THE AUSFTA AND ‘FAST TRACK’ REGULATORY APPROVAL OF MEDICINES: PROBLEMS AND OPPORTUNITIES FOR AUSTRALIAN ACADEMIC INNOVATIONS IN NANOTHERAPEUTICS

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Introduction
This paper examines the proposition that the United States Food and Drug Administration (FDA) and Australia’s Therapeutic Goods Administration (TGA) will soon be coming under increasing pressure to prioritise so-called ‘fast-track’ approval pathways for innovative nanotherapeutics. It considers the relative risk this may result in compromised standards of safety and efficacy for such products. It also, however, investigates the opportunities this presents for developing new regulatory approval pathways for Australian academic innovations in nanotherapeutics.

‘Fast-tracking’ may be defined, for the purposes of this paper, as any regulatory pathway or process that a developer/manufacturer may utilise to secure more rapid quality, safety and efficacy regulatory approval prior to marketing of a therapeutic product. Although cost-effectiveness analysis in many jurisdictions (such as Australia) is another recognised regulatory hurdle prior to marketing approval, its role is not generally considered as part of ‘fast-track’ procedures. ‘Fast-tracking,’ however, may also be described, from a patient’s point of view, as any regulatory pathway or process that allows speedier access to new and presumptively ‘innovative’ health technologies.

One highly contentious area of the Australia-United States Free Trade Agreement (AUSFTA) in this context concerns the extent to which the Medicines Working Group (MWG) established under Annex 2C (3) of the AUSFTA (annexes in such trade agreements allow obligations to be imposed on only one nation) will become a policy-making forum related to drug regulatory approval issues for ‘innovative’ medicines (despite a current Annex 2C prohibition on this). The crucial AUSFTA provision here is Annex 2C (4) which requires ‘fast track’ regulatory approval discussion between the FDA and TGA.

3. Medicines Working Group
(a) The Parties hereby establish a Medicines Working Group.
(b) The objective of the Working Group shall be to promote discussion and mutual understanding of issues relating to this Annex (except those issues covered in paragraph 4), including the importance of pharmaceutical research and development to continued improvement of healthcare outcomes.
(c) The Working Group shall comprise officials of federal government agencies responsible for federal healthcare programs and other appropriate federal government officials.

4. Regulatory Cooperation
The Parties shall seek to advance the existing dialogue between the Australian Therapeutic Goods Administration and the U.S. Food and Drug Administration with a view to making innovative medical products more quickly available to their

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Nanotechnology refers to the study, manipulation and application of materials at the nanoscale (1-100 nanometres). Nanoparticles occur naturally (for example in volcanic eruptions), but engineered nanoparticles (ENPs) have a number of unique properties that make them attractive to developers of medical technologies. They have, for example, a greater surface area to mass ratio when compared with larger sized compounds of the same chemistry, rendering them more biologically active, and their small size facilitates uptake into potentially sensitive target sites such as bone marrow, lymph nodes, spleen, heart and central nervous system.

Nanotherapeutics may be broadly defined to include products resulting from the application of nanotechnologies and ENPs to medicines, medical devices, and biotechnologies. It is likely to be characterised by greater levels of convergence between these fields. As of mid 2006, approximately 130 nano-based drugs and drug delivery systems and 125 devices or diagnostic tests are in pre-clinical, clinical or commercial development. Every major pharmaceutical company in the world has begun to engage in nanotechnology research.

Examples of Australian products in development include Alchemia’s VAST, a nanoscale drug discovery tool which may be used to identify candidates for therapeutic indications for cancer, CeramiSphere’s sol-gel encapsulation, a technology where active molecules are encapsulated in nanosized ceramic particles allowing advanced drug delivery, and Xceed Biotechnologies’ Novosorb biodegradable bone cement. The University of Wollongong is developing bio-nanotechnological artificial nerve cell communication systems, and Starpharma Holdings’ VivaGel, a dendrimer based microbicide gel which may be used in the prevention of sexually transmitted diseases such as AIDS. Nanotechnology Victoria Limited (NanoVic) is a joint venture between Monash University, Swinburne University of Technology and RMIT University. NanoVic is a Company incorporated in Victoria, limited by guarantee of its Members and governed by a Board with the number of independent Directors - including the Chairman - exceeding the number of Member-appointed Directors. NanoVic with Monash University College of Pharmacy, Eiffel Technologies Ltd and MiniFAB are developing nanotherapeutic products allowing, for example, painless delivery of vaccines, peptide hormones and other drugs from skin patches through the stratum corneum of the skin.

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3 One nanometre is equal to one-billionth of a metre. To put this in perspective, a human hair is approximately 80,000nm wide. See generally, United Kingdom, Royal Society Report, Nanoscience and Nanotechnologies: Opportunities and Uncertainties (2004); See also, Brumfiel, G, ‘A Little Knowledge’ (2003) 246 Nature 424


Clearly nanotherapeutics represents an area of research and development that is presumptively innovative in a technical if not necessarily a health outcomes sense. It has high potential for both public health benefit and economic profit. The market size for nanotechnology based drug delivery systems alone in 2005 was US$1000 million and is expected to grow rapidly over the next five years.10

This chapter will initially examine, through consideration of the evolutionary history of the FDA, whether an increasing interest in ‘fast-tracking’ is likely to compromise regulatory risk-benefit analysis in relation to nanotherapeutics It will critically examine the consequences of industry pressure increasing on the TGA to prioritise ‘fast-track’ approval within its regulatory framework in harmony with that of the FDA, as a result of obligations in Annex 2C (4) of the Australia and United States Free Trade Agreement (AUSFTA). It will also consider whether Annex 2C (4) and the policy dialogue it may promote creates opportunities to develop unique regulatory pathways to foster Australian academic innovations in nanotherapeutics for the public good.

