Researching safety and cost-effectiveness in the life cycle of nanomedicine

Thomas Faunce and Kathy Shats

Nanotechnology is rapidly emerging as a transformational influence on many industry sectors. This is particularly true of medicines and medical devices. This article argues that, as policy interest in devising an appropriate regulatory framework for nanotherapeutics escalates, it will be important for public health to ensure that a broad life-cycle approach to both safety and cost-effectiveness is adopted. It charts some of the most important issues likely to be faced and begins to map how they can best be addressed.

INTRODUCTION

The term “nanotechnology” was first coined by Feynman in 1959. The nanotechnology industry since then has boomed, with investment worldwide expected to reach US$1 trillion by 2015. The technological impact of nanotechnology has been compared to that of the Industrial Revolution. It has even been heralded as a possible solution to pollution and climate change in developed nations and food and water problems in the developing world.

Yet, as interest and promise in the industry grows, concerns regarding safety and societal implications are rapidly emerging in academic literature and government, international and non-governmental organisations (NGOs), as well as within the private sector. Some critics are calling for a moratorium on all nanotechnology research, development and marketing until all the risks can be assessed. Other critics have recommended a complete moratorium on production of nanomaterials. Their concerns are echoed by scientists, ethicists and scholars, as evidence of potential risks and dangers emerges within an “ethical-legal void”.

In 2004, an influential report by the United Kingdom Royal Society and Royal Academy of Engineering became a catalyst for the debate on regulation of nanotechnology. One area that seems to have received insufficient attention in these debates is cost-effectiveness analysis, ensuring that the community receives real value for the money it spends on presumptively innovative nanotechnology. This will be a particularly important concern in relation to...
medical applications of nanotechnology. This article argues that a broader approach to regulation of nanotherapeutics needs to be taken than merely a focus on traditional safety issues.

**REGULATING NANOTHERAPEUTICS SAFETY RISKS**

One of the greatest regulatory challenges will lie in the risk assessment of nanotechnology generally, and particularly in nanotherapeutics. Nanoparticles (NPs) pose new risks to health (both in the manufacturing process and consumer use) and consequently to the environment. While there is a lack of research and agreement regarding the effects of NPs on biological systems, it is generally accepted that, due to the decrease in size, and consequent changes in surface area to volume ratio, NPs may exhibit new and different properties to the equivalent substance on the macro level. As a result, NPs are more toxic and reactive within biological systems. Issues of risk assessment arise in relation to the manufacturing process, the use of nanotherapeutics in health care, and the environmental consequences.

It is accepted that size has a significant impact on the toxicity to human health of any materials. Many materials which are harmless in bulk have been known to become toxic to human health when broken down into small particles. There is strong evidence that apparently non-toxic particles on a fine or nano scale can cause inflammatory lung injury, and have toxic effects on cells and organs. It is easy to see why many commentators are concerned about “the possibility that NPs could become the asbestos of the 21st century”.

Risk assessment models must also consider the bioaccumulation and redistribution of NPs within various organs and tissues. NPs between 20 and 50 nm have the potential to enter the central nervous system and cells, while gold NPs are able to move through a mother’s placenta to the fetus. Concerns about the ability of NPs to cross the blood-brain barrier, as well as to accumulate in the liver, have also been highlighted by numerous sources. There is also evidence that macrophages may not recognise NPs smaller than 70 nm, allowing them access into the pulmonary interstitium. Gwinn and Vallyathan reviewed the toxicity of ultrafine particles (UFPs) to human health and compared the risks to NPs, concluding that “there is reason to suspect that NPs with size and surface characteristics similar to UFPs are likely to cause diseases – some with a long latency”. The ability of NPs to pass directly into the brain has also raised claims that, when combined with metals, NPs may cause Alzheimer’s disease.

