10 June 2008

The Hon Tony Catanzariti MLC
Chair
Standing Committee on State and Development
Parliament House
Macquarie St
Sydney NSW 2000

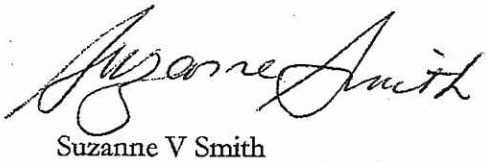
Dear Mr Catanzariti

Nanotechnology in New South Wales Inquiry.

Thank you for the invitation to address the Standing Committee on State Development on Nanotechnology in NSW.

I have attached a copy of my opening remarks and look forward to an opportunity to address any specific questions or aspects of this report with the committee.

Sincerely



Suzanne V Smith
Research Programme Leader
Institute of Materials Engineering
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Nanotechnology in New South Wales

Public Hearing Tuesday 10 June 2008 4.15 pm

Dr Suzanne Smith, Research Programme Leader, Institute of Materials Engineering ANSTO

Opening Remarks

Firstly let me thank the enquiry for the opportunity to address this forum. Before I address your questions, I would like to take this opportunity to explain my background and my interest in this process. I am the Research Programme Leader in the Institute of Materials and Engineering (IME) at ANSTO. I use radiotracers (ie. radioisotopes incorporated into molecules) to determine the relationship between the structure and function of materials for various applications. I have worked in the Institute for the last 6 years. Prior to that I worked in various medical research divisions of ANSTO for 13 years, as well as research fellow at Harvard Medical School, Boston, USA. During my time at ANSTO, I have led teams in the research and development of radioisotopes and radiopharmaceuticals [1]. I developed intellectual property and patented technology in the production of radioisotopes, radiolabelling technology for Positron Emission Tomography (PET) imaging applications, and radiolabelling of platinum chemotherapeutics for use in prognosis of disease. I have also been intimately involved in the preparation of products [employing Good Clinical Research Practices (GCRP) and Good Manufacturing Practises (GMP)] and submissions for clinical trials protocols and the registration of drugs.

Rapid advances and unusual and often unpredictable properties of materials in the nanosciences created a strong personal interest to apply many of the strategies employed in the research and development (R & D) of radiopharmaceuticals to the R & D pathways of new materials. Measuring the performance of these new materials requires their analysis with tools that are significantly more sensitive and specific than the readily available conventional tools. The high sensitivity of radiotracers and, more importantly, the ability to design "purpose built" radiotracers (much like one does in drug targeting) make them ideal for investigating the properties of many of the new nanomaterials. Furthermore, as radioisotopes can be detected in solid, liquid and gas states, they are independent of media, so can be used to probe interactions between solid and liquid interfaces.

The nation's investment in the OPAL reactor meant we could be flexible and develop a wide range of radiotracer probes (with short half-lives - hours to months) to address the rising and changing challenges of the international materials science research community. The high sensitivity of the radioisotopes could enable scientists to monitor the *whole of the life cycle* of these materials, and develop strategies to enhance screening and scale up the engineering processes of new materials, as well as conduct risk assessment of materials and track their movement in production, biological and environmental systems. This information could be used to support advances in research, industry and regulatory bodies.

Reflecting on the pharmaceutical drug development arena, one is mindful of the costs of developing technology. Indeed, the challenges of this field are not unlike what we are facing in the commercialisation of the nanosciences. In attempting to identify areas where radiotracer technology could contribute to *reducing time to market* and the *risk assessment* of materials, it is worth highlighting some of the challenges in R & D of the pharmaceutical industry, and where lessons might be learned as we advance nanotechnology to the marketplace.

1) *Identifying Lead Compounds.* At present only 1 in 8,000 to 10000 compounds synthesized in the pharmaceutical industry make it to the marketplace. This illustrates not only why the process of identifying a good drug candidate is so costly, but also why it is so difficult to develop a compound that targets the site of interest well but does not cause toxicity to the rest of the body. At ANSTO we are developing methods for the rapid, high through-put screening of the performance of materials using radiotracers. This information is used to determine structure/activity relationship of novel materials which we use to feedback into the materials engineering process in order to enhance the design of new materials. The high sensitivity of radiotracers produced at the National Medical Cyclotron and OPAL reactor, as well as neutron activation, enables us to assess very small quantities of material (milligram to microgram quantities) in static and dynamic systems that are relevant to the desired application of the new material. This strategy can also be used to provide on-line monitoring of processes, and, therefore, used to rapidly detect changes that cannot be registered easily by other techniques. This approach can aid in reducing the time taken, and increase confidence in, the selection of lead candidate materials.

