



Australian Government

Department of Health

Therapeutic Goods Administration

Regulation of Nanomedicines

by the Therapeutic Goods Administration

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Nanoparticle Therapeutics 2016:

Nanoparticle Safety and Characterisation

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TGA Health Safety
Regulation

Overview

- TGA's approach to regulation of therapeutic products
- TGA activities under the National Nanotechnology Strategy
- Nanomedicines approved by the TGA (including Sunscreens)
- Future challenges



Regulation of Therapeutic Products by the TGA





TGA Regulation of Therapeutic Products

- **Legislation:** *Therapeutic Goods Act 1989*
- **The TGA plays a role in the management of risks associated with therapeutic goods by:**
 - pre-market product assessment or evaluation
 - evaluating the risks posed by a manufacturing process before a manufacturer is issued with a license to manufacture therapeutic goods; and
 - evaluating risks that may arise following approval of the product and licensing of the manufacturer (post-market surveillance)



Standards and Guidelines for Prescription Medicines

- The TGA closely aligns its regulatory approaches to therapeutic products with those of comparable international regulatory counterparts wherever possible
- Technical data requirements are closely aligned with requirements set out in relevant European Union (EU) and ICH Guidelines
- EU and ICH technical Guidelines adopted in Australia are generally not mandated in Australian legislation they provide guidance to sponsors to assist them to meet the legislative requirements



Definitions of Nanotechnology

TC299 WG1:

- **Nanotechnology:** The application of scientific knowledge to control and utilize matter at the nanoscale, **where size-related properties and phenomena can emerge**
- The term nanoscale is the size range between approximately 1 nanometre and 100 nanometre

TGA Website:

- The term nanotechnology is used to describe a wide range of methods involved in the production and engineering of structures and systems by controlling size and shape at the nanometre scale



EMA working definition of Nanomedicines

- Purposely designed systems for clinical applications
- At least one component at nano-scale size
- Resulting in definable specific properties and characteristics related to the specific nanotechnology application and characteristics for the intended use (route of admin,dose)
- associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution)
- And needs to meet definition as a **medicinal product** according to European legislation.



The National Nanotechnology Strategy





National Nanotechnology Strategy Initiatives

- **The National Nanotechnology Strategy** (NNS; superceded by the National Enabling Technologies Strategy or NETS) aimed to allow Australia to capture the benefits of nanotechnology while addressing any safety concerns
- **The Monash Review (2007) considered:**
 - Whether Australia's regulatory frameworks are triggered by nanotechnology-based materials, products, applications, and their manufacture, use and handling
 - Which, if any, groups of nanotechnology-based materials, products and applications are not covered by our existing regulatory frameworks?



Monash Review 2007

Key findings

- Australia's regulatory frameworks are generally well suited to the task of regulating nanotechnologies
- All regulatory frameworks apply to nanotechnology based products
- There was no immediate need for major changes to the regulatory regimes, but minor amendments would be required



TGA responses to the NNS report

Establishment of TGA Nanotechnology Focus Group to:

- Review the capacity of existing regulatory arrangements for therapeutic products to adequately manage issues
- Review of the science
- Build scientific capacity within the organisation
- National and International engagement



Conclusions of the TGA nanotechnology focus group

The TGA is well placed to regulate products incorporating nanomaterials in that it:

- generally operates in a data rich environment
- has a high level of expertise to bring to bear on the assessment of new technologies
- has the legislated authority to require additional data in support of the safety assessment of new materials
- and, in the most part, deals with applicants that have the technical expertise to adequately address key safety issues
- We need to maintain capacity building and engage internationally to ensure development of appropriate guidelines and advice to industry