Introduction to “Fast Tracking’
The Therapeutic Goods Act 1989 (Cth) provides a national framework for the regulation of therapeutic goods in Australia to ensure their quality, safety, efficacy and timely availability.11 The framework is based on a risk management approach, designed to ensure public health and safety while at the same time freeing industry of unnecessary regulatory burdens, a key focus being to ensure that consumers have timely access to medicines.12 The United States FDA has a closer and more detailed involvement in the clinical development program of new health technology products than the TGA (and consequently a considerably more expanded bureaucracy). Before a clinical trial can go ahead in the US, the sponsor must submit an Investigational New Drug (IND) application which includes data on toxicity and pharmacologic effect obtained from animal studies, as well as details regarding trial design.13 The FDA scientifically reviews the IND application and if it does not raise any objections within 30 calendar days, the trial may commence. The FDA does not recover any costs from the applicant for this review.14 Once the initial IND has been approved, subsequent clinical trials involving the same product must be notified to the FDA, but do not go through another FDA approval process.15 All clinical trials are subject to separate ethics approval by an Institutional Review Board (IRB) similar to Human Research Ethics Committee (HREC) review in Australia.16 Approval to conduct a clinical trial in Australia may be obtained under either the Clinical Trial Notification (CTN) scheme or Clinical Trial Exemption (CTX) scheme.17 The initial choice of which scheme to utilise is made by the company that is developing the product (the sponsor).18 Under the CTN scheme, the sponsor notifies the TGA that an

12 Ibid.
15 Ibid.
16 Ibid.
18 Ibid.
application to conduct a clinical trial has been made, but the actual review of the application is undertaken by a HREC. The CTN scheme was introduced with the intention that it would be used for trials that did not require detailed scientific evaluation or which had already been evaluated and approved for clinical trials in the US or UK. This is reflected by the fact that HRECs, where they believe that more detailed scientific analysis is required, may refer an application to the TGA for review under the CTX scheme and by the differing cost structure. CTN review for all phases of clinical trials costs $240 per trial site, whereas CTX reviews cost $1240 for phase I trials and $15,300 for phase II and III trials. An application under the CTX scheme is similar to an IND application at the FDA, in that an application detailing data on toxicity and pharmacologic effect obtained from animal studies, as well as details regarding trial design is submitted to the TGA for scientific evaluation. However, unlike the FDA’s IND review, the TGA charges a fee for this evaluation and has a much longer review period, 75 days as compared with the FDA’s 30 days.

It has been suggested that, once approved, it is up to five times cheaper to run a clinical trial in Australia than in the US. Following the introduction of the CTN scheme in 1991, the number of CTX approved trials has dwindled to only a few per year, whilst the number of CTN approved trials has steadily increased.

The fundamental dichotomy faced by therapeutics regulators has traditionally been framed as arising between the interests of public health, in maintaining high safety, quality and efficacy standards, and having timely access to innovative therapeutic products. Risk-benefit analysis pervades all stages of therapeutics regulation both in the TGA, the FDA and similar organisations worldwide. From a regulatory standpoint, risk-benefit analysis is based on utilitarian or consequentialist principles. ‘Risk’ in this biomedical context is generally held to refer to a possible future harm, where harm is defined as a setback to interests. ‘Benefit’ refers to something of positive value, usually in life, health and welfare. Analysis of these risks involves an evaluation of the ratio between the probability and magnitude of a potential harm and the probability and magnitude of a potential benefit. Traditionally regulatory bodies, such as the TGA and FDA, protect the public welfare by placing the burden of proof on manufacturers, to meet rigorous outcome standards in demonstrating the safety and efficacy of new therapeutic products.

In some circumstances, however, utilitarian risk-benefit analysis may conflict with the autonomous risk-benefit analysis of individuals, or particular sub-groups of patients. Furthermore, utilitarian benefits will not be realised where the satisfaction of this burden of proof becomes too costly and thus stifles innovative research into new therapeutic products.

‘Fast-tracking’, as previously mentioned, represents any regulatory pathway that industry may utilise to secure more rapid regulatory marketing approval for a therapeutic product. The processes involved with ‘fast tracking’ in relation to pharmaceutical products in the US FDA involve these common features: a) a shorter review time, b) closer collaboration between industry and the FDA prior to approval, whereby clinical trial protocols are developed in consultation with the FDA and data is submitted to, and evaluated by the FDA whilst further phases of clinical trials are conducted, and c) a shorter clinical trials process through the

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19Ibid.
20Ibid.
21Ibid.
22Ibid.
23Ibid.
24Ibid.
26Ibid.
27Ibid.
adoption of surrogate endpoints for efficacy. A surrogate endpoint is an indication that is said to be correlated to the clinical end-point for the treatment of a disease. For example, reduction in the size of a tumour is a surrogate end-point for the treatment of cancer.

‘Fast-tracking,’ however, as also previously mentioned, may also be described, from patients’ point of view, as any regulatory pathway or process that allows speedier access to innovative therapies. Indeed, this accelerated approval pathway arose from intense political pressure imposed on the FDA by patient advocacy groups during the AIDS epidemic in the 1980’s. For groups of patients facing imminent death from a serious disease, the magnitude of risk associated with a particular experimental treatment is considerably diminished in comparison to the potential benefit of the treatment even where the probability of that benefit actually accruing is unknown. Such groups may see rigorous pre-approval safety and efficacy testing procedures as overly paternalistic, risk-averse and exacerbating a healthcare crisis by impeding access to new medications.

These types of groups are powerful lobbying agents and this has not escaped the notice of the brand-name pharmaceutical industry whose representatives fund many such activities. The FDA’s response to this pressure represented an evolutionary change in the FDA’s risk-benefit analysis for new drugs. By allowing patients access to drugs with less well developed safety and efficacy profiles, the FDA shifted the focus of public protection from protection against risks caused by new drugs, to protection against the risks associated with not being able to access potentially beneficial drugs.