2) *Scale up of the production Processes.* For example, the concept of targeting disease with an antibody was first proposed in 1975, but it took many years before its large scale production was possible - at considerable cost to the industry. Sometimes scale-up of a process requires invention of new technologies, but mostly it requires a deeper knowledge of the chemical reactions on a large scale. We are designing radiotracers (radiolabelled precursors) that can be employed during the engineering process that can act as *on-line* monitoring systems. This approach has the potential to contribute to the optimisation of engineering processes, in areas such as reducing time and improving yields of the process. The radiotracers can also be used to assess manufacturing environments, by monitoring the movement of nanoparticles, therefore providing valuable information for both industry and regulatory bodies to define safe work practises.

3) *Toxicity.* Often compounds deemed good targets do not make it through clinical trials, or survive in the marketplace, due to toxicity. A withdrawal of an approved product from the marketplace can have a devastating impact on the company in question; also to other similar technologies under development. The cost to the industry can be hundreds of millions of dollars. For example, when the first antibody imaging agent (produced by murine source) was used, there were many reported allergic reactions. Furthermore, patients' immune systems recognised it as a foreign object, and cleared it rapidly from the body. Hence a repeat injection (which was the original intention) of the product was not possible, rendering the imaging agents useless for these patients.

This result severely impacted on the progress of other products under development or in the pipeline throughout the industry. It also severely impacted on further uptake of this type of technology by the clinical community, even though the original proposal of targetting with an antibody came from very sound scientific reasoning. Hence, the research community not only had to go back to the drawing board to develop humanised antibodies that would not be recognised by the body as foreign, and therefore would be safe to use, but also had to make substantial efforts to change perceptions of the marketplace and regulatory bodies. Today we talk about the success of *Herceptin* for breast cancer treatment. It is an antibody based technology that did not have a very clear path to market. This is reflected in its cost - that is now shared between patients, the insurance industry and government bodies around the world. Obviously, this is a situation that everyone would like to avoid for the nanotechnology arena. Therefore, developing toxicity assays that are meaningful and relevant to the applications are

key to the commercialisation of new materials. Using assays that are already available will be one strategy, but they will need to be adapted for the nanotechnology arena, and specific to application. Ensuring the engagement of the user community, and that their issues are addressed in these processes early in the development path, will be essential for uptake of any nanoscience technology. Because the applications of nanotechnology are so diverse, the "footprint" of these technologies will vary. Hence, they will require the development of a wide range of risk assessment assays.

Furthermore, in describing the field of nanotechnology to the general public, we have failed to clearly define areas where one nanoparticle is not like another and therefore clearly defined where it might be used in various technologies. This has created the perception that all nanoparticles are the same. Therefore, poor management in the risk assessment of any aspect could impact widely in the field. The cost (both financially and to market penetration) to each community within the nanoscience arena could be significant if not addressed adequately. It is perhaps now timely to emphasise that the properties of nanoparticles are dependent on size, shape and composition. This means that some toxicity assays of these materials will be relevant to some applications, but totally irrelevant to other applications.

4) *Regulatory process* (including the clinical trial [phases I, II and III] and time to market). These processes are essential, but they can be conducted over many years, and are extremely costly ($US800 million to $US1 billion over 10-15 years)[2]. The impact on the public community is such that less affordable drugs make it to the marketplace, and governments have to subsidise the cost of treatments using them. The industry focuses its efforts on products that are "block busters" that will produce the greatest revenue in the shortest period of time (largely forced on them due to the limits on the lifetime of patents). Years ago, R & D programs of pharmaceutical companies could develop products for both small and large markets. However, this approach is not commercially viable today, due to time taken by, and the cost of, the regulatory process.

Today there is a significant push in the pharmaceutical industry to develop imaging agents (radiopharmaceuticals) for clinical trials and for "proof of mechanism". The estimates are that only one in five drugs make it through all phases (I, II, III) of clinical trials to market. This is due to a steady decline in the number of products specifically passing phase II of clinical trials (only 1 in 5 products are successful). However, if this number could be increased to 2 or 3 in 5, then the cost to develop a product for the market would be reduced substantially (estimated to be up to 50%). Pharmaceuticals groups like Pzifer have proposed using imaging agents during the phase I trial of their therapeutic agents - to reduce the risk of false positives (ie decrease the number of drugs that are less effective), and to increase the risk of false negatives (reduce the number of drugs that have the potential to cause toxicity). This company reported that if it could increase the success rate in phase II, it could substantially reducing the overall cost of their R & D programs. The argument here is that a "no go" is just as valuable as a "go" answer.

In conclusion, because properties of nanoparticles are thought to be dependent on their shape, chemical composition and size, and little is understood about the interactions of nanostructured materials with living systems, it is essential for companies to implement precautions to protect their staff, the environment and consumers. As the applications of nanomaterials can be quite diverse, it is essential that their risk assessment is conducted under relevant conditions. Determining the toxicity of any material can be expensive; however, developing assays that are sensitive and relevant to the application as early as possible in the development path will undoubtedly keep the cost to industry R & D programs to a minimum.

