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EVIDENCE BASED MEDICINE?
ACCESS TO INFORMATION & MEDICINES REGULATION IN NEW ZEALAND

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I Introduction

A Purpose

This paper explores one very important issue in the regulatory regime for medicines in New Zealand and around the world- the deficit of information about medicines available to doctors, patients and independent researchers. Much of the information about safety, efficacy and quality of drugs is held and controlled by pharmaceutical companies and regulators. The public is entitled to this information in full.

Medicines have removed the spectre of many preventable illnesses from daily life, increasing our lifespans and easing suffering. The pharmaceutical industry has an invaluable role in developing and distributing these drugs. However there are strong economic incentives behind the production, patenting and marketing of medicines. In New Zealand, the major suppliers of medicines are large multinational companies, for example Pfizer, GlaxoSmithKline and Roche.[1] While some generic (off-patent) drugs are manufactured domestically, most medicines are developed and manufactured overseas. Similarly, clinical trials to establish a drug's effectiveness, safety and quality are predominantly undertaken overseas.[2]

This paper investigates the issues present in New Zealand's medicines regulation and provides suggestions for greater transparency and disclosure of data. The analysis will also be put in the context of the present development of a joint trans-Tasman regulatory agency- the Australia New Zealand Therapeutic Products Agency (ANZTPA).

The key propositions contained below are:

- That there should be a mandatory clinical trials registry for all trials done in Australia and New Zealand, with ethics committees and trial sponsors holding responsibility for populating the register. Sufficient enforcement

1 "Members" (22 April 2013) Medicines New Zealand < http://www.medicinesnz.co.nz/>.
2 Mark Broatch "Bitter Pills" *The Listener* (New Zealand, 17 November 2012) at 17.

powers and resourcing should be provided for in legislation or Rules to ensure the efficacy of this scheme.

- That a statutory duty should be imposed on the ANZTPA to make all the unpublished information it holds about medicines that pass through the approval process publicly available.
- That, generally speaking, the arguments for preventing disclosure of official information containing clinical study reports and other unpublished raw data would not outweigh the significant public interest in disclosure.
- That administrative law 'tools' such as Official Information Act requests, Regulations Review Committee complaints, and use of the Ombudsman may assist in facilitating disclosure of trial data and clinical study reports held by Medsafe or the ANZTPA.

B *Key Terms*

'Medicine' includes any substance or article that is manufactured, imported, sold or supplied for administering to humans for a therapeutic purpose or an ingredient in the preparation of a therapeutic substance.[3] In this paper, the terms 'medicine' and 'drug' will be used interchangeably. Both hold the above meaning.

'Medical devices' are another important medical intervention. They are machines or instruments with a therapeutic use, such as a defibrillator or dialysis machine. Most of the discussion in this paper refers to 'drugs' or 'medicines'. However the points made are equally applicable to medical devices and information or trial data relating to these devices.

'New medicine' means any medicine that has not previously been available in New Zealand.[4] The manufacturer must seek New Zealand Medicines and Medical Devices Safety Authority (Medsafe) approval before it markets, manufactures or promotes a new

3 Medicines Act 1981, s 3(1) and (2).
4 Medicines Act 1981, s 3(3).

medicine in New Zealand. New medicines tend to be more expensive and protected by patents. This can be contrasted to off-patent drugs such as paracetamol (often referred to as 'generic' drugs).

'Unapproved medicine' means a medicine that has not received approval at all, or is unapproved for the purpose or dosage it is being prescribed for. This is not a statutory definition in New Zealand, but is the common terminology used to refer to a 'new medicine' or a purpose or dosage that an approved medicine does not have approval for. For example, if a medicine approved for adults is prescribed for a child, for a different ailment, or at a higher dosage, then it is being prescribed for an 'unapproved' use.

'Complementary health products' are products provided as alternative or supplementary to conventional medicines and medical devices. Examples include vitamins and other dietary supplements, homeopathy, herbal remedies, or indigenous medicine. Currently these products are regulated under either the Dietary Supplements Regulations 1985 or the Medicines Act 1981 but will soon be dealt with under new legislation- the Natural Health and Supplementary Products Act.[5]

A 'clinical study report' is where the most complete and informative technical information about a drug can be found. These reports are produced by the researchers for every trial on a medical intervention and contain vast amounts of information. They detail the experimental methods, results and analysis, and provide appendices that list all the data from every individual involved in a clinical trial. Journal articles and other documents about the drug are written and published using this information.

C Methodology

The research for this paper was done predominantly using secondary sources. However, some primary research was undertaken. A small number of people with expertise in areas relevant to this paper were approached and interviewed. The Victoria University Human Ethics Committee granted ethics approval in August 2013 before interviewing commenced. Additionally some employees at Medsafe were emailed with questions

5 Currently the Natural Health and Supplementary Products Bill 2011 (324-2).

about Medsafe's approval process. The information received from these interviews and email communication is cited in footnotes and anonymised where appropriate. Only factual information has been taken from the emails and they are therefore not anonymised. All opinions and information given in interviews are attributed anonymously using a general description of the person offering them apart from the information and opinions received during an interview with two Ombudsmen, in which permission was granted to attribute the comments directly.

II The Current Regime for Medicines Regulation

A Medsafe and the Medicines Act 1981

The Medicines Act 1981 (the Act) and Medicines Regulations 1984 control the use, approval, manufacture, sale and promotion of pharmaceutical drugs in New Zealand. Medsafe is authorised by the Ministry of Health to monitor and approve medicines and medical devices and administer the Medicines Act. Medsafe is accountable to the Minister of Health as a business unit within the Ministry.[6] It is also accountable to the pharmaceutical industry for those activities funded by fees.[7] Medsafe is responsible for pre-market approval and post-market monitoring of medicines.[8] It analyses new medicines for safety, efficacy and quality as well as monitoring reported side effects and continuing to evaluate drugs and medical devices once they are on the market.

Another key entity is the Pharmaceutical Management Agency (Pharmac). Pharmac was created in 1993 to provide funded access to pharmaceuticals in New Zealand with a primary focus on optimising public health outcomes.[9] It is in charge of subsidising medicines and also plays a public information role advising on the responsible use of pharmaceuticals.[10] Pharmac undertakes its own clinical analysis as part of its funding

6 "About us" (10 April 2013) Medsafe <www.medsafe.govt.nz>.
7 "About us", above n 6.
8 "About us", above n 6.
9 New Zealand Public Health and Disability Act 2000, s 46.
10 New Zealand Public Health and Disability Act 2000, s 47 and 48.

decision process and is working currently to expand its procurement role to include medical devices.[11]

Medsafe's approval for new medicines is given for very specific uses.[12] Medicines are usually approved by regulators to treat a specific symptom or illness or in a particular dosage. Approval is given for a substance for certain indications only, for example, 'for use in the treatment of condition X in adults at a dosage of 100mg every 24 hours'. Use of a medicine in a higher dose, for a different symptom or illness, or for a different type of patient (e.g. pregnant women, or children) requires separate and additional approval. Approval must be sought again separately if there are any material changes to an approved medicine.[13] An application must contain details of the ingredients, dosage, purposes of use, claims made in relation to effectiveness, reports of any studies and trials on safety and efficacy, evidence of approval in other countries, and the details of the manufacturer and manufacturing process.[14]

The evaluation of a medicine in the approval process is based on information supplied to Medsafe by the pharmaceutical company making the application and evidence from other relevant published studies. This includes the clinical study report for the medicine and data from countries where it is already on the market.[15] Medsafe may also request more information from the applicant if it considers it appropriate; this can include an order that further studies be undertaken.[16] Medsafe focuses on information that relates to the specific dosage and use being applied for, although applicants are expected to submit all

11 Pharmac "Establishing how PHARMAC will apply its model for medical device management" (19 August 2013) < http://www.pharmac.health.nz>.

12 Medicines Act 1981, s 20.

13 Medicines Act 1981, s 24.

14 Medicines Act 1981, s 21(2).

15 Such as the USA or Europe, see "Quality and Safety of Medicines: Medsafe's Evaluation & Approval Process" (23 April 2013) <www.medsafe.govt.nz>.

16 Medicines Act 1981, s 21(4); Email from Chris James (Manager, Clinical Risk Management, Medsafe) to the author regarding enquiry about Medsafe's powers (11 April 2013); Email from Susan Martindale (Principal Advisor, Regulation, Medsafe) to the author regarding queries about the regulation of medicines (24 April 2013).

studies that relate to safety.[17] Failure to disclose all relevant information may result in a penalty issued under section 36 of the Act such as suspension of approval, breach of which could result in a $5,000 fine or 6 month imprisonment.[18]

Unapproved medicine can be prescribed if a doctor believes it will be beneficial for their patient.[19] It may be necessary for patients to use unapproved medicines for rare conditions, for different purposes to what approval is granted for, or to try treatments that are approved overseas but not in New Zealand. In these instances section 29 of the Act requires that the Director-General of Health be notified. In prescribing medicine (approved or otherwise) the practitioner must always adhere to adequate professional and ethical standards and seek the informed consent of the patient.[20] Pharmac also funds some unapproved medicines, usually in the rare circumstances where there are no alternative medicines with a current approval on the market.[21]

B Clinical Trials and Ethics Committees

Few drugs and devices are developed or trialled in New Zealand compared to the rest of the world. However at the time of writing there are 179 centres nationwide where clinical trials could be carried out and about 1865 trials voluntarily registered with the Australia New Zealand Clinical Trial Register citing New Zealand as the country of recruitment.[22] All clinical trials in New Zealand must be approved and reviewed by the relevant university ethics committee or regional Health and Disability Ethics Committee (HDEC).[23] The HDECs apply the Ethical Guidelines for Observational Studies and Ethical Guidelines for Intervention Studies.[24] These standards are set and reviewed by the

17 Email from Susan Martindale (Principal Advisor, Regulation, Medsafe) to the author regarding queries about the regulation of medicines (29 April 2013).

