Nanotherapeutics: new challenges for safety and cost-effectiveness regulation in Australia

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ABSTRACT

- Nanotechnology is a revolutionary field of micro-manufacturing involving manipulation, by chemical or physical processes, of individual atoms and molecules.
- Pharmaceutical and medical device manufacturers, both in Australia and internationally, have significant investments in nanotechnology research and development.
- It is important that safety regulation of nanotherapeutics keep pace with this growing level of industry interest. A recent senate inquiry recommended the establishment of a working party, including representatives of the Therapeutic Goods Administration, to consider whether bulk materials classified as safe should be routinely reassessed for use at the nanoscale level by a permanent, distinct nanotechnology regulator.
- Safety regulation of nanotherapeutics may present unique risk assessment challenges, given the novelty and variety of products, high mobility and reactivity of engineered nanoparticles, and blurring of the diagnostic and therapeutic classifications of "medicines" and "medical devices".
- Nanotherapeutics is likely to make increasing claims on a particular area of Australian health care regulatory strength: scientific cost-effectiveness assessment of innovation in medical products.
- Any review of Australian regulation of nanotechnology should include a critical analysis of both safety issues and cost-effectiveness assessment systems for nanotherapeutics.

MJA 2007; 186: 189–191

Medical nanotechnology involves the engineering design, fabrication, application and regulation of drugs and therapeutic devices that are about 1–100 nanometers in size (ie, consist of atoms, molecules or macromolecules) (a nanometer is 10^{-9} m).[1] Nanostructures have much greater strength, stability and surface area per unit mass than standard materials, and those less than 10 nm in size possess quantum effects whereby size may control, for example, conductivity, the specific wavelength of emitted light, transparency, or capacity to be a catalyst.[2]

Nanotherapeutics is a rapidly expanding area of medical research and development, with revolutionary implications for orthopaedics, drug delivery and gene therapy.[3] Most major pharmaceutical companies have substantial investments in nanotechnology as a way to improve targeting, efficacy and bioavailability of therapeutic products, reduce systemic side effects and increase income from off-patent drugs (Box 1).[14] Manufacturers of invasive medical devices (for example, producers of cardiac stents) are also showing increasing interest in nanotechnology applications.[15] In Australia, nanotherapeutics is a rapidly growing industry sector (Box 2).

Assessing safety risks of nanotherapeutics

A major concern with this unprecedented research and development is that engineered nanoparticles (ENPs) may present unique health risks when used in medical applications.[16] They are highly reactive and mobile within the human body, and there are currently no effective methods of monitoring ENP exposure risks in patients or health care workers.[17] Preclinical safety evaluations of nanotherapeutics by the Australian Therapeutic Goods Administration (TGA) appear likely to rely on established risk-assessment criteria for new medicines. These require expert interpretation of, and evaluation reports on, raw data from carefully controlled and documented lifetime animal studies in independently audited facilities.[18] Yet a report recently commissioned for the Australian Safety and Compensation Council (ASCC) has found that the health risks of nanostructures cannot be predicted a priori from their bulk equivalent and that animal studies in this area, although limited, raise serious concerns (Box 3).[19]

Despite such findings, one of the first nanomedical devices approved by the United States Food and Drug Administration (FDA) bypassed the requirement for a lengthy and costly clinical study because regulators deemed that its constituent nanoscale calcium phosphate fitted a category of existing approved macroscale products.[23] Similarly, a nanoparticulate reformulation of an existing drug has been deemed by the FDA not to require an Abbreviated New Drug Application because bioequivalence was established.[24] Public confidence in such determinations is challenged by recent intense scrutiny of the FDA for perceived inadequacies and conflicts of interest.[25]

1 Nanotherapeutic applications

- Supraparamagnetic iron oxide nanoparticles may allow magnetic forces to target drug delivery[4]
- Functionalised amyloid fibrils may create tuneable nanobiomaterials that display ligands and interact with specific cells[5]
- The world's first successful cancer vaccine is composed of self-assembling biomolecular nanostructures called "virus-like particles"[6]
- Micro-nanoprotection array patch technology may allow delivery of biomolecules to specific skin cells and organelles within them, bypassing cold-chain problems[7]
- Peptide nanotubes have been investigated as the next generation of antibiotics[8] and as immune modulators[9]
- Nanogenerators are being engineered that utilise an antibody to direct a caged radioactive atom (actinium-255) to destroy cancer cells[10]
- Nanoparticles may provide an efficient delivery system for DNA vaccines[11] and gene therapy[12]
- In 2005, the US Food and Drug Administration announced approval for a silver nanotechnology coating that purports to render common invasive medical devices (such as urinary and intercostal catheters) relatively impervious to infection-causing bacteria[13] ◆

2 Some current Australian nanotherapeutic applications

- Advanced Nanotechnology Limited produces a range of nano-scale powders for use in cosmetic coatings, pharmaceuticals and medical devices
- Micronisers Pty Ltd exports transparent, non-allergenic sunscreens and talc powders to cosmetic and sunscreen manufacturers
- Alchemia Limited's nanotech heparin product will be commercialised in 2008 in partnership with the Dow Chemical Company and American Pharmaceutical Partners Inc.
- Starpharma Holdings Limited, in partnership with the US-based company Dendritic NanoTechnologies Inc, is developing VivaGel (an HIV-prevention microbicide gel), the first dendrimer-based drug to be approved for human trials by the US Food and Drug Administration
- pSivida Ltd, an Australian-listed public company with a substantial shareholding in pSiMedica Ltd (UK), has patented its nanotech silicon drug delivery system (BioSilicon) in China ◆

