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STATE DEVELOPMENT COMMITTEE
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Responses to questions posed by the Standing Committee on State Development regarding the TGA's activities in respect of nanotechnologies.

1) The Committee understands that the TGA, along with other relevant agencies, is reviewing the existing regulatory frameworks to ensure they appropriately address the impacts of nanotechnology. Can you advise the Committee on the progress of your review and any indicative outcomes to date?

Nanotechnologies as they are applied to therapeutics have been defined as the application of nanotechnologies (or nanomedicine) for the purpose of making a medical diagnosis or treating disease. Nanomedicines may exploit the improved and sometimes novel physico-chemical properties of materials at the nanoscale. These improved characteristics may offer potential benefits to patients including a reduction in toxicity (side effects) due to the specific distribution of the drug to a target organ, increased efficacy in the treatment of disease, and lower systemic drug exposures.

Already, therapeutic products containing nanomaterials in the form of metal oxides, liposomes, polymer protein conjugates, polymeric substances and suspensions have been registered in Australia and/or granted marketing authorisations in the US and EU under existing regulatory frameworks. Additionally, soluble macromolecules of nanometre size such as recombinant peptides or oligonucleotides are examples of nanoscale materials currently used therapeutically, clearly demonstrating that nanoscale dimension does not imply novelty *per se*.

There are four general characteristics of the regulation of therapeutic goods relevant to a discussion of the impact of nanotechnology on this commodity group;

(1) Therapeutic goods are regulated as the end product with each product available for sale considered to be a separate and distinct good and regulated individually. In general, any change to the composition or form of that product creates a new product &/or requires reassessment.

(2) Regulation starts with the manufacturing facility itself and follows a product throughout its marketing life.

(3) The TGA has extensive post marketing surveillance mechanisms in place which facilitate early and rapid identification and reaction to adverse product outcomes that were not identified in premarket assessments.

(4) Although data requirements vary between commodities, the TGA receives extensive data sets in support of therapeutic goods and these are subjected to detailed, independent scientific review prior to a product being permitted onto the market.

Therefore, the TGA applies a system of oversight for identifying, analysing and evaluating the risks associated with the product itself, and the manufacturing process. To date this system has proven to be effective in managing therapeutic products incorporating a range of new and emerging technologies including nanotechnologies. In that respect there is currently no evidence from post-market surveillance that regulatory arrangements prior to marketing are insufficient to identify hazards associated with therapeutic goods that incorporate nanotechnologies.

The TGA is committed to ensuring that this remains valid in the face of an increased number and sophistication of nanotechnologies and to modifying existing regulatory arrangements where necessary. In order to facilitate that process the TGA is conducting a thorough review of its regulatory guidelines and a scientific review of the literature in particular with respect to therapeutics incorporating nanotechnologies. Present indications are that although it is possible that nanomaterials may elicit novel toxic effects (*cf* conventional materials) there is no reason to believe that nanomaterials may pose hazards not addressable by a rational scientific approach under the TGA's regulatory framework.

Nevertheless the TGA recognises that nanotechnologies and other emerging technologies will continue to present significant scientific and policy challenges now and into the future. The best response to such challenges is the maintenance and continued development of high quality scientific expertise within the agency together with ongoing interaction with sponsors, researchers, regulators and policy makers throughout Australia and internationally. The TGA will continue to closely monitor developments around nanotechnology internationally to ensure a rapid response to any new issues identified.

2). The Committee understands that new products which contain nanomaterials and that are classified as registered medicines are subject to rigorous and detailed assessment and regulation. It is with listed medicines/products that contain nanomaterials where some concern may lie. TGA website information notes that "Listed medicines may only contain well known established ingredients, usually with a long history of use, such as vitamin and mineral products or sunscreens. They do not contain substances that are scheduled in the SUSDP."

To date has the TGA considered nanomaterial ingredients as well known and established on the basis of the knowledge of the bulk form of the material?

In the context of this question it is important for the Committee to note that while different regulatory arrangements apply to registered and listed goods both commodities are evaluated for quality and safety.