18 Email from Susan Martindale, above n 16.

19 Medicines Act 1981, s 25.

20 Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996, schedule 1, rights 4, 6 and 7.

21 Information received from a confidential source in the government medicines/health area.

22 Connect Clinical "Search Listings: New Zealand" <www.connectclinical.com.au>; Australian New Zealand Clinical Trials Registry <www.anzctr.org.nz> (as at July 2013).

23 Established under New Zealand Public Health and Disability Act 2000, s 11.

24 National Ethics Advisory Committee *Ethical Guidelines for Intervention Studies: Revised Edition* (Ministry of Health, Wellington, 2012); National Ethics Advisory Committee *Ethical Guidelines for*

National Advisory Committee on Health and Disability Support Services Ethics (NEAC).[25] Clinical trials using a new medicine require separate additional approval from the Director-General of Health.[26] All trials in New Zealand must be conducted in accordance with the Note for Guidance on Good Clinical Practice issued by the European Medicines Agency (EMA), which reflects international best practice.[27]

III The ANZTPA

In 2003 Australia and New Zealand signed the Agreement between the Government of Australia and the Government of New Zealand for the Establishment of a Joint Scheme for the Regulation of Therapeutic Products (the Treaty). This Treaty provides for a joint trans-Tasman regulator for medicines and medical devices; the Australia New Zealand Therapeutic Products Agency (ANZTPA).[28] The agreement adds a further component to the Australia New Zealand Closer Economic Relations Trade Agreement (CER) and the subsequent framework this has created.[29] The CER envisages the eventual creation of a 'seamless trans-Tasman business environment', or single economic market.[30] However laws relating to complementary medicines and therapeutic goods are exempt from the arrangement. The Treaty is an attempt to incorporate medicines regulation into the CER framework.

There are several issues that arise when considering the ANZTPA framework in a more general sense. Loss of sovereignty and the extent to which the Australian majority may

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Observational Studies: Observational research, audits and related activities: Revised Edition (Ministry of Health, Wellington, 2012).

25 Established under New Zealand Public Health and Disability Act 2000, s 16.

26 Medicines Act 1981, s 30.

27 E6 (R1) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) 1996 (European Union).

28 Agreement between the Government of Australia and the Government of New Zealand for the Establishment of a Joint Scheme for the Regulation of Therapeutic Products (signed 10 December 2003, not yet in force) [Joint Therapeutic Agency Treaty].

29 Australia New Zealand Closer Economic Relations Trade Agreement 1329 UNTS 175 (signed 28 March 1983, entered into force 1 January 1983); Joint Therapeutic Agency Treaty, above n 28, preamble.

30 New Zealand Ministry of Foreign Affairs and Trade "CER and SEM" (16 November 2010) <www.mfat.govt.nz>.

overbear New Zealanders' interests are concerns, as are the implications that such a scheme will have for Pharmac and its corresponding Australian body.[31] However most parties seem to agree that the joint agency has the potential to increase efficiency, decrease cost and improve the current systems in Australia and New Zealand. Due to the constraints of this paper, these more general and wide-ranging issues will not be discussed. This paper is restricted to its particular focus - the provisions relating to public access to information and how the system will function in this particular area.

This part of the paper provides a general overview of the history and development of the ANZTPA as well as a description of the way that the proposed scheme will operate according to the information presently available. The anticipated medicines approval process of the Agency is included in this overview. Discussion of particular issues relating to information accessibility and recommendations for improvement is in Parts IV and VI below.

A Development

The switch to ANZTPA regulation is scheduled for 2016, upon passage of legislation in both countries, thereby ratifying the Treaty.[32] The Medicines Act will be repealed entirely and replaced with the implementing legislation for the joint agency. This ratification process was initially intended to occur several years ago. However political opposition in New Zealand hindered its progress.

1 The Therapeutic Products and Medicines Bill 2006: initial opposition

In 2006 the Therapeutic Products and Medicines Bill (103-1) (the Bill) will be the domestic implementing legislation in New Zealand required to ratify the Treaty. The Bill narrowly passed its first reading.[33] However the Select Committee recommended that it

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31 For discussion of this issue in the intellectual property context see Susy Frankel, Chris Nixon, Megan Richardson and JohnYeabsley "The Challenges of Trans-Tasman Intellectualy Property Coordination" in Susy Frankel and Deborah Ryder (eds) *Recalibrating Behaviour: Smarter Regulation in a Global World* (LexisNexis, Wellington, 2013) 101 at 102.

32 "About ANZTPA" (26 April 2013) ANZTPA <www.anztpa.org>; Joint Therapeutic Agency Treaty, above n 28, art 23.

33 (12 December 2006) 636 NZPD 7067. The Bill passed by 61 votes to 59.

not progress.[34] During the Bill's first reading there was vocal opposition to a joint agency from several political parties (New Zealand National, Green Party, Māori Party, and ACT New Zealand) and frustration over lack of consultation and a refusal by the Labour Government to take a cross-party approach to the development of the scheme.[35]

The major point of opposition for New Zealand has always been the inclusion of complementary health products in the scheme, particularly the effect that might have on traditional Māori medicine (Rongoā).[36] The objection with regards to complementary medicine is that inclusion in a full-blown medicines regime will result in excessive compliance and approval costs for businesses and consumers. Alternative health products are generally low-risk (although not always) and therefore the medicines approval process is seen as unnecessary, resulting in prohibitively expensive products. Rongoā medicine was not included in the Bill and is not regulated at all when administered in the traditional way.[37] This relieved the concerns over the place for traditional Māori medicines but the impact of the scheme on other complementary medicines in New Zealand remained contentious.

2 Recent developments

In 2011 the New Zealand and Australian Governments revived the joint scheme.[38] Through these negotiations it was agreed that New Zealand could remove its domestic complementary health products industry from the ANZTPA scheme.[39] Those products are now to be separately regulated via the Natural Health and Supplementary Products legislation (when enacted).[40] The separate regulation will be reviewed after five years

34 Therapeutic Products and Medicines Bill 2006 (103-1) (select committee report) at 3.

35 (12 December 2006) 636 NZPD 7067.

36 Health Committee *Inquiry into the Proposal to Establish a Trans-Tasman Agency to Regulate Therapeutic Products* (December 2003), at 30, 38 and 48.

37 (12 December 2006) 636 NZPD 7067.

38 John Key "Australia, NZ Announce Intention on ANZTPA" (press release, 20 June 2011); "Statement of Intent" (27 November 2012) Australian New Zealand Therapeutic Products Agency <www.anztpa.org>.

39 *Description of a Possible Joint Regulatory Scheme for Therapeutic Products under ANZTPA [ANZTPA Discussion Paper]* (ANZTPA, discussion paper, January 2013, at 9.

40 Natural Health and Supplementary Products Bill 2011 (324-2).

from commencement.[41] The resolution of the major objections to the joint regulator paved the way for renewed negotiations and both countries are now moving towards implementation of the joint scheme. At the time of writing the progress is still in its early stages, with a discussion document containing high-level policy proposals circulated at the beginning of 2013.[42] Submissions made in response to this document are currently being considered.

3 Nature and Makeup of the Agency

The ANZTPA will be overseen by and accountable to the 'Ministerial Council' comprised of the two Ministers holding the Health portfolios in their respective countries.[43] The Ministerial Council will appoint members of the ANZTPA Board, which will comprise a Chair, Managing Director (the chief executive), one person each from New Zealand and Australia with broad experience in public health and regulatory matters, and a person with commercial experience.[44] Both Ministers must agree on the candidate for the Chair and Managing Director positions. However the members from their respective countries will be appointed on recommendation of the relevant Minister where consensus is not reached.[45] Appointment of the fifth member and provisions for removal of Board members will be provided for in the Rules.

The Board is directly responsible to the Ministerial Council for financial matters, the administration of the ANZTPA, efficiency and effectiveness of ANZTPA performance, the strategic direction of the Agency and reporting to the Ministerial Council on these matters.[46] Management of the ANZTPA is the responsibility of the Managing Director, as chief executive officer.[47]

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41 *ANZTPA Discussion Paper*, above n 39, at 9.
42 *ANZTPA Discussion Paper*, above n 39.
43 Joint Therapeutic Agency Treaty, above n 28, art 4.
44 Joint Therapeutic Agency Treaty, above n 28, art 6(1).
45 Joint Therapeutic Agency Treaty, above n 28, art 6(2).
46 Joint Therapeutic Agency Treaty, above n 28, art 6(5).
47 Joint Therapeutic Agency Treaty, above n 28, art 7.

The ANZTPA will be constituted as a body corporate in Australia, but will not have international legal personality.[48] This means that, while it will have such rights, powers and privileges as required to perform its regulatory functions in New Zealand, the ANZTPA will have legal personality in Australia only and will be based in Australia. However the 2006 Bill emphasises that both countries will have an equal voice in the governance of the scheme and envisages that the ANZTPA will look and behave in a way similar to a Crown Entity in New Zealand.[49]

B The ANZTPA Regulatory Scheme

The Treaty provides the overarching rules governing the ANZTPA and powers afforded to it, which will then be recognised in implementing legislation in Australia and New Zealand. The Agency itself will be given the power to create delegated legislation in the form of Rules and Orders, which will provide the detail for the scheme. The Rules must uphold the primary purpose of the scheme, which is set out in the Treaty:[50]

> … [T]o safeguard public health and safety in Australia and New Zealand by establishing and maintaining a joint scheme consistent with international best practice for the regulation of the quality, safety, and efficacy or performance of therapeutic products, and of their manufacture, supply, import, export and promotion.