The high sensitivity of radiolabelling techniques, and the ability to design radiotracers that are specific to the applications, means they could contribute to many steps in the R & D path through to the market for nanomaterials. Radiotracers can provide unique and valuable information that can benefit research, industry, government and regulatory bodies alike.

Protection of know-how and information generally occurs when the investments are high, ie later in the R & D process. This approach has severely impacted on the pharmaceutical industry, and now we see the costs transferred to the healthcare industry and government. If information on the toxicology of material is readily available to the material science community early in their development programs, then there can be real cost savings for everyone: researchers, industry, government and the consumer.

Overall, the commercialisation of the nanotechnology field would benefit from research efforts and funding in four key areas:

- Developing internationally acceptable standards (scientific community and general public) for the characterisation of nanomaterials, and modifying relevant existing toxicity assays to meet the needs of the nanotechnology field. Then, implementing these toxicity assays early in the R & D pathway.

- Developing research programs to accurately monitor the *footprint* of these new materials, incorporating consideration of recycling processes, so that appropriate measures can be put in place to manage risk and impact to the environment. These will need to be adapted to the requirements of each industry, and the applications, as they arise.

- Disseminating widely the information collated so that those developing technology in similar fields may make the necessary adjustments early in their R &D programs.

- Developing a *National Hub* in the risk assessment of nanotechnologies. This hub should support both industry and non-industry researchers. It could serve to develop technologies for the risk assessment of new materials, transfer of technology to industry, research and regulatory bodies, and train staff and students in each of these communities. A national facility that is transparent in its processes, and is seen to have "no conflict of interest", could become the source of information vital to the development of nanotechnology at national and state levels.

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[1] The radioisotope or radionuclide is an atom that has an unstable nuclear that decays to to a stable atom by giving of a radiation, or gamma ray. They are commonly incorporated into molecules, knowns radiopharmaceuticals of radioactive drugs, that are used to imaging or track disease in the body of a patient or to treate the disease. Radioisotopes can occur naturally but can also be artificially produced, such as those produced in a reactor or a cyclotron.

[2] Nunn AD: The cost of developing imaging agents for routine clinical use. *Invest. Radiol.* (2006) **41** (3): 206 - 212; Dimasi JA, Hansener W, Grabowski HG: The price of innovation: new estimates of drug development costs. *J. Health Econ.* (2003) **22** : 151 -185; Frank RG: New estimates of drug development costs. *J. Health Econ.* (2003) **22**: 325 -330.

Nanotechnology in New South Wales

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Dr Suzanne Smith, Research Programme Leader, Institute of Materials Engineering ANSTO

1) *Are there standards in place for toxicity assessment that can be applied to nanomaterials? Is there a range of methodologies for tracking nanomaterials or nanoparticles when assessing their toxicity, and, if so, does this pose any problems?*

There are a number of assays that are used or could be used to determine the toxicity of small molecules that could be adapted for nanoparticles. However, due to their design and relatively poor sensitivity, it is often difficult to fully interpret the results relevant to nanoparticles. For example, many assays use cell death as a measure of toxicity. For these assays researchers expose a certain number of cells to a fixed number of particles and then monitor the number of cells that die or a biological response of the cells over a period of time. They relate the measured response to toxicity. However, determining the number of nanoparticles that are required to gain a particular response is not easily achieved with these assays. Determining if the particles have aggregated and formed a larger entity, or whether the measured response is due to the particle non-specifically binding to the cell wall, or being internalised, are important parameters than need to be determined. Ensuring the assay is based on exposure to a "realistic" concentration of nanoparticles is also important in determining the risk or hazard of a material.

The present detection systems used to monitor transport of nanoparticles cannot be easily adapted to bulk high through-put assays. Hence, we are developing methods for radiolabelling nanoparticles with radioisotopes that can be used to track nanoparticles *in vitro* and *in vivo*. The radiolabelling methods are highly sensitive; essentially, we change less than 0.001 % of the atoms of a single nanoparticle. We can tailor the radiolabelling technquie to suit the applications. So, if we want to image where the nanoparticle is going, we can change the radioisotopes to suit the imaging tool (such as single photon emission computerised tomograpy [SPECT] or positron emission tomography [PET]).

For determining the ecotoxicology, it is important to be able to track nanoparticles via a number of processes. Hence we radiolabel the nanoparticles with long lived radioisotopes and monitor their transport through water, soils, algae and various animal species. These studies can be conducted safely on a small scale using simulated scenarios at ANSTO. They can provide valuable information and input for modelling processes to predict pathways that might occur in the real life situations environment. They can be conducted easily to ensure safe management of materials and radioactive waste, and can substantially reduce overall cost, because they would not need to be conducted at numerous external sites. More importantly, evaluation of proposed control measures for the prevention and/or control of risk can be tested and applied at each point in the product's life cycle.