Gathering, analysing, categorising and characterising safety data for individual nanotherapeutic products may be unusually difficult.[21,22] Recently, for example, TGA regulators reviewing the scientific literature on nanoparticulate titanium dioxide and zinc oxide in sunscreens found evidence, from isolated cell experiments, of DNA-damaging free radical formation on light exposure, but apparent lack of penetration below surface layers of the skin.[26] Related issues include whether nanotherapeutic devices should fall within international regulatory harmonisation processes permitting provisional safety approval linked with post-marketing surveillance, although this challenges the precautionary principle.[27,28]

Additional challenges for Australian nanotherapeutic regulation involve recent obligations acquired under the Australia–US Free Trade Agreement (AUSFTA), which require discussion between the FDA and the TGA about making "innovative" pharmaceutical products more speedily available (Annex 2C.4).[29] These are also likely to apply to operation of the proposed Australia–New Zealand Therapeutic Products Agency.[29]

The issues of ENP safety, quality and efficacy regulation are pressing. The US Nanoscale Science, Engineering and Technology Subcommittee has indicated that a regulatory crisis involving nanomedicine safety — similar to that surrounding severe cardiovascular side effects from the anti-arthritis medication rofecoxib or the public concerns about genetically modified food — could cripple public, shareholder and investor confidence in the nanotherapeutics industry.[30]

Assessing the cost-effectiveness of nanotherapeutics

Reimbursement for new and often "innovative" pharmaceuticals and medical devices (such as those likely to use ENPs) is a significant and increasing component of government health care expenditure. In this context, cost-effectiveness assessment of allegedly innovative medical products, linked to a central government price negotiation, is internationally becoming an accepted part of the health technology regulatory approval process.[31] Potential challenges here for Australian nanotherapeutic cost-effectiveness regulation involve the inclusion of industry lobbying principles in the AUSFTA requiring greater policy recognition of the undefined concept of pharmaceutical "innovation". This may be achieved either through the operation of "competitive markets" (requiring a greater role for competition regulators) or through expert evaluations of "objectively demonstrated therapeutic significance" (supporting evidence-based assessments of the comparative community value of allegedly innovative medical products by the Pharmaceutical Benefits Advisory Committee [PBAC]) (Annex 2C.1).[32]

3 Issues for safety and cost-effectiveness regulation of nanotherapeutics[19-22]

- Terminological definitions and standards used in differing nanotherapeutic assessments need to be clarified.
- Long-term safety of engineered nanoparticles (ENPs) in humans needs to be established. ENPs in isolated cell experiments have caused DNA damage. Short-term ENP exposure in animals has produced dose-dependent inflammatory responses and pulmonary fibrosis. Chronic in-vivo exposure studies (in particular, of reproductive toxicity) are yet to be published. Some ENPs preferentially accumulate in mitochondria and inhibit function. Others may become unstable in biological settings and release elemental metals.
- Gaps in nanotherapeutic safety data need to be systematically determined, and government support needs to be directed to the relevant fields of nanotoxicological research.
- Individual nanotherapeutic applications may overlap different classifications of medicines, medical devices, and diagnostic and therapeutic risk assessment classifications and pathways. Potential or actual weaknesses in the existing regulatory framework need to be located and addressed.
- Workable and consistent standards and guidelines for therapeutic ENP use and handling, monitoring and labelling need to be developed.
- Any revised regulatory system needs to factor in the likely high cost for "innovative" nanotherapeutics, as well as difficulties in classifying nanotech versions of existing off-patent pharmaceuticals as "generic".
- Medical device regulation, which nanotechnology is likely to completely reshape, has a limited cost-effectiveness literature compared with that of pharmaceuticals.
- In Australia, the Medical Services Advisory Committee (MSAC) may have a role that is equally important to that of the Pharmaceutical Benefits Advisory Committee (PBAC) in cost-effectiveness regulation of nanotherapeutics. But the MSAC differs from the PBAC in having ad-hoc rather than standing expert evaluation committees, no distinct statutory criteria, much longer assessment time frames, and different transparency processes. ◆

The availability of relatively inexpensive "generic" medicines is important for fulfilling the goal of equity of access under the Australian National Medicines Policy. However, the generic (rather than innovative) status of nanoparticulate versions of off-patent drugs will be problematic. Blurring of the categories of "medicines" and "medical devices", and inherent regulatory differences between the two, may cause particular difficulties for cost-effectiveness evaluations of nanomedicines by the PBAC, assessments of nanomedical devices by the Medical Services Advisory Committee (MSAC) and related price negotiations in the public interest (Box 3).[33]

Is gene technology regulation a good model?

A recent senate inquiry recommended creation of a working party, including TGA representatives, to consider whether bulk (macro-

scale) materials classified as safe need reassessment for use at the nanoscale level. The inquiry also examined the value of a distinct, permanent regulatory body for nanotechnology.[34] This approach was taken with gene technology under the *Gene Technology Act 2000* (Cwlth).[35] This broad licensing strategy, encompassing regulatory industrial, agricultural and therapeutic applications, has worked well, but suffers from not explicitly emphasising Australia's regulatory strength in cost-effectiveness evaluations. On the other hand, merely employing or adapting existing TGA, PBAC and MSAC models, with or without elements of self-regulation, may lead the public, prematurely, to assume that nanotherapeutics raises no unique risks or hazards.

Risk assessment of nanotechnology is emerging as a complex and significant issue for public health in Australia. It is critical that any regulatory review in this area not overlook the importance of strengthening safety and cost-effectiveness assessment systems for nanotherapeutics.

Competing interests

I am Project Director of an Australian Research Council (ARC) Discovery Project (DP0772231) on safety and cost-effectiveness regulation of medical applications of nanotechnology. The ARC was not involved in the preparation of this article.

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(Received 22 May 2006, accepted 18 Oct 2006) ❑