The Department of Foreign Affairs and Trade has stated that Australia’s commitment under Annex 2C (4) of AUSFTA, does not require the TGA to approve FDA approved products. This statement is in line with recommendation 2.1 of the KPMG Review, which states that “the Government should re-affirm its commitment to maintain a sovereign, high quality and efficient drug regulation capacity in Australia.” Nonetheless the TGA is likely to be under considerable pressure to approve new medical products such as nanotherapeutics in accordance with international benchmark times, such as those set by the FDA, or risk falling behind internationally. Further, given that the US drug market is the largest in the world and thus industry is likely to seek access to this market first it is likely that industry will seek to exercise leverage to obtain fast-track TGA approval of FDA approved drugs. In this paper we examine issues arising from the manner in which Annex 2C (4) of AUSFTA may be used as a leverage mechanism by industry to target existing TGA fast-track approval pathways with a view to gaining speedier approval for innovative, FDA approved, nanotherapeutics.

Yet the 1997 KPMG review of the TGA identified three levels of information sharing

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29 See generally, above n 18; see also, above n 13.
31 Ibid.
32 Ibid.
33 Ibid.
between regulatory agencies that may facilitate ‘fast-track’ approvals. Level 1 is the “exchange of evaluation reports following independent evaluation by both [agencies]”, level 2 is the “exchange or supply of an evaluation report, with the recipient country using the report in part or in whole instead of undertaking its own evaluation”, and level 3 is that “countries agree that they will [divide and] share the evaluation of an application”.  

**Nanotherapeutics and Nanotoxicology**

The risks specifically associated with nanotherapeutics can essentially be divided into two categories; a) toxicological risks, which may exist at all stages of a products life-cycle, production, distribution, consumption and end of life, but, for the purposes of this paper will be confined to consumption risks borne by the consumer and b) financial risks, which are, initially, borne by corporate investors, but subsequently by the public as the opportunity cost of increased expenditure on nanotherapeutics in limited health budgets. The second category is usually not a major focus of ‘fast-track’ regulatory considerations.

Whilst it is likely that standard models of safety assessment will apply to nanotherapeutics, within these models, data needs and technical questions might be very different given the special biological, chemical and physical properties that arise at the nanoscale. These issues are currently being studied in the emergent field of nanotoxicology. Nanotoxicology can be defined as safety evaluation of engineered nanostructures and nanodevices. This is a broad definition which extends to include the industrial and environmental safety of nanoproducts. Within the sub-discipline of nanomedicine, toxicological effects may exist at all stages in the lifecycle of a nanomedical product, production, distribution, clinical administration/consumption and end of life.

Relevant considerations in the development of a safety evaluation framework for nanotherapeutics include, the unique physiochemical properties of the nanoparticles, routes of exposure (oral, dermal and injection) and translocation, accumulation and retention rates at critical target sites. It is likely that the biological activity of nanoparticles will depend on physiochemical properties that may not be routinely considered in toxicity screening studies, including, particle size and distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge and porosity.

To date, studies investigating the mechanisms of interaction of nanoparticles with cells and their components, including their effects on blood vessels, the skin, heart and nervous system have shown distinct cytotoxic effects. However, the lack of relevant lifetime animal studies raises a number of pertinent considerations in safety assessment of nanotherapeutics. The ultimate fate of nanoparticles in the body is largely unknown. Studies have suggested that nano-sized particles can translocate across the plasma membranes of epithelial cells by unconventional means, nanoparticles may compromise respiratory function in the lungs, the capacity of nanoparticles to cross human skin is largely unknown and nanoparticles preferentially accumulate at the sub-cellular level in the mitochondria potentially inhibiting

38 Above n 36.  
42 Above n 21  
43 Ibid.  
mitochondrial function.\textsuperscript{45} A further issue is the extent to which results of cellular and immunological studies in animal models can be translated to humans, as there are distinct intra and interspecies variations.\textsuperscript{46} Of particular concern in this context, is the absence of studies into the effect of nanoparticles on reproduction.\textsuperscript{47}

A recent FDA report has found that current ability “to detect nanoscale materials in the body or in products regulated by the FDA is limited, and development of appropriate analytical methods for classes of products and of nanoscale materials may require substantial effort. Further, new analytical methods, and methods that FDA reviewers are generally less familiar with, are often used to characterize nanoscale materials. The strengths and limitations of these methods may vary in ways relevant to evaluating characteristics such as particle size, size distribution, surface charge, surface properties, and particle interactions (such as aggregation) that may be relevant to dose, stability, or other characteristics significant to biological interaction or product quality”.\textsuperscript{48}

The report also noted,

there may be a fundamental difference in the kind of uncertainty associated with nanoscale materials compared to conventional chemicals, both with respect to knowledge about them and the way that testing is performed. For conventional chemicals, there is a relatively long history of exploring, and a correspondingly relatively robust understanding, of interactions of molecular classes (such as compounds with particular structures or functional groups) with biological systems… There is, comparatively speaking, more familiarity with the predictive value of such tests for molecules than for nanoscale materials.\textsuperscript{49}

A general finding of the report was that,

nanoscale materials present regulatory challenges similar to those posed by products using other emerging technologies. However, these challenges may be magnified both because nanotechnology can be used in, or to make, any FDA-regulated product, and because, at this scale, properties of a material relevant to the safety and (as applicable) effectiveness of FDA-regulated products might change repeatedly as size enters into or varies within the nanoscale range. In addition, the emerging and uncertain nature of the science and potential for rapid development of applications for FDA-regulated products highlights the need for timely development of a transparent, consistent, and predictable regulatory pathway… Other recommendations suggest that FDA provide guidance to manufacturers about when the use of nanoscale ingredients may require submission of additional data, change the product's regulatory status or pathway, or merit taking additional or special steps to address potential safety or product quality issues.