The implementing legislation will deal with details such as offences, enforcement, judicial review matters, governance and accountability of the ANZTPA and the recognition of Rules and Orders.[51] It appears that the 2006 Bill will be resurrected and amended to create New Zealand's implementing legislation.

This section will provide a combined overview and analysis of the proposed provisions in the Treaty, the Bill and the discussion document indicating the possible framework and regulatory provisions for the trans-Tasman scheme (the Paper).[52] The analysis will be mostly centred on those provisions relating to the central issue in this paper- the

48 Joint Therapeutic Agency Treaty, above n 28, art 5(4), (5) and (6).
49 Therapeutic Products and Medicines Bill 2006 (103-1), explanatory note.
50 Joint Therapeutic Agency Treaty, above n 28, art 2(1).
51 *ANZTPA Discussion Paper*, above n 39, at 6.
52 *ANZTPA Discussion Paper*, above n 39.

information deficit. It is useful to bear in mind that these proposals are subject to potentially significant changes as the ANZTPA process progresses. Recommendations for the ANZTPA legislation and Rules in light of the issues explored in earlier parts of this paper will be detailed in Part VI.

1 Rules and orders

The Ministerial Council will have the power to make Rules pertaining to most aspects of the ANZTPA and providing the detail of the regulatory scheme.[53] These Rules are a form of delegated legislation and must give effect to the objectives of the Treaty.[54] The Ministerial Council may also use Rules to further delegate functions or powers of the Managing Director or the ANZTPA Board.[55] These Rules will cover areas such as the representations and promotion allowed in respect of therapeutic products, requirements for provision of information to the ANZTPA, establishment of advisory committees, and the approvals process for therapeutic products.

The Agency itself may make Orders dealing with several more technical and detailed aspects of the regulatory framework.[56] ANZTPA will determine, in Orders, standards for the information provided to consumers and professionals as well as for other matters concerning the quality, safety and efficacy of medicines.[57]

The New Zealand and Australian Parliaments have the opportunity to disallow in whole (not in part) any Rules or Orders at the time they are tabled in both Parliaments. If a Rule or Order is disallowed by the Parliament of one party it ceases to have effect in both countries.[58] The ANZTPA will consider and determine applications for an approval in relation to the manufacture, supply, import, export or promotion of a therapeutic product in accordance with the Rules.[59] Approval will be effective in both territories unless the

53 Joint Therapeutic Agency Treaty, above n 28, art 9.
54 Joint Therapeutic Agency Treaty, above n 28, art 9.
55 Joint Therapeutic Agency Treaty, above n 28, art 9 (1)(g) and (o).
56 Joint Therapeutic Agency Treaty, above n 28, art 10(1).
57 *ANZTPA Discussion Paper*, above n 39, at 10.
58 Joint Therapeutic Agency Treaty, above n 28, art 9(4) and 10(4).
59 Joint Therapeutic Agency Treaty, above n 28, art 11(1).

Approval expressly provides that it only applies in one country but such exceptions will be rare and usually temporary. There is also provision to allow one party to depart from the scheme in exceptional circumstances. These circumstances may pertain to public health, safety, third country trade, or environmental or cultural factors that affect the party seeking departure.[60]

2 The medicines approval process

The ANZTPA scheme will split medicines into two classes. Class 1 medicines are products that are low risk, such as sunscreen.[61] Medicines meeting the criteria and containing permitted ingredients will be regulated in Class 1 and will have subsequently lower compliance obligations.[62] All other medicines will be considered Class 2 and full product approval will be required.[63] The Paper states that the information provision requirements for an application will vary depending on the risk of the medicine but it does not elaborate further. ANZTPA will have regard to whether the quality, safety and efficacy of the medicine has been satisfactorily established in accordance with the state of contemporary scientific knowledge and may seek advice from a relevant expert committee.[64]

The Paper proposes strict standard conditions be applied to approved medicines. It will be a condition of approval that applicants comply with monitoring requirements for the drug and it will be an offence not to report serious adverse effects.[65] Approved medicines may not be advertised for unapproved uses, and the approval holder must provide information about any overseas regulatory action that has been taken in relation to the medicine or product in question.[66] In addition, ANZTPA may impose specific conditions on the approval at its own initiative.[67] Holders of approval for a Class 1 medicine must also

60 Joint Therapeutic Agency Treaty, above n 28, art 12.
61 *ANZTPA Discussion Paper*, above n 39, at 14.
62 *ANZTPA Discussion Paper*, above n 39, at 14 to 16.
63 *ANZTPA Discussion Paper*, above n 39, at 17.
64 *ANZTPA Discussion Paper*, above n 39, at 17.
65 *ANZTPA Discussion Paper*, above n 39, at 20; Therapeutic Products and Medicines Bill 2006 (103-1), cl 76.
66 *ANZTPA Discussion Paper*, above n 39, at 20.
67 *ANZTPA Discussion Paper*, above n 39, at 20.

retain information or evidence supporting any claims made about the medicine and provide it to the Agency on request.

A major deficit of the system in place today, which is not fully addressed in the legislation and discussion paper for the ANZTPA, is the appropriate scrutiny for combination medicines, and medical devices. Medical devices are not currently required to submit to a pre-market approval process. They are only monitored for adverse effects post-market. Therefore, medical devices that are not properly assessed, possibly with risks that outweigh their benefits, are introduced onto the market through this legislative deficiency.[68] Two examples of this are DePuy ASR artificial hips and Poly Implant Prothese silicone breast implants- both of which have recently been found to cause unacceptable adverse effects.[69] The ANZTPA scheme will require that medical devices obtain pre-market approval although some academics suggest ANZTPA should go further and undertake safety assessments of these products itself.[70] Before the ANZTPA begins to operate, Pharmac will have begun its procurement model for medical devices. There is potential for overlap with Medsafe's role -Pharmac will need to do clinical testing of the devices, especially because it cannot rely on Medsafe approval as is the case with medicines. The ANZTPA scheme will resolve this issue once ANZTPA begins to approve and assess medical devices pre-market.[71]

A 'combination product' is "a therapeutic or diagnostic product that combines a medicine, device, and/or biological product into a single entity."[72] These products straddle the boundary between medicines and medical devices, as they achieve a therapeutic function with a combination of physical and mechanical actions. Many therapeutic products now on the market are combination products but the ANZTPA legislation does not make provision for such products nor suggest how they might be

68 Dhruva SS, Redberg RF "Medical Device Regulation: Time to Improve Performance" (2012) 9 PLoS Med e1001277.

69 Jennifer Moore "Proposed Changes to New Zealand's Medicines Legislation in the Medicines Amendment Bill 2011" (2013) 10 Journal Bioethical Inquiry 59, at 65.

70 Moore, above n 69, at 66.

71 Information received from a confidential source in the government medicines/health area.

72 Moore, above n 69, at 64.

properly regulated under the scheme- as medicines or as medical devices.[73] Again, this needs clarification and clear provisions to be enacted to cater for these novel but fast-growing types of medicine. The ANZTPA scheme must be able to meet the future needs of patients and apply to novel therapeutic products as well as the more traditional pharmaceutical drugs.

IV The Information Deficit in Medicine

Patients expect medical decisions to be based on scientific evidence. They expect that new drugs be tested in fair, replicable clinical trials before applications are made for market approval. They expect regulators to make fully informed, transparent approval decisions on the basis of reliable data and information provided by the applicant. Finally, they expect that when their doctor is considering a treatment for their condition they have access to all the information necessary to weigh up the costs and benefits of the drug for them. However, this does not always occur. Doctors and independent researchers do not have access to all the available information about medicines, only that which is published. As will be explored below, this published information contains bias and conceals data relevant to the drug's safety and efficacy. Medsafe receives more information than is shared with doctors. Furthermore, industry-funded clinical trials can be compromised by a strong financial incentive to hide unflattering results. In this paper, the situation described above is termed the 'information deficit'.

This part of the paper outlines the issues concerning access to information and hidden data that occur in our current system. Part V discusses pharmaceutical companies' role in information provision and some strategies used by the industry when presenting information about drug trials. Part VI contains recommendations to address these issues. Additional examples of the implications of this information deficit are provided in the three appendices attached at the end of the paper.

73 Moore, above n 69, at 64.

A Hidden Data and its Impact on Public Health

There is a large body of evidence that suggests that a significant number of negative or unflattering clinical trials for medical interventions remain unpublished.[74] This is known as publication bias. It occurs in both industry-funded research and in academia generally. While not necessarily wilful or malicious, many data remain hidden. This can be for a variety of reasons, such as difficulties with and disincentives to publishing trials with inconclusive or negative results in journals, or a decision to discontinue a trial or drug development. The result is that the scientific literature may give the impression that a drug is effective or safe when the sum of all research on a drug may actually indicate that the risks outweigh the benefits. This is misleading for independent researchers, doctors and patients relying on the published literature.

Regulators, including Medsafe, receive the clinical study report for drugs submitted for approval and use it to make their approval decision. However, pharmaceutical companies do not make the clinical study reports for their medicines publicly available and regulators are also likely to refuse to disclose them, citing reasons of commercial sensitivity.[75] This means that in most cases clinical study reports are out of the reach of independent researchers and doctors. The regulators themselves undertake an analysis of the clinical study report during their approval decision but Medsafe does not make its evaluations public.[76]

It must be noted that, even if all information on newly developed drugs was shared from today onwards, this would not be sufficient to address the information deficit. The vast majority of drugs that are prescribed by practitioners were developed and trialled several

74 Chalmers Iain "Underreporting Research is Scientific Misconduct" (1990) 263 JAMA 1405; Lee K, Bacchetti P, Sim I "Publication of clinical trials supporting successful new drug applications: a literature analysis" (2008) 5 PLoS Med e191; Melander H, Ahlqvist-Rastad J, Meijer G, Beerman B "Evidence b(i)ased medicine- selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications" (2003) 326 BMJ 1171; Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ et al "Dissemination and publication of research findings: an updated review of related biases" (2010) 14 Health Technol Assess 1; Written evidence from PLoS (CT20), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013) at 122.