In Australia, it is estimated that there are currently up to 700 workers who may be exposed to NPs in some form, and it has been predicted that globally there will be two million workers employed in nanotechnology-related industries by 2015.
The Australian Senate Community Affairs References Committee report on workplace exposure to toxic dust outlines a number of key concerns about the impact of nanotechnology on workplace safety, including the lack of methods to assess safety or to safeguard workers from exposure, as well as the minimal investment in health and safety aspects of nanotechnology. The report discusses the views of the Australian Institute of Occupational Hygienists (AIOH) and the Australian Manufacturing Workers Union (AMWU) who express concern about the potential for skin penetration and inhalation of NPs in the workplace, and make parallels with asbestos. Many submissions to the committee raised this issue, and were particularly concerned about the long-term effects of NPs which may only manifest after a long time. Dr Wiesner of Rice University has been quoted comparing the shape of carbon nanotubes to asbestos fibres.

The report discusses the views of the Australian Institute of Occupational Hygienists (AIOH) and the Australian Manufacturing Workers Union (AMWU) who express concern about the potential for skin penetration and inhalation of NPs in the workplace, and make parallels with asbestos. Many submissions to the committee raised this issue, and were particularly concerned about the long-term effects of NPs which may only manifest after a long time. Dr Wiesner of Rice University has been quoted comparing the shape of carbon nanotubes to asbestos fibres.

Risk assessment of nanotechnology in health care

The use of nanotechnology in medicine is one of the most promising applications of this technology. There is considerable research into a broad range of medical uses of NPs, including drug delivery, gene therapy and medical imaging. While the risks of NPs in these types of medical applications will overlap with the general toxicological risks identified earlier, it is possible to make more specific predictions as certain parameters such as dosage, biodegradability and size are known and can be controlled to some extent.

The dosage and concentration of NPs have a major influence on toxicity. Wilson discusses studies that have shown pulmonary damage caused by carbon nanotubes in rats and mice, but comments on the danger of attributing this exclusively to the hazards of NPs, as this was a very high dose study. She notes that “high dose studies produce several possible exposure curves, and it is impossible to know which dose curve is being mapped when a high dose is being extrapolated from”. At a low dosage, some chemicals may be completely safe, but can have lethal effects at higher dosages. Wilson also points out that defining a high or low dose is difficult due to the lack of data on exposure levels.

Similar issues arise in relation to the size of the NPs, which can determine their fate in the human body. Wilson compares studies of 1 nm and 5 nm particles, demonstrating considerable differences in their disposition, and consequently health effects, within the human body.

While most policy discussions of nanotechnology centre around the risks and potential for harm, much of the medical literature discusses nanomedicine as a potentially safer alternative to current options. For example, Gwinn and Vallyathan believe that “targeted encapsulated drug delivery using NPs is more effective for improved bioavailability, minimal side effects, decreased toxicity to other organs, and is less costly”. The use of NPs in gene therapy has also been seen as a much safer method than viral vectors, which are currently the primary method of gene delivery. Chan notes that “in theory, nanoparticles are less immunologically reactive than virus vectors and allow delivery of large amount [sic] of genetic material with its large surface area to the target cells”.

Hence, while there is need for more toxicology and safety research, a risk assessment of NPs in nanomedicine needs to be seen in light of current technology, the dangers of which, while perhaps more accepted, may still be very high. Lacerda et al discuss the fact that many fields of medicine, such

---

22 Australia, Senate Community Affairs References Committee Report, n 9, pp 88-89.
26 Wilson, n 25 at 708.
27 Wilson, n 25 at 709.
28 Gwinn and Vallyathan, n 3 at 1819.
29 Chan, n 12 at 220.
as oncology, rely on techniques known to be inherently dangerous, such as nuclear technology. The side effects and dangers are assessed through toxicological studies, and the same should be done for nanotherapeutics. The authors note that “such toxicological and pharmacological characterisation is already part of the process of pharmaceutical development and approval, so nanomedicines should not be considered more harmful than any of the cytotoxic drug molecules being developed”.