It also recommended encouraging manufacturers to communicate with the FDA early in the development process for products using nanoscale materials, particularly with regard to such


\textsuperscript{49}Ibid.
highly integrated combination products.\(^{50}\)

Perhaps the most surprising omission from this report was the lack of any reference to potential conflicts between these recommendations and existing ‘fast-track’ approval mechanisms in the FDA.

**Opportunities for Ethical Nanotherapeutics Development via ‘Fast-Tracking’**

We previously stated that the fundamental dichotomy faced by therapeutics regulators has traditionally been framed as arising between the interests of public health, in maintaining high safety, quality and efficacy standards, and having timely access to innovative therapeutic products. Increasingly, however, the need to facilitate academic innovations primarily focused on public good rather than profit (for example by facilitating nanotherapeutics to tackle the burden of illness in developing nations) will become an equally important regulatory consideration.\(^{51}\)

Regulation of prescription medicines, by the TGA and FDA, is characterised by the requirement that the quality, safety and efficacy of the product be evaluated by the relevant regulatory agency, prior to being approved for marketing.

Starpharma, a Melbourne based company, was recently granted ‘fast-track’ status by the FDA for its nanotherapeutic VivaGel\(^{\text{TM}}\), which is a topical microbicide gel incorporating nanoscale molecules called dendrimers.\(^{32}\) Dendrimers are synthetic, three dimensional molecules, with branching parts that bind to receptors on the surface of viruses such as HIV and Genital Herpes and inactivate them by preventing them from attaching to the host cells, which they are trying to infect\(^{53}\). Thus, when applied to the vagina prior to sexual intercourse it may prevent the transmission of sexually transmitted diseases.\(^{54}\)

‘Fast-track status’ was granted in the form of placing Vivagel\(^{\text{TM}}\) on the FDA’s accelerated approval pathway, which is designed to accelerate the clinical trials process for innovative drugs designed to treat serious and life-threatening conditions.\(^{55}\) This pathway allows Starpharma to develop clinical trial protocols in collaboration with the FDA, adopt surrogate end-points, and submit trial data for review during the clinical trials process, all with a view to expediting the approval process.\(^{56}\)

VivaGel\(^{\text{TM}}\) has the potential to be a very beneficial preventative treatment for sexually transmitted diseases such as AIDS, a disease that is serious and life-threatening, and the very same disease that caused patient advocacy groups to pressure the FDA for speedier access to innovative treatments. However, it is questionable as to whether these benefits are likely to be consistently realised in the context of a ‘fast-track’ approvals process.

VivaGel\(^{\text{TM}}\) is a preventative treatment, that is likely to be frequently and widely used by

\(^{50}\) Ibid.


\(^{55}\) See above n 30

\(^{56}\) Above n 18
healthy people, as opposed to those facing imminent death from AIDs. Further, given the potential long-term risks associated with nanoparticles, along with the fact that there are other preventative measures, such as condoms, which have been shown to be both safe and effective, ‘fast-track’ approval based on surrogate end-points for efficacy and an underdeveloped safety evaluation, may unjustifiably compromise public health, in this situation.

A nanotherapeutic product will be classified as a medicine under the TGA’s regulatory framework if it is “represented to achieve, or is likely to achieve, its principal intended action by pharmacological, chemical, immunological or metabolic means in, or on, the body of a human or animal”. Currently the majority of prescription drugs are evaluated by the TGA following submission of a category 1 application, detailing quality, safety and efficacy data based on both clinical and pre-clinical study reports, for which the statutory review period for the approval of prescription medicines is 255 working days.

At present, gaining FDA marketing approval for a nanomedicine does not result in fast-track TGA approval as either category 2 applications or priority evaluations, a special type of category 1 application for medicines whose therapeutically active component is not already listed on the Australian Register of Therapeutic Goods (ARTG). Emend®, for example, a nanoparticulate drug containing a new active pharmaceutical ingredient, developed by Merck, was granted marketing approval by the FDA on 26 March 2003. Following FDA approval Merck submitted a regular category 1 application to the TGA which was approved late in 2005. The two and a half year delay between US and Australian marketing approval may have been alleviated, to some extent, by adoption of level 2 information sharing between the FDA and TGA, whereby an FDA evaluation report alone will activate the category 2 pathway. Under the current regulations, a nanomedicine will be a candidate for a category 2 application, which has a statutory review period of 175 days, where it has been independently approved by two acceptable countries, which include, the United States, Canada, Sweden, the Netherlands and the United Kingdom. The application involves the submission of the reports of both countries along with quality, safety and efficacy data as per a category 1 application.

Nanomedicines such as these currently will be a candidate for priority evaluation where they are indicated for treatment or diagnosis of a serious, life-threatening or severely debilitating disease or condition and there is clinical evidence that they may provide an important therapeutic gain. These are very similar conditions to those required for a product to receive fast-track status via the accelerated approval pathway in the FDA. Thus nanotherapeutics that receive fast-track status from the FDA are ideal candidates for priority evaluation by the TGA. Indeed the TGA’s regulatory framework already allows data packages for such medicines to be submitted in the United States format rather than the usual European Union format which is required for most other applications. Under the TGA’s current regulatory framework priority evaluations are still category 1 applications and as such have a statutory review period.

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59 Ibid.
61 Ibid
62 Ibid
63 Ibid
64 Ibid
65 Ibid
evaluation time of 255 days, but the TGA is committed to performing the evaluation as rapidly as possible.\textsuperscript{66} Would it not be possible to develop a special category in such abbreviated approval pathways for academic innovations in nanotherapeutics specifically focused on the needs of developing nations?