75 Email from Susan Martindale, above n 16.

76 Email from Susan Martindale, above n 16.

years, or even decades, ago. Therefore manufacturers and regulators must also release information from clinical trials retrospectively in order to create a meaningful solution to this issue.

The latest high-profile example of withheld data arose in 2012 and is on-going. Tamiflu (oseltamivir) was purchased in bulk by governments all over the world, including New Zealand, during the outbreak of the H1N1 influenza virus in 2009. This decision was predominantly based on a selection of published trials stating that it reduced secondary complications of influenza and hospital admission.[77] Parts of the clinical study reports were obtained by a group of researchers from the Cochrane Collaboration through Freedom of Information Act 2000 (United Kingdom) requests and negotiations with the manufacturer, Roche. The researchers subsequently found that some serious adverse effects that occurred in the trials were not published and some of Roche's claims appeared inconsistent with the results of the trials.[78]

1 Examples of the ramifications of the information deficit

The following examples illustrate the impact that publication bias and hidden data can have on public health.

Drug X has been tested in 80 clinical trials. 44 of these indicate that X is overall beneficial for adults with Condition Z. 32 indicate that X is no better than any other treatment for Z on the market, or that X is not better than placebo based on statistical significance. Four trials show that several participants dropped out of the trial because of unbearable side effects or that some participants died during the trial (the death may not

77 Kaiser L, Wat C, Mills T, Mahoney P, Ward P and Hayden F "Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations" (2003) 163 Arch Intern Med 1667.

78 Peter Doshi, Tom Jefferson and Chris Del Mar "The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience" (2012) 9 PLoS Med e1001201; British Medical Journal "Tamiflu Campaign" (2013) BMJ <www.bmj.com/tamiflu>. The Cochrane Collaboration is an independent international network of medical experts that aims to compile comprehensive systematic reviews of safety and efficacy data for medicines. It has developed a reputation for providing a 'gold standard' for reviews of pharmaceutical drugs and is committed to advancing evidence-based medicine and transparency. All reviews are publicly available: <www.cochrane.org>.

be caused by X, but these results could indicate a need for more research or investigation). Overall, there are 44 positive trials for X and 36 negative or neutral trials. This shows mixed results. If all trials are published then the literature will reflect that. If 42 positive trials are published and seven negative or neutral trials are published, this presents a very different picture of Drug X. It appears much more effective and safe than it may actually be. Doctors may be unaware of the four trials where patients dropped out or died, and may decide on balance that the evidence comes down overwhelmingly in favour of Drug X and prescribe it for their patient with Z. That patient is exposed to significant risk because their doctors are not fully informed. The literature is skewed in favour of a drug that may do them more harm than good, or may cost them a lot more than an off-patent medicine that performs just as well.

Drug A was developed by PharmaCo in 1980, designed for patients who have suffered heart attacks and now have irregular heart rhythms.[79] A was trialled in 100 patients, 50 were given A and 50 were given placebo. Of the first 50, ten patients died. Of the second 50, only one died. It seemed that Drug A was a failure, commercial funding was stopped and the trial and development discontinued. Because commercial development was stopped, PharmaCo's scientists never published anything about the trial of Drug A. In 1990, MedCo had a similar idea, and developed Drug C- a similar drug to A and also used to treat irregular heart rhythms. C was brought to market and prescribed all over the world. However, Drug C also caused an increased risk of death. By the time this was detected thousands of patients who had been using C had died. Had PharmaCo published its 1980 trial, it may have prevented these deaths as medical professionals and drug developers would have been aware of Drug A's existence and the effects seen in its early trial.

2 Inquiry into hidden data by the House of Commons

The United Kingdom House of Commons Science and Technology Select Committee are currently undertaking an Inquiry into clinical trials and the problem of hidden data in

79 This example is based on the drug Lorcainide and other antiarrhythmic medicines. See Cowley AJ, Skene A, Stainer K, and Hampton JR "The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias" (1993) 40(2) Int J Cardiol 161.

medicine.[80] The Committee has received expert evidence from 61 regulators, academics, and industry representatives in the medicine and pharmaceutical drugs regulation field. The findings from this evidence suggests that pharmaceutical companies and academics do not make public the existence of every trial they conduct in the United Kingdom and Europe, nor do they make the data from these unpublished trials available. Furthermore, regulators also fail to provide the public with the information they receive during the medicines approval process or with details of their evaluations.

Whether wilful or not, this 'hidden data' has created a situation that is injurious to public health and which occurs on a global scale including in New Zealand and Australia. The Inquiry provides important information and recommendations that will also be relevant for New Zealand and Australia. Therefore the evidence and findings of the Inquiry in relation to clinical trials and hidden data will be discussed in this Part. Recommendations made by the Inquiry will also be analysed in Part VI below.

B Health and Disability Services Consumers' Rights

Patients' rights to be fully informed in making treatment decisions are protected in New Zealand in the Code of Health and Disability Services Consumers' Rights (the Code).[81] The applicable rights are Rights 4 and 6. Right 4 provides that every consumer has the right to have services provided that comply with legal, professional, ethical and other relevant standards.[82] Furthermore, every consumer has the right to have services provided in a manner that minimises potential harm and optimises their quality of life.[83] Right 6 enshrines the right to information that a reasonable consumer would expect to receive in the circumstances, including an evaluation of the treatment options available that gives an assessment of the expected risks, side effects, benefits and costs of each option.[84] Before making a choice about a medical intervention, all consumers have the right to information that they need to make an informed choice or give informed consent.

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80 UK House of Commons, Science and Technology Committee *Clinical Trials* (written evidence, 6 March 2013).

81 Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996, schedule 1, cl 2, rights 6 and 7.

82 Schedule 1, cl 2, right 4(2).

83 Schedule 1, cl 2, right 4(4).

84 Schedule 1, cl 2, right 6(1)(b) and (c).

Despite doctors' best efforts there is currently no way to guarantee that patients will receive fully informed advice about the treatment options available to them because doctors cannot access complete information and data about all the trials and studies done on an intervention. Nor can doctors be sure how many trials or data are missing from their review of the publicly available literature. This prohibits patients' ability to give fully informed consent and puts them at unnecessary risk of undisclosed side-effects or problems that might have been picked up in successive assessments or re-analysis of the trial data by subsequent researchers and experts.

A provider is not in breach of the Code if they have taken reasonable actions in the circumstances (including their own resource constraints) to give effect to the rights in the Code.[85] Therefore the issues that this information deficit causes in light of the Code are not enforceable against practitioners so long as they have made a treatment decision on the basis of all the (published) information available to them. This means that patients have no recourse to enforce their rights to be fully informed via the Code in this particular context. Patients are still at risk of breaches of the standard of medical care they are entitled to expect because their practitioners cannot provide them with full information about a treatment despite acting exactly as the law and ethical standards requires. The rights protected by the Code are undermined by the failures in transparency that have been made and continue to be allowed by the current regulatory system.

Without all the information about a treatment, the patient or practitioner cannot make a valid and informed decision.[86] A doctor must be able to access full and accurate information about a drug's safety and efficacy in order to provide quality treatment.[87] When treatment decisions are made in the context of prescribing an unapproved medicine the need for accurate and transparent information to be available to a practitioner becomes even more important. Appendix One below illustrates this point.

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85 Schedule 1, cl 3.

86 *Rogers v Whitaker* [1992] HCA 58; (1992) 175 CLR 479 at [9] to [14].

87 See Appendix One for a case study.

C Clinical Trials Register

A clinical trials register is a list of clinical trials that receive ethics approval and the results of those trials once completed. This list can be checked alongside the published literature to give doctors, researchers, regulators and patients some idea of how much information about a particular drug or device remains unpublished, undisclosed, or subject to further research. There are several clinical trial registers around the world, including the voluntary Australia New Zealand Clinical Trials Registry, which was established in 2005 and is managed by a not-for-profit organisation.[88] However, the effectiveness of a clinical trial register is limited unless it contains all the trials undertaken within its jurisdiction and is populated retrospectively to include past trials for drugs that were developed before it was created. Many medicines that are prescribed today were developed several years ago, meaning that the data publicly available for those drugs will remain insufficient unless the results of all the trials conducted, including those that remain unpublished, are made available retrospectively. While there are many trials listed in the ANZCTR, some of which were registered retrospectively, it will not provide a truly useful resource for doctors and patients until all trials conducted in Australia and New Zealand are contained on the database.

The first jurisdiction to require registration of clinical trials by law was the United States. The Food and Drug Administration Amendments Act 2007 requires that all interventional clinical trials for regulated drugs and devices undertaken in the United States be registered on a new database, Clinicaltrials.gov, and that all results for those trials be put on the database no longer than 12 months after completion.[89] If a trial reaches its completion before the drug is approved for use, then the deadline for posting results is no more than 30 days after approval is given.[90] Violations were supposed to be met with a fine of up to US$10,000 followed by a further US$10,000 for every day the violation was

88 (29 April 2013) Australia New Zealand Clinical Trials Registry < http://www.anzctr.org.au/>.

89 Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904, at 905.