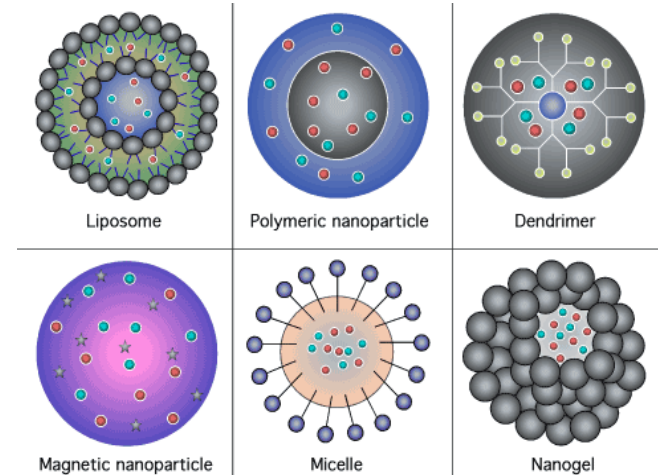
Nanotechnology Training Programme

- **Physical/chemical properties:**

Chemical and physical properties of nanoparticles vs conventional materials; Characterisation, analytical difficulties & considerations; Potential applications; Colloidal drug delivery systems; Using carbon particulates in the clinical setting: benefit and hazards; How do nanomaterials behave *in vitro*?

- **Pharmacokinetics of nanoparticles:**

Introduction to pharmacokinetics: absorption, clearance, volume of distribution, half-life, protein binding, bioavailability; Biological interactions; Routes of exposure to nanoparticles



Source: Gowda et al. J. Nanomedicine Nanotechnol. 2013;
<http://dx.doi.org/10.4172/2157-7439.1000184>



Nanotechnology Training Programme (cont)

- **Toxicology of nanomaterials:**

Toxicity of nanoparticulate TiO_2 and ZnO ; Interactions of synthetic clays and titania with biological systems; Summary of data from *in vitro* toxicity assays; *In vivo* toxicology of nanomaterials

- **Regulation of nanomaterials:**

Risk assessment and Guidelines

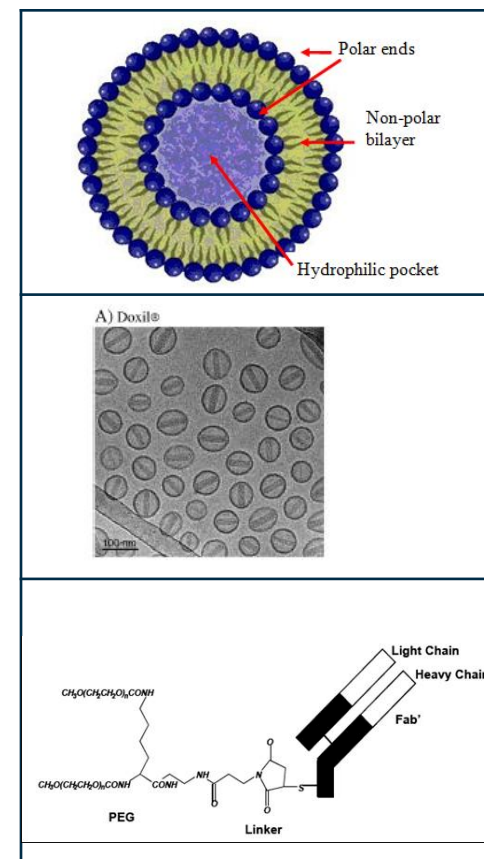
- **Risk assessment of nanomaterials:**

Nanosafety and nanotoxicology issues; Regulatory preparedness strategies; International update on nanomaterials



TGA approved products commonly referred to as 'nanomedicines'

	Commercial name	Active Ingredient	Indication
Liposomes	AMBISOME®, ABELCET®, DEPODUR®, VISUDYNE®	Amphotericin B Morphine Verteporfin	Fungal infections Pain relief Macular degeneration
Pegylated Liposome	CAELYX®	Doxorubicin	Cancer
Pegylated proteins	CIMZIA® SOMAVERT® PEGASYS®, PEGINTRON®	Rh-a/b Fab fragment against TNF- α Growth hormone receptor antagonist Interferon alfa-2a/2b	Rheumatoid arthritis Acromegaly Hepatitis C



Sources: Top - <http://www.horiba.com/scientific/products/particle-characterization/applications/pharmaceuticals/liposomes/>;

Middle - Barenholz 2012; *J. Controlled Release* **160**: 117-134



TGA-approved 'nano' medicines (2)