2) Safety/toxicity testing can be a significant cost for businesses wishing to take a product to commercialisation. Can you advise the Committee on the potential for reducing these costs without compromising safety?

Any effort to introduce simple screening processes into the R & D pathway is well recognised to produce significant cost savings overall for a commercialisation program. However, it is difficult to quantify the cost or savings that a nanotechnology business will achieve by introducing toxicity tests with the little data that is now available for such a vast array of applications. For industry the key driver is to ensure that the company does not progress a new material through the development path that will later fail from a simple risk assessment – or, expressed alternatively, to identify materials that are most likely to succeed and pass the regulatory processes.

For example, a simple stability test of a self-healing material (anti-corrosion paint for your speed boat) can be achieved by neutron activating the inhibitor, and testing its release from the material. in a corrosive environment. Because the radioisotopes can be detected at very low concentrations, the studies can be completed faster than those using conventional technology. Considerably less material is required for these tests, therefore a wider range of assays can be completed using fast throughput techniques (reading can take seconds and minutes).

Also, developing a "national hub" that can simulate miniature manufacturing processes, and product life cycles scenarios for tracking the behaviour of the radiolabelled nanomaterials,

would provide unique information for R & D programs. Sharing of this type of facility or capability among industry and research would provide an opportunity to normalise data, and give a better reference point for benchmarking performance. Furthermore, if the information is made readily available, then those developing technology in the same area can use this information to enhance their materials or simply to re-engineer materials.

3).Currently where does the impetus and funding come from for toxicology research? Can you suggest anything that might make toxicology research attract more funding from the government and industry sectors?

Presently we have collaboration with U QLD which obtained a Smart State Grant to assess the toxicity of materials. ANSTO and Australian Insitute of Nuclear Science and Engineering (AINSE) provide a small amount of funds to support our nanotoxicology project by funding a PhD student from U QLD. Collectively, we have applied for NHMRC funding, and are awaiting a decision on that application.

However, these funds are really only token in terms of solving the overall goal that the nanotechnology community needs to address now and in the near future. As noted in 2) above, a state or nationally driven program "hub" or user program would encourage the sharing of resources and capabilities for the type of research programs necessary to support the commercialisation of Australian nanotechnology. Funding mechanisms should give priority to R & D programs that are implementing risk assessment of their technologies.

A *national facility* much like that developed for the ANSTO neutron scattering facility, which industry and research groups from around Australia could access, would benefit the entire nanotechnology community, and may also attract international interest. Government, industry and the research community could share in the cost of maintaining the facility, expertise and research programs that will need to adapt to meet changes in the field. This type of approach would avoid duplication around the country, and generate better solutions to problems where there is a common goal.

The information and technology developed in risk assessment should be made readily available. Governance of a national facility would need to be transparent, and be able to demonstrate 'no conflict of interest'. Because of the diversity of applications, there will need

to be strong links to the existing regulatory bodies, and information sharing should be strongly encouraged.

4) A number of submissions have argued that toxicology research should focus on nanomaterials that are being researched or developed for commercialisation. Do you agree that this would be the best approach?

I think we should conduct toxicology research on both products already commercialised and those under development. Where products have made it to the marketplace and there is no evidence of toxicity as yet, we can use them as benchmarks for new technology. Understanding how commercialised materials interact with living systems, and their footprint, will help researchers to design toxicity assays and critically evaluate the relevance of these assays to each type of nanoparticles (with consideration of shape, size and composition of the nanoparticles) and their ultimate process application. They can also act as a validation of methods which can be tested in a number of laboratories. If, in the unlikely event that hazards are identified with a product in the market place, corrective action for use and management can be implemented. Not managing this process could harm commercialisation of nanotechnologies that are in the pipeline - and continue to feed public criticism that processes are not transparent.

5). Coordination and the avoidance of duplication are important issues. Can you suggest how toxicology research should best be coordinated nationally?

The costs associated with necessary toxicological and ecotoxicological studies of novel nanostructured materials can be substantial. Generally groups specialise in various aspects of toxicology, and in some instances this requires duplication of some capabilities. However the biggest challenge facing toxicology research for nanotechnology is defining what assays are relevant and sufficiently sensitive. Furthermore, gaining agreement within the research community, and with the public, industry and regulatory bodies, is very important. For this to progress effectively, in the interests of the nation and industry, it would be best to pool work into a national capability. In this way, areas and people would be identified to contribute to certain aspects, and help to promote the advancement and commercialisation of nanotechnologies in a safe manner. Work should be reviewed in open transparent fora, and

funds supplied to work on agreed relevant issues. Funding for this approach could be made available from regular granting bodies, plus national and state governments and industry.