90 Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904, at 914.

not remedied after a 30-day grace period.[91] For government-funded studies that fail to register, the penalty was a withholding of grant funds.[92] However apparent lack of enforcement has meant that drug developers have been able to evade their obligations to register their clinical trials and results.[93] A study in 2012 found that only one in five trials conducted since the legislation came into force has been registered within the legislative deadline.[94]

D Information and Medsafe

As discussed in Part II above, Medsafe receives a lot of unpublished data and information about medicines that are submitted for approval, including clinical study reports. Medsafe can also require that more information be provided and exercises that power routinely.[95] To ensure that all information is given to Medsafe, applicants are required to make a declaration that no relevant information has been omitted from their application.[96] However members of the public, including doctors and independent researchers, cannot access the clinical study reports that are held by Medsafe. Nor are Medsafe's decisions and evaluation of medicines routinely made publicly available. The Official Information Act 1982 (OIA) does apply and Medsafe will release some information about a decision where it is required to do so. [97] However information on safety, quality and efficacy will usually be withheld to protect commercial sensitivity.[98] Regulators in other jurisdictions have similar data-protection policies, although some such as the European Medicines Agency (EMA) are changing their policies towards greater transparency.

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91 Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904, at 921.

92 Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904, at 918.

93 Ben Goldacre *Bad Pharma: How drug companies mislead doctors and harm patients* (Fourth Estate, London, 2012), at 52.

94 Prayle AP, Hurley MN, Smyth AR "Compliance with mandatory reporting of clinical trial results on ClinicalTrial.gov: cross-sectional study" (2012) 344 BMJ d7373.

95 Medicines Act 1981, s 21(54); Email from Susan Martindale, above n 16.

96 Medsafe *New Zealand Regulatory Guidelines for Medicine: Part E: Templates, declarations and checklists* (6.14 ed, Ministry of Health, July 2011) at 1.13.

97 Email from Susan Martindale, above n 16

98 Email from Susan Martindale, above n 16; Official Information Act 1982, s 9(2).

The information that doctors and patients receive from Medsafe is in summary form. Most medicines are accompanied by a 'Consumer Medicine Information' pamphlet (CMI) that contains information written for patients. The relevant pharmaceutical company is responsible for producing CMIs and is not legally required to do so. Medsafe does not approve or evaluate CMIs.[99] Data sheets, on the other hand, are required by the Medicines Regulations 1984 and contain greater detail and technical prescribing information for medical practitioners.[100]

As argued in the following parts of this paper, Medsafe should make its reports and evaluations prepared for the drug approval process publicly available. It should also ensure that all unpublished studies and clinical study reports it receives from applicants are made public.

E Justifications for Restricting Public Access to Clinical Study Reports and Other Unpublished Information

There are several arguments made for restricting public access to clinical study reports, some more valid than others. The following are common justifications for non-disclosure:

- Commercial sensitivity;
- Protection of trial participants' confidentiality; and
- Risk of misinterpretation of large datasets by laypersons or those with a malicious intent.

The following analysis will demonstrate that all of those perceived risks can be resolved without compromising transparency.

1 Commercial sensitivity

'Commercially sensitive' information involves a trade secret or is information that would unreasonably prejudice the commercial position of the person who supplied it if it was disclosed.[101] It is important to protect pharmaceutical companies to some extent in order

99 "Consumer Medicine Information" (23 April 2013) Medsafe <www.medsafe.govt.nz>.

100 Sections 51 to 53.

101 Official Information Act 1982, s 9(2)(b); *Official Information Legislation Guides: Part 5 Common Misconceptions* (Office of the Ombudsman, Guideline) at 7 to 8.

to provide incentives for innovation and to allow them to recover the significant costs associated with developing a new drug. However, the threshold for withholding safety and efficacy information or clinical study reports about a drug in favour of commercial interests should be very high. In fact, it is arguable that commercial sensitivity arguments would not 'trump' the imperative to release this data.

The strong public interest argument for ensuring the safety and efficacy of medicines arguably overrides all but the most critical of commercial interests. Details about the molecular structure of the drug or its manufacture could reasonably be considered commercially sensitive and should be protected.[102] However these clinical study report documents do not include information about the composition or preparation of the drug itself or trade secrets.[103] More relevant in the context of clinical study reports is the commercial impact that negative information revealed in them could have, such as that the drug is no better than its competitors.

A decision by the European Ombudsman in 2010 rebutted the proposition made by the European Medicines Agency (EMA) that releasing clinical study reports and other unpublished data on anti-obesity medicines would prejudice the commercial interests of the manufacturer.[104] As well as the justifications already discussed above, the EMA argued that the data contained in clinical study reports could be used by competitors to develop a similar product and that competitors would also get information about the long-term clinical development strategy of the manufacturing company.[105] The Ombudsman found that the EMA had failed to elaborate on how the clinical study report would be used by competitors and also that the documents in question did not contain details of the development strategy.

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102 *Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency* (P Nikiforos Diamandouros, European Ombudsman, 24 November 2010), at [75].

103 *Decision of the European Ombudsman*, above n 102 at [78].

104 *Decision of the European Ombudsman*, above n 102.

105 *Decision of the European Ombudsman*, above n 102, at [80] to [83].

Redaction is a more suitable way to protect commercial sensitivity in clinical study reports and unpublished trials than complete non-disclosure. A review of clinical study reports to redact any trade secrets or legitimately commercially sensitive information before the regulator releases the reports would not be overly burdensome for a regulator or the manufacturer. Legislative provisions preventing publication of the clinical study report and unpublished trials before Medsafe has made a decision on market approval are also an option. Such a provision already exists in the Medicines Act with regards to innovative medicines.[106] However, following consideration by Medsafe the most appropriate course of action would be to release this unpublished data whether or not approval was given, as the reasons for Medsafe declining to give approval to a particular medicine are also very important for patients and doctors to be aware of.[107]

Patent law requires that the patentee disclose many aspects of the drug that could be cited as commercially sensitive. The Patents Act 1953 requires that patents specifications include a full description of the invention and the best method of manufacture.[108] In the pharmaceutical context this involves the use of the medicine, the manufacture, the active ingredient, the composition of the drug, and the inert carrier compound for the active ingredient.[109] It is safe to assume that before an application for market approval, especially in New Zealand or Australia, the drug in question has already been patented and the information listed above is already publicly accessible on the Patents Register. While an exhaustive analysis of the relevant patent law is outside the scope of this paper, it seems that releasing clinical trial data and unpublished trials to the public will not be prejudicial to any patent application or intellectual property rights.[110]

106 Medicines Act 1981, s 23B.

107 Interview with Ron Paterson and Leo Donnelly, Ombudsmen (the author, Wellington, 11 September 2013).

108 Patents Act 1953, s 10.

109 *Pharmaceutical Management Company Ltd v Commissioner of Patents* [2000] 2 NZLR 529; [2000] RPC 857; (1999) 9 TCLR 429, at [3] and [59].

110 *Decision of the European Ombudsman*, above n 102, at [77].

2 Protection of Patient Confidentiality

Protests against disclosing clinical study reports centre on the risk that the individual trial participants will be identifiable and therefore their confidentiality will be breached.[111] This risk, while legitimate, can be solved. Firstly, it is a basic requirement of the ethics approval process that the privacy of the individuals in clinical trials is maintained. To that end, individuals are referred to in clinical study reports using identification and test centre numbers.[112] The information linking patients to their numbers is not publicly available. However, it is possible that a combination of physical features described in the clinical study report with regards to an individual patient may be enough to identify that person in some circumstances. In cases where the individual patient data may be enough to identify a patient this can be addressed by redaction. The European Ombudsman has pointed out that because clinical study reports are highly structured documents which separate individual patient data from other parts of the report, removing private data by redaction is fairly straightforward and does not create an undue administrative burden.[113]

3 Misinterpretation of the Data and an Information Overload

Concerns have been raised that publicly available clinical study reports and regulatory information or decisions will be misinterpreted by lay people causing health scares, or used by competitors to attack the manufacturer. It is submitted in this paper that these fears are overblown.

The primary benefit from publication of clinical study reports will be the meta-analyses and systematic reviews done by independent researchers using the newly available data. If a study or academic report is written using clinical study report data that has been interpreted wrongly or 'cherry picked' to attack the industry or manufacturer it will not hold much scientific value unless it is substantively true and able to be replicated and tested. In scientific literature the methods must be included in the report or article, so a report using flawed methods or bias when selecting data will not carry much weight, if any, in the literature. Additionally it will have to pass through the peer review process.

111 Doshi et al, above n 78.

112 *Decision of the European Ombudsman*, above n 102, at [86].

113 *Decision of the European Ombudsman*, above n 102, at [37].

Doctors and other interested parties will then have access to these independent assessments and will be empowered to make better-informed treatment decisions.

Most lay people would not be interested in or able to understand the level of detail that is included in the data in clinical study reports. Additionally, most doctors would not attempt or be able to analyse such complex raw data themselves. While it is possible that lay people may misuse the data and clinical study reports, this is a fear that applies to a minority of cases. A lot of information is already available to patients and patient groups about medicines, most of which is in scientific journals and involves complex scientific concepts. However, these are not regularly misinterpreted or misused by patients or other parties to create health scares.

F Positive Reasons for Disclosure

The most significant argument for disclosure of clinical study reports and other unpublished trial data is that there is a significant public interest in the transparency of trial results and data on medical interventions. As discussed in section A above, publication bias and hidden data presents a significant challenge to public health and create unnecessary risk for patients. The competing interests at stake are commercial and financial considerations that should be secondary to safeguarding public health and protecting patient faith in the regulatory system. Making all information available allows for independent assessment of the data and promotes fully informed treatment decisions. Additionally, both Medsafe and the ANZTPA have public health as their primary objective. The New Zealand government more generally is also moving towards a presumption of transparency and openness with regards to official information and decision-making.

It is also important to remember that the developers of a drug have an ethical imperative to publish all the data they glean from clinical trials.[114] A team of Cochrane Collaboration researchers noted:[115]

114 Written evidence from PLoS (CT20), above n 74, at 122; Written evidence submitted by Gly Moody (CT22), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 131.