The essential difference in the processes for registered and listed goods is that the safety of listed goods is established by restricting the use of ingredients to those which have well established quality and safety profiles and common manufacturing processes.

Ingredients that can be used in listed medicines are included in the "List of substances that may be used in Listed Medicines in Australia" and may have further restrictions or conditions placed upon their use.

A number of the ingredients on this list have been included on the basis of safety established through a long history of use such as vitamin and mineral products or sunscreens. New ingredients are also added to the list periodically following evaluation of their quality and safety profiles by the TGA.

The TGA has considered additional safety concerns that may be associated with potential differences in toxicological profiles between nanoparticulate and conventional (bulk) materials where the physical and chemical properties of the material have warranted such consideration, for instance in the cases of some sunscreen ingredients.

The impacts of a potential increase in the number of nanotechnologies on this class of products is under further review as a part of the TGA initiatives under the National Nanotechnology Strategy.

3). The Committee is aware that in 2006 the TGA conducted a review of the scientific literature in relation to the use of nanoparticulate zinc oxide and titanium dioxide in sunscreens, which concluded that the weight of current evidence was that the nanoparticulates remained on the surface of the skin and in the outer dead layer.

That document noted that the TGA was monitoring the emerging scientific literature in this area to ensure that appropriate action is taken if any risks are identified.

The Committee has heard in evidence about on-going research into nanoparticulates in sunscreens. Has the TGA been involved or supported this research? And is it aware of any emerging risks?

The TGA is not directly involved in research into the potential dermal penetration and toxicity of nanoscale zinc oxide and titanium dioxide in sunscreens, however it is aware of such research occurring both nationally and internationally.

The TGA is continuing to monitor the scientific literature with respect to nanoparticulate titanium dioxide and zinc oxide and safety issues associated with their use in sunscreens.

At the present time the weight of evidence in the scientific literature supports the original conclusions drawn in the 2006 review as follows;

"There is evidence from isolated cell experiments that ZnO and TiO2 can induce free radical formation in the presence of light and that this may damage these cells (photo-mutagenicity with ZnO). However, this would only be of concern in people using sunscreens if the ZnO and TiO2 penetrated into viable skin cells. The weight of current evidence is that they remain on the surface of the skin and in the outer dead layer (stratum corneum) of the skin."

The Committee may also note that despite the widespread and long history of use of sunscreens containing titanium dioxide and zinc oxide particles of nanoscale dimension no significant adverse reports of safety have been associated with these products.

4). *If research did conclude that there was an associated risk with a nanoparticulate ingredient that was part of a currently listed medicine what actions could the TGA take to address such risks?*

The TGA has a number of enforcement options that may be used to deal with risks that are identified in therapeutic goods. These are detailed in the therapeutic goods legislation and include the capacity to:

- impose new conditions on the registration or listing or vary or remove existing conditions;
- apply additional conditions to the manufacture of a product;
- cancel the registration or listing of the product meaning that it can no longer be supplied in Australia;
- suspend or cancel a manufacturing licence and

- require mandatory recalls of products.

The enforcement action will depend on the particular circumstances of the case with the dominant consideration being the protection of the health and safety of the public.

5). *The Committee understands that NICNAS is responsible for assessing some chemicals that are included in therapeutic goods. What reference or use does the TGA make of the NICNAS assessment? If NICNAS re-assessed such a chemical what implications does this have for the TGA?*

The TGA considers a number of sources in assessing the safety of ingredients in therapeutic goods in addition to sponsor supplied data.

These include scientific publications in the open literature as well as reports by other regulators of therapeutic products, for example the FDA and EMEA, and reports by relevant sources such as NICNAS where those reports highlight a specific risk related to an ingredient, impurity or degradation product in a therapeutic good.

The implications of a review of a specific ingredient by NICNAS would depend on the specific scientific issues associated with that substance.