**Fate of nanoparticles: Environmental and ecological concerns**

After consumer use (whether medical, cosmetic or technological), the eventual fate of NPs must also be addressed. Although research on potential environmental hazards such as soil and water toxicity is scarce, these risks have been identified and are an essential consideration in any cost-benefit analysis. The UK Royal Society Report expressed concern over the lack of literature and study in this field, but pointed to research on largemouth bass, in which NPs (fullerenes) were found to have translocated to the brain, causing oxidative damage. As with other chemicals, NPs have the potential to enter the food chain through degradation in the water or soil. The report identifies the sources of NPs in the environment as waste streams from factories and laboratories, as well as the widespread use of medicines and cosmetics containing NPs. The greatest source will come from the use of NPs in water and soil treatment, which may have a significant impact on the ecosystem. However, the UK Royal Society Report suggests that although much more research would be needed, it is possible that “any negative impacts on ecosystems will be outweighed by the benefits of the clean up of contaminated land and waters”.

**Toward a broader view on regulatory issues for nanotherapeutics**

Although the potential risks of nanotechnology vary considerably, most commentators believe that some form of regulation is needed, or at least that it is inevitable. Marchant and Sylvester argue that “despite nanotechnology’s generally unfettered past, its future will, in large part, be determined by the legal choices made in the next few years”. As it is almost universally acknowledged that public acceptance will determine the fate of the nanotechnology industry, this must be considered before implementing any particular regulatory scheme. As stated above, many believe that “the future of nanomedicine depends on the degree to which nanotechnology as a whole garners wide-scale public support”.

As evidenced by experience with biotechnologies such as genetically modified (GM) foods and gene therapy, public involvement in the safety and regulatory debate is crucial to secure confidence, and hence the success of the technology. Mehta argues that GM foods failed to gain public support because the public were not involved in the discussion of the risks and benefits of the technology. The benefits flowed primarily to the producers (through agricultural benefits such as herbicide tolerance), while consumers were left with little tangible benefit and a lot of perceived risk. Some authors have expressed concern that lack of government action and public engagement in nanotechnology could have similar results, “where the technology becomes so stigmatized that the public will not accept proof of its safety”.

---

30 Lacerda et al, n 24 at 1461.
31 Lacerda et al, n 24 at 1461.
32 UK Royal Society Report, n 8, p 45.
33 UK Royal Society Report, n 8, p 47.
35 Roco and Bainbridge, n 4 at 7.
37 Mehta, n 36 at 16.
38 Marchant and Sylvester, n 34 at 717.
These concerns carry significant weight. A recent survey showed that the public was more concerned about the risks and implications of nanotechnology than were experts and industry. The research also questioned whether companies were adequately addressing public concerns, particularly when most lack risk-assessment methods to address the issues. This leads to a lack of trust in new technologies, and the authors fear that unless this is remedied, any negative incident arising from nanotechnology could have a severe and perhaps irreparable effect on public perception. This fear is reflected throughout the literature. Mehta contends that unless the risks and benefits are openly assessed and discussed, the technology will evolve in an unstable environment, in which any accident could severely hinder the development of nanomedicine. Wilson illustrates this through a recent example of the cleaning product “MagicNano” in Germany. The bathroom-cleaning product, which claimed to contain nanoparticles, had to be recalled after just three days on the market when nearly 80 cases of severe respiratory problems were linked to its use. Although later it was found that the problems were caused not by NPs but by larger particles, this incident nevertheless caused the public to question the safety of nanotechnology. Similarly, as discussed earlier, many scientists, critics and policy-makers are already drawing analogies between NPs and asbestos. This is an issue about which the public is becoming very well informed and, without open discussion, any adverse links drawn to nanotechnology could easily have a negative impact on public perception.