> "…[C]linical trials are experiments conducted on humans that carry an assumption of contributing to medical knowledge. Non-disclosure of complete trial results undermines the philanthropy of human participants"

V Information and the Pharmaceutical Industry

Pharmaceutical companies provide limited information to patients and doctors, and this information is often tailored to project a positive image of their drug while downplaying its negative aspects. Some of the strategies that are used by the industry include selectively publishing and designing trials of their medicines; the use of medical writers and strategies for publication as part of the marketing of a new medicine; and direct-to-consumer advertising. Failure to properly inform patients of risks and side-effects known to the manufacturer has been held in Australia to be unlawful as misleading and deceptive conduct.[116]

A Flawed Trials and Hidden Data

Industry-funded trials that are reported in academic journals are significantly more likely to show positive results and overstate the benefits of a drug than independent trials or studies.[117] This is caused by a number of factors:

- Publication bias, whereby positive results are more likely to be published than negative or neutral results. This problem is not just limited to industry-funded publications.
- The medicine is sometimes compared to an alternative that the researcher knows is worse- such as a placebo or a competitor drug at a very low dose- rather than the current best treatment for the condition.[118]

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115 Doshi et al, above n 78.

116 *Peterson v Merck, Sharpe and Dohme (Aust) Pty Ltd* [2010] FCA 180.

117 Bourgeois FT, Murthy S, Mandl KD "Outcome Reporting Among Drug Trials Registered in ClinicalTrials.gov" (2010) 153 Annals of Internal Medicine 158; Bekelman JE, Li Y, Gross CP "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: a systematic review" (2003) 289 JAMA 454; Sergio S "Pharmaceutical company funding and its consequences: a qualitative systematic review" (2008) 29 Contemporary Clinical Trials 109; Goldacre, above n 93, at 80; Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, Otavio Clark "Pharmaceutical industry sponsorship and research outcome and quality: systematic review" (2003) 326 BMJ 1167.

- Patients in clinical trials are sometimes selected carefully so that they are more likely to show improvement during the trial.[119]
- Trials may be stopped early or extended beyond the initial end-date. This distorts the data, without the knowledge of the reader.[120]

Because of the huge economic incentive connected to the success of a newly developed medicine, it is unsurprising that industry-funded trials are written-up and publicised in a way that emphasises the positive aspects of a medicine while downplaying or concealing unflattering results. There is a clear conflict of interest because these publications and trials are fully funded and directed by the company developing the medicine. This makes it all the more important to release the clinical study reports and other unpublished data to allow independent analysis of the data collected in clinical trials.

B Medical Writing

As part of their drug development and marketing process, pharmaceutical companies employ medical writers- institutions or freelancers that specialise in writing up clinical trials and provide full 'publication strategy' services.[121] Medical writers meet with senior members of a company's drug development team and clinical researchers to work on manuscripts, posters, presentations about the new medicine, and to discuss the journals that will be targeted for publication.[122]

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118 Safer DJ "Design and Reporting modifications in industry-sponsored psychopharmacology trials" (2009) 190 J Nerv Ment Dis 583; Goldacre, above n 93, at 180.

119 Rothwell PM "External validity of randomised controlled trials: "to whom do the results of this trial apply?" (2005) 365 The Lancet 82; Goldacre, above n 117, at 177.

120 Muellers PS, Montori VM, Bassler D, Koenig BA, Guyatt GH "Ethical Issues in Stopping Randomized Trials Early Because of Apparent Benefit" (2007) 146 Annals of Internal Medicine 878; Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q et al "Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects: Systematic Review and Meta-regression Analysis" (2010) 303 JAMA 1180; Goldacre, above n 117, at 181.

121 Linda Logdberg "Being the Ghost in the Machine: A Medical Ghostwriter's Personal View" (2011) 8 PLoS Med 8; New Zealand-based medical writing companies include: ADIS International; SGS New Zealand; Rata Communications; Biowrite Solutions; Quintiles.

122 Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'.

A medical writer will produce several draft manuscripts to submit to targeted journals and send these drafts to external authors- usually credible academics who have agreed to co-author the articles or act as 'Key Opinion Leaders' by presenting information about the drug to colleagues.[123] The medical writing industry promotes itself as 'quality control', assisting busy researchers to write up the results of their trials without delay. However, the process of medical writing for pharmaceutical company-funded trials is not independent from the company itself. Pharmaceutical companies have first input as to content, full control over the presentation of data and the writing process, and control the key message of these publications.[124] The prevalence of medical writing assistance is difficult to determine, as it is a highly fragmented and unregulated global industry. However it appears that the vast majority of studies with industry-based sponsors are written-up by medical writers.[125]

The association of an external expert 'author' lends articles and trial reports an air of independence and significant academic weight, especially when the contribution of the medical writer and input of the sponsor company has not been disclosed. Many of the more reputable medical journals such as the Lancet or British Medical Journal now demand transparency about the origins and authorship of reports that are submitted to them for publication.[126]

While ensuring declaration of medical writing assistance is a very positive change, there are three issues that it does not resolve:

- Declaration of medical writing assistance for new articles does not affect the literature published for the last few decades on which doctors still rely for most

123 Logdberg, above n 121.

124 Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'.

125 Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'; Logdberg, above n 121.

126 International Committee of Medical Journal Editors "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (August 2013) ICMJE <www.icmje.org>.

medicines that they prescribe. Much of this literature was produced by medical 'ghost-writers' but attributed solely to independent academics.[127]

- The process by which the article is written is not declared. The extent to which the company drove the key message of the article and selectively omitted or manipulated data is therefore still unknown to the reader.
- Less reputable journals are not so rigorous. It has been reported that pharmaceutical companies emphasise speed over quality in their publication strategies; happy to target smaller, less reputable journals in order to claim and cite published articles for promotional materials.[128] It is therefore possible that undisclosed medical 'ghost-writing' may still occur in these articles.

In the United States it has now been suggested that academics who put their names to articles that are predominantly written and analysed by ghost-writers without disclosing those facts can be found guilty of fraud.[129] While it is unlikely that many New Zealand-based academics are acting as guest authors or Key Opinion Leaders for pharmaceutical companies, it is still desirable that the practice of medical writing without disclosure be considered fraudulent and punished if it is discovered.

The peer review process is not an effective solution to the concerns surrounding medical writing, although it does ensure quality of the article in question in the sense that it checks methodology and results analysis presented in the article. There is disparity between different reviewers with respect to the attention placed on each piece they are given. Additionally, the reviewer will be unaware of the data as a whole and therefore, while able to critique the immediate analysis in the paper, will have no way of knowing the extent to which the sponsor has influenced the message or initial selection of the data

127 Logdberg, above n 121; Xavier Bosch, Bijan Esfandiari and Leemon McHenry "Challenging Medical Ghostwriting in US Courts" (2012) 9 PLoS Med e1001163; Lacasse JR, Leo, J "Ghostwriting at Elite American Medical Centers in the United States" (2010) 7 PLoS Med e1000230; Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'.

128 Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'.

129 Simon Stern and Trudo Lemmens "Legal Remedies for Medical Ghostwriting: Imposing Fraud Liability on Guest Authors of Ghostwritten Articles" (2011) 8 PLoS Med e1001070; Bosch et al, above n 127.

used in the article.[130] It is unrealistic to hold the peer review process out as a solution to the issues of bias and hidden data found in academic articles, including those articles that are written by medical writers.

New Zealand's major contribution to medical writing is as a source of writers and a jurisdiction in which there is a strong medical writing industry. Most medical writers, while usually highly qualified, do not hold medical degrees or qualifications in statistical interpretation.[131] Instead medical writers are usually educated in research or biomedical science. A former medical writer interviewed for this paper, who did have medical training, stated that their eventual reason for leaving the profession was that the things asked of them as a medical writer sometimes came into conflict with their professional ethical obligations as a doctor.[132] The example given was that they were often asked to present data in a way that concealed negative aspects of the drug, thereby misleading patients and doctors who would eventually read their manuscripts. This could create outcomes that were damaging to the best interests of patients. The interviewee expressed doubt that someone trained in medicine could ethically act as a medical writer due to the conflicts of interest that were present. The interviewee also expressed concerns that medical writers are charged with writing-up the statistical interpretation of the data but do not usually have a background in statistics. Also recalled were a series of manuscripts worked on for a large pharmaceutical company in which data points from individual patients that indicated problems were selectively omitted from the PowerPoint slides that were to be used in poster presentations or for speakers.[133]

130 Information received from a confidential source in the medical industry with background as a medical writer.

131 Information received from a confidential source in the medical industry with background as a medical writer; European Medical Writers Association "Medical Writing" (2009) EMWA

132 Information received from a confidential source in the medical industry with background as a medical writer.

133 Information received from a confidential source in the medical industry with background as a medical 'ghostwriter'.

There are some guidelines for medical writers, created mostly by various industry associations.[134] However there is no official set of guidelines and no official recognition of the industry by the Ministry of Health or any other official body in New Zealand. It is submitted that full regulation of the medical writing industry would be difficult, expensive, and ineffective due to the fragmented nature of the profession and the high number of freelance writers. However, it is still desirable that the Ministry of Health publish a set of best practice guidelines or a similar document pertaining to the medical writing industry. This would not be expensive nor impose any compliance costs, but would give a soft incentive to the industry to comply with officially-authorised guidelines for best practice and transparency. While small, this step may increase transparency and more clearly enunciate the ethical issues involved in medical writing to those members of the profession.