6). *On 1 May 2008 the Committee heard evidence (please refer to page 59 of transcript) that raised concerns about a potential conflict of interest at commercial laboratories that conduct the self-assessment evaluations of products and that the scientific data presented to the TGA might be filtered information in some respects. What processes does the TGA employ to ensure the integrity of the evaluation data that is presented to it?*

Presumably this question relates to comments offered by Dr Brahmbhatt from EnGenIC Pty Limited (see Attachment 1).

The sponsor of a therapeutic product that intends to market that good in Australia is required to provide adequate data to allow the TGA to assess the quality, safety and in some cases the efficacy of that product.

The TGA requirements for data are based on the European Union requirements. Within the European system there is a series of guidelines which deal specifically with the issue of data requirements, most of which have been adopted by the TGA. These guidelines while not intended to be prescriptive provide a conceptual basis for the testing and assessment of therapeutic products.

The majority of nonclinical studies (generally studies in cells or animals to demonstrate the pharmacodynamics, pharmacokinetics and toxicity of the drug) will usually be generated in the company's laboratories or under contract in private testing facilities.

These studies must generally be performed in compliance with agreed international standards of quality (Good Laboratory Practice; GLP). GLP is a quality system concerned with the organisational process and the conditions under which non-clinical studies are planned, performed, recorded, archived as well as reported.

Under the requirements of GLP, final reports must be inspected to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies.

National procedures for monitoring compliance with GLP principles exist based on laboratory inspections and study audits and the TGA receives notifications of serious non-compliance issues.

The TGA also conducts an independent and comprehensive assessment of the submitted data, including individual animal data, to ensure that the conclusions of the study authors and sponsors can be adequately supported by that data.

This process is rigorous and has to date been generally sufficient to identify hazards associated with therapeutic goods whether those goods may or may not contain nanomaterials.

The TGA also applies risk management procedures to risks that may be posed through the manufacturing of medicines.

The TGA identifies, analyses and evaluates risk posed through manufacturing by licensing and auditing of manufacturers of medicines.

To obtain a licence to manufacture therapeutic goods a manufacturer must demonstrate compliance with manufacturing principles including Good Manufacturing Practice (GMP).

Before a licence is granted the TGA assesses the manufacturer's compliance through an on site audit.

All licensed manufacturers are subject to ongoing audit by the TGA to check for ongoing compliance with the manufacturing principles.

Those audits may be based on, for example, results of testing by TGA laboratories arising from random or targeted sampling of products, any recalls of products not meeting safety standards or adverse comments from other agencies or bodies.

Therefore, the TGA applies a system of oversight for identifying, analysing and evaluating the risks associated with the product itself, and the manufacturing process.

Significant penalties apply under the Therapeutic Goods Act for a range of offences including for example where there has been a failure to comply with standards, false statements made in applications for entry of goods on the Australian Register of Therapeutic Goods (the Register), breach of a condition of a manufacturing licence (including failure to comply with the manufacturing principles) and false statements made in a conformity assessment declaration and the counterfeiting of therapeutic goods.

recd 25 June 2008

NSW Food Authority

23 June 2008

Mr John Young
Principal Council Officer
Legislative Council
Parliament House
Macquarie Street
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Dear Mr Young

Nanotechnology in New South Wales – Corrected Transcript

Enclosed please find a corrected transcript of the evidence I provided to the Standing Committee on State Development on Friday 6 June 2008.

I noted a portion of text on page 15 of the transcript was highlighted in yellow. It encompasses a question raised by the Hon. Melinda Pavey in relation to whether there is research available concerning the speed of uptake of titanium dioxide and silicon dioxide in the nanoform following ingestion.

I can inform the committee that a search for literature in this area revealed one *in vitro* study with silicon dioxide in the nanoform and none with titanium dioxide. The research on silicon dioxide (authored by Chen and Mikecz in 2005 and published in the journal *Experimental Cell Research* Vol 305, p 51-62) showed that particles smaller than 70 nm could enter a cell's nuclei and impair cell function. It is not known whether comparable effects occur *in vivo* particularly through the gastrointestinal route.

Yours sincerely

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