While some aspects of risk assessment will be specific to nanotherapeutics, many broader issues such as workplace safety and environmental impacts cannot be ignored. Therefore, the regulation of nanotherapeutics cannot be addressed in isolation from broader nanotechnology risk assessment and regulatory issues. However, without more research regarding these issues, it is difficult to gauge the impact of the use of NPs in medicine on, eg, the environment. As discussed in the UK Royal Society Report, the use of nanotechnology in water and soil treatment could potentially be justified if the benefits were found to outweigh the risks. In this case, the environmental impact of NPs from medical applications would be significantly less, and the regulation of nanotherapeutics separately may not be an issue. However, until further research is done, this cannot be assumed, and many activist and environmental groups such as ETC and Friends of the Earth are calling for the precautionary principle to be applied.

Attempting to regulate nanotherapeutics separately also appears illogical in light of the cosmetic industry. As Wilson points out, “While drugs face exacting scrutiny, cosmetics receive no pre-marketing screening. The FDA does not have authority to directly recall a cosmetic that harms consumers.” As there is some evidence that NPs have the potential to penetrate the skin, and as NPs used in many cosmetic products may also enter the body, it would seem logical that the risks they pose are similar to those posed by nanotherapeutics, or the OH&S issues in the manufacturing process.

Rejeski, of the Woodrow Wilson International Centre for Scholars, believes that our current regulatory frameworks will not be able to keep pace with the speed of technological innovation. He argues that “many of our environmental regulations were built on the assumption that industrial

---

40 Mehta, n 36 at 17.
42 UK Royal Society Report, n 8, p 47.
43 Australia, Senate Community Affairs References Committee Report, n 9, pp 89-90.
44 Wilson, n 25 at 708.
production and associated pollution would stay put". Wilson also discusses evidence showing that current environmental laws will not be able to respond to the new risks posed by NPs.

Many NGOs and interest groups are calling for a strict application of the precautionary principle, based on the lack of research into the risks and social ramifications of this technology. Swiss Re, an insurance company, has expressed concern that, as with asbestos, the effects of nanotechnology may be latent, and may result in huge liability for the insurance sector. On this basis, it, too, calls for a strict application of the precautionary principle. In its simplest form, this would shift the burden of proof onto the manufacturers to prove the safety of the product. Marchant and Sylvester discuss the problems arising from this approach. They point to a lack of consensus regarding the exact meaning of the precautionary principle, noting that at least 19 different versions have been identified. They also argue that no version actually addresses Central risk management decisions such as: (i) What level of risk is acceptable? (ii) What early indications of potential hazard are needed to trigger precaution? (iii) How much data must proponents produce to demonstrate that a product or activity is sufficiently “safe” to proceed? (iv) How are costs and risk tradeoffs factored in? (v) What type of action is required to satisfy the precautionary principle? Without being able to specifically address these questions, no regulatory framework can be established. Only the strictest formulation, which would ban all nanotechnology, could be applied before more research is done. This would inevitably halt any development in the technology, and potentially never allow the risks to be assessed.

Bowman and Hodge discuss the differences between the regulatory approaches taken by the United Kingdom and the United States. In response to the United Kingdom Royal Society Report, the United Kingdom Government has taken a proactive approach, and is encouraging all relevant regulatory bodies to assess any possible gaps in the system. Based on the report, the United Kingdom has also accepted NPs as new chemicals, and is looking at new regulatory mechanisms to reflect this. In contrast, the United States does not recognise this approach, and maintains that materials containing NPs do not warrant different treatment, resulting in them being assessed as equivalent to conventional products on the macro scale. This approach has been criticised, with the suggestion that the current regulatory framework within the United States is inadequate to address nanotechnology.

