD Environmental Directorate; 2007
21. Nijhara R, Balakrishnan K. Bringing nanomedicines to market: regulatory challenges, opportunities and uncertainties. Nanomedicine 2006;2:127-36
22. Kramer JA, Sagartz JE, Morris DL. The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. Nat Rev Drug Discov 2007;6:636-49
23. Smy J. When cash is no objective. Hospital Doctor 2006;4:29
24. Editorial. Tackling global poverty. Nat Nanotechnol 2007;2:661

Affiliation

Thomas A Faunce LLB (Hons) BMed PhD
Associate Professor and Director Globalisation and Health Project
Australian National University Medical School and College of Law,
College of Law,
Fellows Road, Acton,
Canberra ACT 0200, Australia
E-mail: Thomas.Faunce@anu.edu.au