**‘Fast-Tracking’ Nanotherapeutics By Bulk Scale Comparisons**

We now examine whether comparing a nanotherapeutic product with a bulk scale equivalent (same compounds) is likely to alter the rigour and pace of premarket regulatory review. Two relevant case studies involve Rapamune\textsuperscript{®} and Nanoss\textsuperscript{TM}. Rapamune\textsuperscript{®}, is a nanoparticulate reformulation of an approved medicine and is thus a candidate for approval as an ‘essentially similar’ medicine. Nanoss\textsuperscript{TM} is a precipitation of calcium phosphate nanocrystals which may be used to form implants used in orthopaedic surgery.\textsuperscript{67} Calcium phosphate has been used in medical devices with non-load bearing applications for years, however Nanoss\textsuperscript{TM} nanocrystalline structure provides it with increased strength and bioactivity enabling it to mimic the properties of natural bone crystals, which may grow around, and eventually replace the implant.\textsuperscript{68}

An ‘essentially similar’ medicine is a product that has the same qualitative and quantitative composition in terms of active substances, is in the same pharmaceutical form (e.g. oral dosage as opposed to injection), and is bioequivalent, unless it differs significantly from the original product as regards to safety or efficacy in light of scientific knowledge.\textsuperscript{69} An application for an essentially similar medicine does not require the submission of safety and efficacy data where appropriate studies showing bioequivalence have been submitted.\textsuperscript{70} Such applications are still category 1 applications however the TGA has a non-statutory target time frame of 45 working days for evaluation of these applications.\textsuperscript{71} However, typically a nanoparticulate form of an existing drug will not be bioequivalent, due to a combination of factors associated with the advantages of nanoparticulate reformulation including, enhanced bioavailability, reduced toxicity and smaller and more stable dosage forms.\textsuperscript{72} Thus it is unlikely that this pathway could be utilised to secure fast-track approval of nanoparticulate reformulated medicines. In fact, Rapamune\textsuperscript{®}, was approved following an evaluation of a regular ‘category 1’ application by the TGA and NDA by the FDA.\textsuperscript{73} Nevertheless it may be advisable for the TGA to take into account the significantly different properties of nanoparticles and subject all nanoparticulate reformulations to ‘category 1’ applications, even if bioequivalence is shown.

**‘Fast-Tracking’ Problems with Convergent Nanotherapeutics: Medicines v Devices**

The distinction between a medicine and a medical device under the TGA’s regulatory framework essentially turns on the words ‘principal intended action’. Where a therapeutic product achieves its ‘principal intended action’ by pharmacological, chemical, immunological or metabolic means it will be regulated as a medicine; where a therapeutic product is merely assisted in its function by such means or achieves its principle intended action by another

\textsuperscript{66} Ibid.  
\textsuperscript{68} Ibid.  
\textsuperscript{69} Ibid.  
\textsuperscript{70} Ibid.  
\textsuperscript{71} Ibid.  
\textsuperscript{72} Till, M, Simkin, M, Maebius, S., ‘Nanotech Meets the FDA: A Success Story about the First Nanoparticulate Drugs Approved by the FDA’ (2005) 2 Nanotech Law & Business 163.  
\textsuperscript{73} Australian Register of Therapeutic Goods nos: 73921, 79504, 97766, 104340, 125629, 125630: see also: Till, M, Simkin, M, Maebius, S., ‘Nanotech Meets the FDA: A Success Story about the First Nanoparticulate Drugs Approved by the FDA’ (2005) 2 Nanotech Law & Business 163.
means it will be regulated as a medical device.

Angstrom Medica’s success in framing its product Nanoss™ as essentially similar to pre-existing calcium phosphate implants, and obtaining FDA approval as a class II medical device, reflects the disparate rigour of regulatory evaluation between medical devices and medicines. A nanotherapeutic product, classified as a medical device (from here on in nanomedical device) includes, any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article intended for diagnosis, treatment, monitoring, prevention, alleviation or compensation for an injury, handicap or disease, contraception, disinfection of medical devices or in vitro diagnosis, that does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but may be assisted in its function by such means.\(^{74}\)

The regulation of prescription medicines is characterised by the requirement that the quality, safety and efficacy of the product be evaluated by the relevant regulatory agency, prior to being approved for marketing. The regulation of medical devices, however, is characterised to some extent, by industry self-regulation, whereby the sponsor of the device is able, to some extent, to frame the level of regulatory risk assessment applied to the product. The sponsor must first classify the device as, class I, low risk; class IIa, low-medium risk; class IIb, medium-high risk; class III, high risk, according to its intended use, the level of risk and the degree of invasiveness in the human body.\(^{75}\) The sponsor then makes a declaration, notifying the TGA, that the device complies with the 14 essential principles, including that the product’s safety and efficacy have been proven in clinical trials.\(^{76}\) Following this notification, all devices may be subject to an audit by the TGA, in which the TGA reviews, among other things, a summary of the clinical trial evidence used to establish conformity with the 14 essential principles.\(^{77}\) However, whilst most medium-high risk products (including all class III devices) are subject to an audit, most low-medium risk products are automatically listed on the ARTG as approved products.\(^{78}\) In gaining approval as a class II medical device Nanoss™ was not subject to the FDA equivalent of an audit.\(^{79}\)

The TGA has recognised that some therapeutic products do not fit neatly within either definition and provides a list of device/medicine boundary products that have been approved and whether they were classified as a medicine or a device.\(^{80}\) However, this list provides little assistance in determining the classification of new therapeutic products. The distinction is likely to become increasingly important in the regulation of nanotherapeutics, as the development of therapeutics on the nanoscale allows manufacturers to combine components of devices and medicines into a single therapy\(^{81}\) and, as we have seen, regulatory evaluation of medicines is far more comprehensive than regulatory evaluation of medical devices.