	Commercial name	Active Ingredient	Indication
Protein-drug conjugate	KADCYLA® ABRAXANE®	Anti-HER2-G1/DM1 Albumin-bound paclitaxel	HER2-positive breast cancer Cancer
Nanocrystal	EMEND® LIPIDIL® RAPAMMUNE®	Aprepitant Fenofibrate Sirolimus	Chemo-associated nausea Hypercholesterolaemia Organ transplant
Nanosuspension	RISPERDAL CONSTA®	Risperidone	Schizophrenia
Emulsions	NEORAL® LIPURO®	Cyclosporine Propofol	Immunosuppression Anaesthesia



TGA-approved 'nano' medicines (3)

	Commercial name	Active Ingredient	Indication
Polymeric Nanoparticles	COPAXONE® RENAGEL®	Glatiramer acetate Sevelamer	RR-MS Hyperphosphataemia
Metal/metal oxides	VENOFER®	Iron sucrose Zinc oxide Titanium dioxide Silver	↓Fe in haemodialysis Sunscreen, skin cancer prevention Wound dressings
Vaccines	PANDEMRIX® GARDASIL®	Split virion, inactivated HPV vaccine	Immunisation
Monoclonal Antibodies	MabCampath® YERVOY®	Alemtuzumab Ipilimumab	Leukaemia Advanced melanoma



Ongoing scientific review of the safety of TiO_2 and ZnO nanoparticles in sunscreens

- Sunscreens are regulated as medicines by the TGA
- A review on the safety of TiO_2 and ZnO nanoparticles in sunscreens was first published in 2006 (about to be updated)



Australia has one of the highest rates of skin cancer in the world





Key points from the sunscreen review

- Dermally applied ZnO and TiO₂ NPs do not reach viable cells or the systemic circulation, even via diseased or damaged skin
- In the presence of UV light, specific forms of ZnO and TiO₂ NPs can induce free radical formation *in vitro*, which may damage cells
- The systemic exposure to Zn following use of an uncoated ZnO NP-containing sunscreen is multiple orders of magnitude below the levels of Zn naturally present in diet and deposited within the body
- Skin damage (e.g. skin cancer) is caused by free-radical generation following repeated exposure to UV radiation or other similar assaults, and sunscreens containing ZnO and TiO₂ NPs (and other molecular UV-absorbers) offer protection against such assaults



National and International Engagement

National:

Participation in the Health, Safety & Environment (HSE) Working Group (a whole of government group established to deal with new technologies)



International:

Attendance at International Regulators Meetings on Nanotechnology

Membership of the nanomedicines international working group

Indirectly:

- OECD Working Party on Manufactured Nanomaterials
- OECD Working Party on Nanotechnology



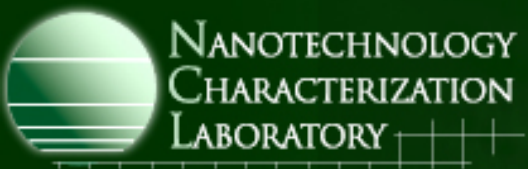


Examples of Guidelines and Reflection papers relating to Nanomedicines

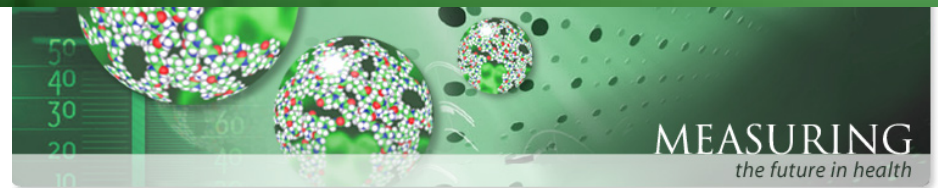
- Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (EMA)
- Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products
- Liposome Drug Products **Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation** Guidance for Industry (draft FDA document)
- Guideline for the Development of Liposome Drug Products (MHLW, Japan)
- Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products (MHLW, Japan)



Nanomedicine characterisation at the NCL



- <https://nanolab.cancer.gov/>



- Common pitfalls of NP formulation:
 - Sterility and endotoxin content
 - Adequate physicochemical characterisation;
 - Residual manufacturing components;
 - Biocompatibility of components;
 - Batch to Batch consistency
 - Nanoparticle *in vivo* stability
 - Drug Release Rates



Future Regulatory Challenges

- Next generation' nanomedicines: advances in nanoscience leading to creation of more complex, hybrid structures
- Wave of new pharmaceuticals, imaging agents and combination products
- 'Nanosimilars' - evaluation of follow-on nanomedicine products