C Direct to Consumer Advertising

In New Zealand pharmaceutical drugs are advertised directly to the public. This practice is only legal in two OECD countries- New Zealand and the United States.[135] The internet also provides a direct avenue to consumers, something that regulators around the world have been slow to catch up with and which the ANZTPA scheme also has not yet provided for in detail.[136] The practice of advertising directly to consumers has been shown to dramatically increase market share and cause wholesale switching to the advertised brand.[137] It does not provide objective information to patients, has a negative effect on health funding, has a negative effect on the doctor-patient relationship, and can damage public health.[138] However supporters of direct to consumer advertising, amongst

134 Adam Jacobs and Elizabeth Wagner "Commentary: European Medical Writers Association (EMWA) guidelines on the role of medical writers in developing peer-reviewed publications" (2005) 21 Current Medical Research and Opinion 317; the Australasian Medical Writers Association subscribes to the Media, Entertainment & Arts Alliance Code of Ethics.

135 Les Toop and Dee Richards "New Zealand Deserves Better. Direct to Consumer Advertising (DTCA) of prescription medicines in New Zealand: for health or profit?" (2003) 116 NZMJ 1180.

136 Hall, Dr Sandy *Submission on the Description of a possible joint regulatory scheme for therapeutic products under ANZTPA* (Women's Health Action Trust, February 2013).

137 Toop and Richards, above n 135.

138 Toop and Richards, above n 135; Elizabeth Almasi, Randall Stafford, Richard Kravitz, Peter Mansfield "What are the Public Health Effects of Direct to Consumer Advertising?" (2006) 3 PLoS Med e145.

them being former Health and Disability Commissioner Ron Paterson, suggest that it allows patients to be better informed and facilitates more effective participation in healthcare.[139]

This issue has received a great deal of academic attention in New Zealand and consequently will not be addressed further in this paper.[140] It is, however, relevant to draw attention to direct to consumer advertising in the context of the information deficit. The information which most consumers receive on a day-to-day basis about medicines and medical interventions is provided by the pharmaceutical industry. Advertising of medicines and medical devices is of course subject to the requirements in Part 4 of the Medicines Act. Nevertheless, information in medicines advertising is presented in a biased way to further a commercial cause and is designed to display the medicine or device in a favourable light. This serves to exacerbate the current information deficit. Patients need access to independent, balanced material about drugs to be truly informed and to feel that they are effectively participating in decisions about their healthcare.

D Summary

Pharmaceutical companies frequently withhold important information and overstate the benefits of their medicines.[141] This is unsurprising, given that they exist fundamentally to make a commercial profit. Independent, transparent assessment of the data and methods of clinical trials for new medicines is imperative. While Medsafe undertakes rigorous analysis and evaluations, it is essential to have as many eyes as possible on this information so that doctors and researchers can 'check the working', offer criticism and spot trends that might have been missed.

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139 Ron Paterson *Advertising in the Age of Consumer Empowerment* (Health and Disability Commissioner, September 1998); Almasi et al, above n 138.

140 See for example, Manuel Evertz "Direct to consumer advertising of prescription drugs in New Zealand: justifications for a complete ban" (LLM Dissertation, Victoria University of Wellington, 2010).

141 Bourgeois et al, above n 117; Bekelman et al, above n 117; Sergio, above n 117; Goldacre, above n 93, at 80; Lexchin et al, above n 117.

VI Making Changes

The public health impact of hidden data, publication bias and refusal by regulators to make public the information they hold about medicines is significant: Doctors cannot make fully informed treatment decisions, exposing patients to unnecessary risks and breaching patients' right to give informed consent to treatments. Participants in clinical trials cannot be sure that the experiments done on them will be published and written up to contribute to the scientific literature. The New Zealand government and Pharmac spend millions of dollars on subsidising medicines and purchasing drugs like Tamiflu. Taxpayers, patients and doctors deserve to know that these important decisions are made according to all the information available, not a biased selection cherry-picked by medical journals, pharmaceutical companies and academics. The following sections explore legal options for reversing, combating and preventing the information deficit.

The proposed solutions are twofold:

- Firstly, to create a statutory duty to register the existence of all clinical trials undertaken in New Zealand or on New Zealand citizens on the ANZCTR and require that the sponsor of the trial update the register with the results of the clinical trial within a reasonable time after completion.
- Secondly, to include in the ANZTPA Rules and regulatory framework a requirement that the Agency maintain a publicly available database of all information, published or unpublished, submitted to it for drugs and medical devices that are approved for market. This information should include complete clinical study reports and the regulatory analysis.

These solutions assume that the ANZTPA legislation and Treaty ratification will progress as planned by 2016. However it should alternatively be considered for the inevitable Medicines Act 1981 reform that would have to occur if the trans-Tasman agency does not proceed.

There are also administrative law options for doctors, patients or independent researchers wishing to access information from the regulator. These will continue to be available with regards to medicines under the trans-Tasman framework, although the exact functioning of these administrative law components in the ANZTPA context is yet to be established. The avenues explored are:

- The Official Information Act 1987;
- the Ombudsman; and
- the Regulations Review Committee.

A The ANZTPA Regime

The entirely new regulatory environment created for the ANZTPA presents a golden opportunity to create a transparent, thorough, patient-focused regulatory scheme for Australia and New Zealand. To be truly effective, the Agency must ensure that it receives all necessary information from applicants for drug approval as well as provide patients, doctors and independent researchers with the information they need to make fully informed decisions.

In Europe and the United States steps towards greater transparency and effective information access are also being taken.[142] These proposals will not make Australasia uncompetitive nor will they stymie innovation and drug development. In fact, they will bring the ANZTPA in line with international practice.

1 Information provided to the Agency

Medsafe currently receives all information held by the applicant about the medicine submitted for approval, including clinical study reports, and also ensures that more studies are done if necessary. The same situation will apply in the ANZTPA scheme and the Agency will also be able to require former approval holders, former licensed manufacturers, and those lawfully supplying products that are exempt from approvals or

142 See UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013); Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904.

licences to provide relevant information.[143] Failure to provide information for an approved product may result in regulatory action such as the suspension or cancellation of an approval.[144] These provisions are a great improvement and must be rigorously enforced.

The 2006 Bill gives the ANZTPA power to issue 'information requirement notices' (to be defined in the Rules).[145] The Bill also provides for significant enforcement options, including penalties of up to 5 years' imprisonment for submitting materially false or misleading information.[146] Additionally, the holder of a product licence for a therapeutic product will be required, on becoming aware of adverse effect information, to give written notice to the Authority of that information.[147]

The ANZTPA should demand full clinical study reports and trial data. Situations such as the problems that regulators and researchers are currently having obtaining full information about Tamiflu must not be repeated.[148] If the proposed provisions are enacted and properly enforced they will create a robust information-gathering system for the ANZTPA that will ensure that the Agency receives all the information necessary to analyse new medicines and avoid repetition of past problems.[149]

2 Information provided by ANZTPA to the public

Data protection is important, especially in relation to medicines that are innovative and have not yet received approval. However the current protection that is given globally to data held by the industry has come at too high a price for public health.[150] It is important to normalise a situation in New Zealand where manufacturers and regulators are encouraged to proactively disclose all information about safety, quality and efficacy of drugs. Medsafe's mission statement is "To enhance the health of New Zealanders

143 *ANZTPA Discussion Paper*, at 39.
144 *ANZTPA Discussion Paper*, at 39.
145 Clause 78.
146 Clauses 74(4) and 79(5).
147 Clause 76(1).
148 See British Medical Journal "Tamiflu Campaign", above n 78; Doshi, et al, above n 78.
149 See Appendices one, two and three.
150 See Appendices.

by regulating medicines and medical devices to maximise safety and benefit".[151] Similarly, the ANZTPA Treaty indicates that the joint Agency's primary concern will also be safeguarding public health and safety.[152] Protection of public health and safety and ensuring public confidence in the regulatory system are factors that incline towards greater openness.[153]

If the ANZTPA is truly to be a regulator that operates according to international best practice, it must provide transparency and release all the information, published and unpublished, that it receives from applicants for medicines approval proactively. This section proposes that ANZTPA create and maintain a searchable and accessible database containing all information it holds about medicines submitted for approval. Legislation is the most effective means for establishing this scheme, and will serve to normalise greater disclosure and transparency.[154] Some possible provisions will be discussed below.

Data protection and disclosure are not mentioned at all in the Treaty, leaving such provisions to be decided by Rules. The Discussion Paper deals with data protection very briefly. It states that the ANZTPA will not be able to use 'protected information' about an existing approved medicine when evaluating an application for a new medicine.[155] 'Protected information' will include information about the active ingredient of the existing medicine if that information is not in the public domain. 'Use' was not defined in the Paper and could be interpreted extremely broadly. Information will be protected for a period of five years from when an innovative existing medicine receives approval. Finally, information will also be protected if the drug's sponsor has not given ANZTPA permission in writing to use it. The discussion of this proposed data protection spans just a paragraph in the Paper. However, it does not arguably indicate intention to prohibit use of the clinical trial data, such as by disclosing it on a database. These data protection

151 "About Medsafe" (10 May 2013) Medsafe <www.medsafe.govt.nz>.

152 Joint Therapeutic Agency Treaty, above n 28, Preamble and art 2.

153 Interview with Ron Paterson and Leo Donnelly, Ombudsmen (the author, Wellington, 11 September 2013).

154 Evidence submitted from the Editor and Deputy Editor of the British Medical Journal (CT23), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 136.

155 *ANZTPA Discussion Paper*, at 39, at 22.

provisions seem to be predominantly concerned with information relating to active ingredients and composition of the medicine.

Clear legislative provisions should be enacted stating that one of the ANZTPA's roles will be to proactively make all information it receives publicly available for every medicine that has been considered by it for approval, once Medsafe's decision regarding approval has been made. This will initially involve significant resources and time as information currently held by Medsafe and the TGA would be uploaded to the database retrospectively. However once a database is established and properly populated the exercise should involve simply uploading data that is received, as required, after approval is granted. Correspondingly, the costs should drop away.