Most of the risks associated with nanodevices, such as Nanoss™, which incorporate fixed nanoparticles, are likely to arise at the end of the product’s lifecycle.\(^{82}\) In light of this, it may be prudent for the TGA to audit all implantable nanodevices to ensure that sponsors have adequately assessed the safety of their product at this stage. The second conclusion we can draw is that, even where a nanodevice is subject to an audit, safety and efficacy evaluation

\(^{74}\) Above n 61
\(^{77}\) Ibid.
\(^{78}\) Ibid.
\(^{79}\) Ibid.
\(^{80}\) Above n 61
may be far less rigorous than for prescription medicines

Further illustrative of this point is the convergent nanotherapeutic product being developed by the US company, Nanospectra Biosciences, gold nanoshells. These nanoshells are essentially nanosized particles of silica, coated in gold nanoparticles, which, when injected into the blood stream, naturally congregate at tumour sites. The nanoshell then acts as a nanolens, capturing infra-red light and focusing it around itself allowing tumours to be detected and imaged. In vivo diagnostic imaging agents are listed by the TGA as boundary products and are currently regulated as medicines. However, having served its diagnostic function, the gold nanoshell may be used to destroy the tumour, by shining an infra-red laser on the tumour site where the nanoshells have congregated. The area around the nanoshells heats up and the tumour cooks. The effect is similar to that of an implantable radioactive source, which is placed within tumours in order to destroy them. These are also listed as boundary products by the TGA but are currently regulated as devices. Thus, gold nanoshells have two distinct modes of action, both of which are recognised by the TGA as blurring the distinction between medicines and devices and both of which are currently classified differently by the TGA.

Unlike the TGA, the FDA explicitly recognises combination products and assigns regulatory jurisdiction based on the mode of action that is expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. Given that the destruction of tumours is likely to make the greatest contribution to the overall intended therapeutic effect of gold nanoshells it would appear likely that an application of this definition would result in them being regulated as medical devices. However, it is arguable that the risks associated with free nanoparticles, in vivo, should be subject to the more comprehensive safety and efficacy evaluation associated with prescription medicines approval. The FDA has provided that where a product has two modes of action, and neither mode is subordinate to the other, it will be assigned to the jurisdictional area with the most expertise in evaluating the most significant safety and effectiveness questions presented by the product.

“Fast Tracking” Nanotherapeutics and Postmarketing Evaluation

Prior to receiving regulatory approval, the safety and efficacy of therapeutic products is evaluated based on data obtained from clinical trials, which generally involve no more than a few thousand volunteers, forming a largely homogenous group, treated under carefully controlled conditions, by highly trained medical practitioners. However, following approval, a new therapeutic product may be prescribed or used by many hundreds of doctors on thousands of patients.

Attempting to secure approval for multiple modes of action for one product, which would require the submission of data to demonstrate the safety and efficacy for all modes of action, is likely to be both time consuming and costly. Industry may choose to, initially, only provide data demonstrating safety and efficacy for the mode of action that is most likely to secure fast-

83 Above n 61.
84 Above n 32.
85 Above n 61.
87 Ibid.
89 Ibid.
track access to the market. A major problem for regulators is that, once the product is approved for marketing, it is difficult to maintain regulatory control over unapproved uses.

In light of such considerations, postmarketing evaluation of therapeutic products may be required to detect unexpected side effects and interactions and to determine their long term quality, safety and efficacy.\(^90\) Evaluation of these risks postmarketing is likely to be particularly important for nanotherapeutics given that the safety evaluation framework for such products is lagging significantly behind their commercial development.\(^91\) Cost-effectiveness considerations could also become very important at the postmarketing stage, particularly as the Pharmaceutical Benefits Advisory Committee (PBAC) begins to expand capacity in this area and remains funded by taxpayers, rather than industry.

Of particular concern, in this respect, is the increasing trend for the FDA to condition approval based on the manufacturer applicant’s subsequent conduct of postmarketing studies.\(^92\) The FDA has here recognised, at least implicitly, that the end product of fast-track development and evaluation may be a less well developed safety and effectiveness profile.\(^93\) It has been suggested that FDA funding would need to be increased substantially in order to acquire the resources needed to build its own expertise and gather the necessary pre-market data required to get ahead of the commercialisation of nanotherapeutics.\(^94\) One consequence is that the FDA will have to negotiate with industry to provide this funding increase. This may jeopardise the adoption of a risk averse precautionary approach to the regulation of nanotherapeutics, whilst the FDA acquires the requisite resources to develop an effective safety evaluation framework.

There are essentially two methods for evaluating such risks of nanotherapeutics following regulatory approval: postmarketing surveillance and phase IV studies. Sponsors of approved therapeutic products are required, under the regulatory framework of both the TGA and FDA, to conduct a limited form of postmarketing surveillance, whereby they must maintain records of, and report, any adverse safety reports for their product of which they become aware.\(^95\) Generally sponsors will become aware of such matters, as a result of adverse event reporting from doctors, healthcare institutions and others in the field.\(^96\) Thus the data is collected rather haphazardly making epidemiological evaluation particularly difficult.\(^97\) Further, whilst acute adverse reactions are likely to be reported, it is unlikely that long-term adverse effects, or those that occur as an increase in already common conditions, will be detected by this mechanism.\(^98\)

Phase IV studies may be defined to include all post-approval studies to obtain data concerning safety, efficacy or new uses for the product\(^99\) and may take the form of formal trials or active research.

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\(^{91}\) See above n 43.


\(^{93}\) Ibid.


\(^{95}\) Ibid.

\(^{96}\) Ibid.

\(^{97}\) Ibid.