Cost-effectiveness and Reference Pricing in the Regulation of Nanomedicine

Reference pricing is a government price reimbursement mechanism that compares a new pharmaceutical on grounds of independent expert assessment of objectively demonstrated therapeutic significance related to outcomes on its primary clinical indication, against already available products and therapies in the same therapeutic group. Prices of all drugs in such a group are tied to that of the

---

46 Rejeski, n 45, p 47.
47 Wilson, n 25 at 707.
48 Australia, Senate Community Affairs References Committee Report, n 9, p 90.
49 Marchant and Sylvester, n 34 at 721.
50 Marchant and Sylvester, n 34 at 721.
51 Marchant and Sylvester, n 34 at 721.
53 Bowman and Hodge, n 52 at 19.
lowest, or in some cases the average, price.\textsuperscript{56} The reference price does not become the market price for all drugs in the same therapeutic class, but is a benchmark.\textsuperscript{57} Manufacturers can set prices higher than the reference, but in doing so they need to genuinely compete in the open market against equivalent lower-priced medicines. In this sense, reference pricing is an inherently pro-competitive fiscal lever that assists governments to ensure that expensive new technologies that make claims of innovation based on remarkable technical novelty are actually offering genuine benefit to the community on hard clinical outcomes such as quality adjusted life years (not surrogate physiological measures) when compared to existing marketed products.\textsuperscript{58}

A regulatory technique such as reference pricing fulfils a blueprint for a sustainable global health technology industry such as that set out in the Australian National Medicines Policy. The four principles of the National Medicines Policy are:

• timely access to the medicines that Australians need, at a cost individuals and the community can afford;
• medicines meeting appropriate standards of quality, safety and efficacy;
• quality use of medicines; and
• maintaining a responsible and viable medicines industry.\textsuperscript{59}

A regulatory system for nanotherapeutics will need to ensure the preservation and enhancement of fiscal levers that expertly value health technology innovation transparently and accountably against scientific criteria of objectively demonstrated therapeutic significance. Particularly important in this context will be the maintenance of reference pricing for those allegedly innovative nanomedicines that are unable to prove greater efficacy or safety than any existing therapy (drug or otherwise).

This is why recent amendments to the \textit{National Health Act 1953} (Cth) fracturing the unitary PBS formulary into an F1 category (for patented medicines) and F2 (for generics) (new ss 85AB and 85AC) should be repealed. Such amendments limit evidence-based reference pricing between those categories and by creating the prior and almost unachievable standard of “interchangeable on an individual patient basis” between two comparators (new s 101(3BA)), leave open the door to escalating prices in Australia for patented nanomedicines.

\textbf{CONCLUSION}

Positive and negative aspects have characterised national and international regulatory models of biotechnology regulation.\textsuperscript{60} National regulatory systems can be tailored to meet local social and economic demands, allowing countries to experiment in order to find the most suitable model. However, these approaches may ignore potential security risks, such as cross-border pollution or even the possibility of an arms race. The GM food industry suffered significantly as a result of different national regulatory schemes. The different social and legal issues within each country resulted in “a substantial burden on GMO researchers and scientists to assure regulatory compliance in the development, export, and use of GMO technologies”.\textsuperscript{61} It has been proposed that nanotechnology will inevitably have to be regulated at an international level due to the global scope of the environmental, security and economic issues.


\textsuperscript{60}Marchant and Sylvester, n 34.

\textsuperscript{61}Marchant and Sylvester, n 34 at 717.
It also has been suggested that current international regulatory frameworks may be developed to incorporate nanotechnology governance. Bowman and Hodge discuss the possible roles of the World Trade Organisation (WTO) and the Organisation for Economic Cooperation and Development (OECD) in international nanotechnology regulation. They conclude that while they will not provide a complete system, “the OECD’s effort to establish guidelines (ie, forms of ‘soft law’) is likely to become a foundation for any emerging consensus on global frameworks and codes of conduct”.

Perhaps the best mechanism for ensuring a balance of public and private goods, and for revitalising markets towards responsible sustainability, is an international treaty on health technology safety and cost-effectiveness. Such a treaty could play a critical role in regulating the global nanotherapeutics to ensure community value as well as sustainable profits.

62 Bowman and Hodge, n 52.
63 Bowman and Hodge, n 52 at 36.