\(^{98}\) Ibid.

monitoring efforts. There are essentially three situations in which phase IV studies will be conducted. The FDA has explicit regulatory authority to condition approval on the conduct of phase IV studies, in order to verify the clinical efficacy, predicted on the basis of pre-approval surrogate endpoints, where a medicine has been approved under the accelerated approval pathway. In these circumstances the FDA has the authority to pull the drug off the market, where the sponsor does not perform the tests or the predicted benefits are not realised. However the FDA is now conditioning the approval of about half of all New Drug Applications on the conduct of phase IV studies. It is suggested that conditioning approval on phase IV studies may represent a compromise for review panels, subject to considerable pressure to fast-track approvals, where safety and efficacy concerns arise from ambiguities in pre-marketing data.

Outside of the accelerated approval pathway the FDA’s authority to condition approval on, and enforce the conduct of, phase IV studies is somewhat questionable derived from its records and reports provision, which is similar to the Conditions Standard and Specific Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989 and requires that the sponsor provide the TGA with periodic safety update reports containing information relevant to the safety of approved therapeutics, including the status of postmarketing studies. Whether or not this provision gives the TGA the authority to condition approval on, and enforce the conduct of phase IV studies, is outside the scope of this paper. However it is worthwhile noting that in the FDA context, a recent investigation by the Office of the Inspector General revealed that 35 of the periodic safety update reports that should have been submitted in the fiscal year 2004, were either missing or did not contain information regarding phase IV study commitments.

The report concluded that the FDA lacks an effective management information system for monitoring phase IV study commitments. Further it appears that the FDA has few options, short of withdrawing marketing approval, available to force sponsors to carry out their postmarketing commitments. Whilst this is a substantial threat in theory, in practice, the FDA is unlikely to withdraw approval unless a medicine is shown to be unsafe through adverse event reporting which as we have seen is difficult to evaluate. It would appear likely that the TGA is in a similar situation in these respects.

The final situation is where the sponsor of a therapeutic product voluntarily conducts a phase IV study. Such studies are most commonly conducted by companies wishing to test a therapeutic product for a new treatment indication or to show increased efficacy of their product compared to other similar products on the market. However, such studies may also reveal safety issues. For example Vioxx® was found to be unsafe and voluntarily recalled by Merck in 2004 because it was found to increase the risk of heart attacks or strokes, following the results of two phase IV studies, (the 2001 VIGOR study which was designed to assess the gastrointestinal safety of Vioxx® relative to that of an older drug (naproxen) and the 2000

\[100^\text{Ibid.}\]
\[101^\text{Ibid.}\]
\[102^\text{Ibid.}\]
\[104^\text{Above n 95.}\]
\[105^\text{Ibid.}\]
\[106^\text{Ibid.}\]
\[107^\text{Ibid.}\]
\[108^\text{Ibid.}\]
\[109^\text{Above n 95.}\]
\[110^\text{Ibid.}\]
APPROVe study, designed to study the protective effects of Vioxx® in preventing colon polyps).\textsuperscript{112} It is questionable whether Vioxx® should have been approved at all given that there was data, available to the FDA prior to approval, of increased risk of cardiovascular events occurring in patients receiving Vioxx® compared to the control group.\textsuperscript{113} However this data was dismissed as statistically insignificant based on the size of the trial and further was not considered reason enough, by the FDA, to condition approval on the conduct of phase IV studies.\textsuperscript{114} The Vioxx® scandal highlights the difficulty of identifying and imposing critical phase IV studies prior to approval, even where there is evidence to suggest the need for further investigation and further highlights the fact that regulatory agencies may be unable or unwilling to force sponsors to conduct specified phase IV investigations in response to evidence that comes to light postmarketing.\textsuperscript{115}

An Alternative to Industry ‘Fast-Tracking’ of Nanotherapeutics?

From industry’s point of view, the development of a new therapeutic product is expensive and time consuming. Reliable and objective data on the costs of pharmaceutical production is difficult to obtain. Reasonable estimates not created by pharmaceutical industry apologists, controversially place it at approximately US$403 million in 2000 for an average innovative product.\textsuperscript{116} On average a new drug takes 9 years to get to the market and it is risky, with many new drug applications failing between the IND and the New Drug application (NDA).\textsuperscript{117} The skewing of pharmaceutical development towards escalating shareholder profit rather than the global burden of disease is likely to lead to increasing interest in alternative models of nanomedical development, such as those emphasising a greater role for academics and their public-funded institutions in the development process.

The introduction, in 1992, of user fees in return for services that the FDA up until that time had been providing for free, provided industry with the perfect opportunity to shape regulatory procedures in such a way as to reduce their risks, associated with the development of new drugs. Industry negotiated with the FDA to come to a quid pro quo agreement whereby the introduction of user fees would be accompanied by a commitment by the FDA to expedite the review of new drug applications.\textsuperscript{118} The effect of this agreement is encapsulated by the following quote by the then director of the FDA taken from a 1999 newsletter.

In exchange [for the user fees], FDA makes a commitment to meet certain goals for review times. [The agency] has exceeded almost all of the goals, and it expects to continue to exceed them. Basically, the number of new approved drugs has doubled, and the review times have been cut in half.\textsuperscript{119}

The renegotiation of the fee structure every five years along with the willingness of the FDA to link fees with performance goals continues to give industry a substantial say in the way in which the fees will be spent.\textsuperscript{120} It has been suggested that the introduction of user fees has essentially created a system whereby industry is paying for the services of the FDA. This has

\textsuperscript{112} Above n 103.
\textsuperscript{113} Above n 95.
\textsuperscript{114} Ibid.
\textsuperscript{115} Ibid.
\textsuperscript{120} Above n 18.
lead to concerns that industry may be able to exert undue influence over the FDA, compromising its objectivity and independence in product approvals.\textsuperscript{121} One reasonable conclusion, especially in light of recent scandals such as Vioxx, is that the FDA may be compromising safety and efficacy concerns in order to meet demanding targets for approval times and that this may be the result of a cosiness between the FDA and industry.\textsuperscript{122}

Compounding the already substantial leverage industry is likely to have to pursue its interest in fast-tracking approval processes, is the secondary consequence that, at least initially, the FDA and other regulatory bodies, including the TGA, may face a deficit of knowledge as compared to industry, regarding fundamental aspects of nanotherapeutic design and function. This means that industry may be able to frame nanotherapeutics, particularly those characterised by convergence of technologies, in a manner that is most likely to result in fast-track approval.

Regulatory oversight of the clinical trials phase of therapeutics development is becoming increasingly important as a means of ensuring public safety. The FDA's adoption of designated 'fast-track' approval pathways may mean that clinical trials are no longer a precursor to regulatory approval but increasingly an integral part of it. Regulatory review of clinical trial protocols for emergent technologies such as nanotherapeutics provides an important opportunity for regulatory agencies to develop expertise and input in the design of safety evaluation frameworks. Given that the TGA does not have the equivalent of FDA designated 'fast-track' approval pathways, in this section we will consider whether there may be an unofficial 'level 3' style division of evaluation, facilitated by industry 'fast-track' tactics, with respect to the approval of clinical trials, between Australia's HRECs and the FDA.

A number of inferences arise regarding likely industry strategies for obtaining 'fast-track' approval to conduct clinical trials for nanotherapeutics. First, where a product is being developed for a serious or life-threatening condition, the best option for the sponsor is to seek accelerated approval status from the FDA, as this secures speedier access to the US market. In this situation clinical trial protocols, often utilising surrogate rather than clinical end-points will be developed and approved in consultation with the FDA but the actual clinical trials may be conducted in Australia to reduce costs. It would appear that a strategy of this type was adopted by Melbourne based company, Starpharma, for its product VivaGel\textsuperscript{TM}, which, as we have seen, was recently granted accelerated approval status by the FDA. On 24 August 2006 Starpharma announced the commencement of phase I clinical trials in Australia following successful review by the FDA and approval by local ethics committees.\textsuperscript{123}

Second, there are likely to be significant differences in the type of review between a HREC and FDA or TGA review under the CTX scheme. When reviewing an application under the CTN scheme, HRECs are likely to primarily focus on trial design and the ethical conduct of research, as such, the review may be less rigorous in terms of pharmacological, toxicological and chemical data than the TGA or FDA.\textsuperscript{124} With this in mind, we may predict that a legitimate strategy for the sponsor of a nanotherapeutic product would be to submit an initial application under Australia’s CTN scheme, on the assumption that it will not be subject to stringent scientific review. Finally, if the HREC does refer the application to the TGA for scientific review, under the CTX scheme, it is likely that the sponsor would withdraw the application and seek approval under the FDA’s much more time and cost effective IND.

\textsuperscript{121}Ibid.
\textsuperscript{122}Ibid.
\textsuperscript{124}Above n 47.
Thus there may be an unofficial ‘level 3’ style sharing of clinical trial review between Australian HRECs and the FDA, with very minimal scientific review being conducted by the TGA. The consequences of this, in terms of the regulation of nanotherapeutics in Australia, are twofold. First, Australian research participants risk being exposed to the potential toxicological risks associated with nanotherapeutics where those risks have either not been subject to stringent scientific evaluation at all, or have been assessed by the FDA with no input from the TGA. The second consequence is that if the present state of affairs continues, the TGA may not be given sufficient opportunity to gain expertise in, and have input into the development of, a safety evaluation framework for the burgeoning area of nanotherapeutics. The TGA essentially has two options to address this situation: take a more active role in the monitoring of clinical trials, which would involve expanding its bureaucracy, the costs of which would have to be recovered,125 or push for the establishment of level 1 style information sharing between it and the FDA.

Conclusion

Nanotechnologies have the potential to revolutionise the development of innovative and beneficial therapeutic products. In this paper we have examined the proposition that the FDA and TGA are under increasing pressure to ‘fast-track’ approval of innovative nanotherapeutics, that this will be heightened for the TGA by Annex 2C (4) of the AUSFTA, and that this pressure may compromise high standards of safety and efficacy and, potentially, the protection of Australian public health. Analysis of the risks and benefits associated with ‘fast-tracking’ nanotherapeutics revealed however that, even though the framework for assessing the safety risks of nanotherapeutics was underdeveloped, this did not justify the adoption of a risk averse regulatory approach which would likely stifle innovation thus nullifying the potential public health benefits of this technology. Indeed, we have argued here that the ‘fast-track’ obligations in Annex 2C (4) of the AUSFTA may actually facilitate the creation of policy and regulatory structures that promote Australian academic innovations in nanotherapeutics for the public good.

We conclude by suggesting that if Australia is to maintain sovereign, high standards of public healthcare in the wake of advances in nanotherapeutics, the TGA must reconcile the dual goals of ensuring high standards of safety and efficacy, and providing timely access to innovative therapeutic products, not just for Australian citizens but those of developing nations capable of being served by an expanded, more academically-controlled and ethically-focused Australian nanotherapeutics sector. To do this, the Australian Government should take a proactive stance toward utilising mechanisms, such as Annex 2C (4) of AUSFTA, to allow the TGA to efficiently develop the requisite evaluative framework for nanotherapeutic products that adequately represents both the precautionary principle through industry and taxpayer-funded sponsored mandatory postmarketing evaluations (which may include cost-effectiveness considerations) in the evidence-based global ‘health innovation’ or ‘community value’ of ‘fast-track’ processes.

125 Ibid.