This paper does not advocate for disclosure of any information about products before they have been approved for the market. This would be unreasonable and would considerably damage commercial interests.[156] However, once approval has been granted or declined the ANZTPA should be mandated to upload the information it receives, with appropriate redaction, onto a public database. There is a definite public interest in the reasoning behind Medsafe's decisions and risk/benefit analysis including for those drugs that are declined approval.[157] Those drugs might still be prescribed to patients as unapproved medicines in certain cases.

The type of information that may be redacted should be made very clear in legislation. Information about the active ingredient or production methods, for example, is not relevant to safety or efficacy and therefore does not need to be disclosed publicly. Similarly, information that allows trial participants to be identified should also be redacted. In most cases clinical study reports and other unpublished information will not contain identifying particulars. It is also worth noting that information about manufacture, active ingredient and molecular composition of a drug is available on the patents register.

156 Written evidence of Sir Alasdair Breckenridge (CT12), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 64.

157 Interview with Ron Paterson and Leo Donnelly, Ombudsmen (the author, Wellington, 11 September 2013).

B Clinical Trial Register

In addition to provisions requiring greater transparency from regulators, legislation should be put in place that requires all trials carried out in Australia or New Zealand and the results of those trials to be registered on the ANZCTR, which already provides a framework for voluntary trial registration. This will have a positive effect on scientific research and will also increase patient safety because of the improved likelihood that patterns in the data that indicate side effects will be detected. It will also allow patients and doctors to be better informed of all the research that has been done on a drug, not just that which is published.

1 Registration

The responsibility for the initial registering of clinical trials should fall on the ethics committee responsible for approving that trial. This should not be an onerous task. It would involve registering the new trial on the ANZCTR and entering basic details such as the sponsor's identity, what is being tested, and how many participants are involved. All this information will be provided by the applicant for ethics approval and will therefore not require much extra time or work for the ethics committees to upload to the ANZCTR website. Alternatively, it could be a condition of approval that the trial be registered by the applicant before ethics approval is sought. To avoid any doubt, a provision in the ANZTPA ratifying legislation or a Rule requiring registration of all trials could be enacted. This would be desirable to ensure clarity and to empower the ethics committees with enforcement capabilities.

Responsibility to update the register with the results of clinical trials should rest with the sponsor and researcher of each trial. Most of the information that the ANZTPA receives will be about drugs that were trialled in different jurisdictions, as relatively few clinical trials are done in New Zealand and Australia. Furthermore, not all clinical trials undertaken are for new medicine and are often testing or focused on improving current medicines. It is therefore impractical to expect that the ANZTPA assume responsibility for uploading the results of these trials, although it should have the power to enforce any breaches. In light of the dependence that Australia and New Zealand have on overseas

regulators and manufacturers and the small number of trials undertaken in the jurisdiction, the ANZTPA should have a separate statutory obligation to maintain a public database of the information it receives in applications, as discussed in Section A above.

2 Legislative provision for the register

Many experts giving written evidence in the UK Science and Technology Select Committee in March 2013 stated that regulation was needed to ensure that all clinical trial results are published.[158] Such legislation has already been enacted in the United States, with mixed success due to inadequate enforcement.[159] This subsection of the paper examines possible legislation for the enactment of the system for compulsory clinical trial registration discussed in subsection 1 above. Along with provision for the registration obligations discussed above, the following paragraphs provide an overview of legislative provisions that would be necessary for a compulsory clinical trial register.

There are several key definitions that must be clearly set out, all of which have been recently defined in the United States legislation. 'Results' should be defined in such a way as to exclude individual patient data while expressly including full clinical study reports and other trial data, suitably anonymised. The precise requirements for anonymising patient information should also be prescribed to avoid confusion and ensure consistency. 'Completion date' is defined in the Food and Drug Administration Amendments Act 2007 as 'the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome', or when the trial was terminated.[160] 'Reasonable time' after the completion of the trial in which to post results will vary according to the context and circumstances of the trial, including the

158 Antes G, Chalmers I "Under-reporting of clinical trials is unethical" (2003) 361 Lancet 978; Chalmers I, Glasziou P, Godlee "All trials must be registered and the results published: academics and non-commercial funders are just as guilty as industry" (2012) 346 BMJ f105; Written Evidence Submitted by Sir Ian Chalmers, UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 57; Written Evidence Submitted by Dr Ben Goldacre (CT55), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 294; Written Evidence Submitted by Professor Lesley Stewart (CT15) UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 75.

159 See Part IV, Section C above.

160 § 801, 121 Stat 904, at 905.

number of participants and the complexity of the data. The United States imposes a blanket rule of one year, with the option of extension upon application.[161] The same rule is appropriate in Australia and New Zealand, with the ANZTPA able to grant extensions upon application. It was submitted in the Select Committee in the United Kingdom that after an appropriate time of checking the registry once the one-year deadline is up, a study that has not been reported upon could be flagged on the registry as "not published within x years".[162] This would serve as a 'black mark' against the trial and as a soft form of deterrent against suppression of clinical trials data.

By legislating for a mandatory clinical trial register New Zealand and Australia will be improving accessibility to information about medicines and guaranteeing that participants in clinical trials make meaningful contributions to the development of our knowledge about medical interventions. Given that the ANZCTR framework already exists, this legislation does not require an entirely new scheme to be created, merely the upgrading of a pre-existing structure. Legislating for a mandatory clinical trial register will also be a move that aligns the Australasian regime with those in the United States and Europe.

C Implications of the Proposed Changes

There are potential risks associated with a public database for clinical trial data. As is the case whenever the risk profile of a system is changed, the behaviour of those being regulated may alter. Companies might elect to avoid undertaking certain trials which risk exposing an unfavourable aspect of their drug if they know that all the unpublished information that they must share with the regulator will be made public.[163] It may seem more attractive for companies to withhold information from the regulator and risk the punishment of being found in breach of their obligations.[164]

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161 Food and Drug Administration Amendments Act 2007 Pub L No 110-85, § 801, 121 Stat 904, at 912 to 914.

162 Written evidence from Medical Schools Council and Association of UK University Hospitals (CT18), UK House of Commons, Science and Technology Select Committee *Clinical Trials* (written evidence, 6 March 2013), at 90.

163 Opinion given by a confidential source in the government medicines/health area.

164 Opinion given by a confidential source in the government medicines/health area.

There is also the threat of loss of competitiveness and consumer variety if regulations become too constraining and costly to justify entry into the market. This outcome has equally important public health risks and effects on consumers' access to healthcare. The Australian and New Zealand markets are small, even when combined. Pharmaceutical companies target markets in North America and Europe first and foremost. Therefore there is a risk that by making the regulatory environment too restrictive, applications for medicines approval will be seen as commercially unviable and decline. Should this occur, New Zealand and Australian consumers will not be able to access the newest and best medicines. It seems, therefore, that the Australasian regulatory environment may be constrained to follow the North American and European markets with regards to disclosure requirements and transparency.

There is a definite move towards transparency and greater disclosure in the northern hemisphere markets. The United States has legislated for compulsory clinical trial registration, the United Kingdom is undertaking a select committee inquiry into hidden data, and the European Union is moving towards practices that promote greater transparency and disclosure. It is important to manage the risks discussed in this section to ensure competitiveness is maintained in the Australasian market. However, by 2016, when the ANZTPA is scheduled to begin, it is likely that there will have been a further international shift towards greater transparency and disclosure. Creating a culture in which unpublished information is routinely made available and transparency is the norm is vital. While Australasia should be mindful of the situation in the northern hemisphere, this should not prevent it from making some progress towards greater disclosure in this area.

VII Administrative Law: Alternative Methods for Obtaining Information

The following section explores the options provided by administrative law for patients, doctors and independent researchers to access unpublished information on the safety and efficacy of drugs that is held by the regulator. The options investigated are: use of the Official Information Act (OIA), seeking assistance from the Ombudsman, and lodging a

complaint with the Regulations Review Committee (RRC). These public law tools can be employed in New Zealand under the present Medicines Act regime and will continue to be available when the ANZTPA takes over.

The ANZTPA will be accountable to the Australian and New Zealand Governments in the way that would normally apply to a regulatory agency established by domestic legislation.[165] However it seems that extensive discussion will take place with Australia regarding the exact application of the systems in each country in relation to the ANZTPA. New Zealand's systems may require some modification in respect of their application to the ANZTPA. The following subsections apply the current New Zealand law.

A Official Information Act 1982

The OIA will continue to apply to information held by ANZTPA and can be used at present to request official information held by Medsafe.[166] It is unclear how often Medsafe receives OIA requests about medicines approval. The agency has made one OIA release in the past two years and six between 2005 and 2011.[167] These releases involve information about the approval process taken for a particular medicine, adverse reaction information and investigations, and one Intensive Medicines Monitoring Programme report. This indicates that Medsafe is willing to release some information about particular medicines including information about effectiveness and safety, although mostly such information is given in the context of adverse effects monitoring and investigations rather than pre-emptively on the basis of information received from the medicines approval process.

As discussed in Part IV above, Medsafe will make summaries of approval decisions and minutes of committee meetings available when requested.[168] Summaries of approval decisions will also be available from the ANZTPA. However in general OIA requests asking for safety, efficacy or quality information received in the course of an approval

165 Joint Therapeutic Agency Treaty, above n 28, art 8.

166 Therapeutic Products and Medicines Bill 2006 (103-1), cl 170.

167 "Recent Official Information Act Releases" (17 April 2013) Medsafe <www.medsafe.govt.nz>; "Archive of Official Information Act Releases" (13 April 2013) Medsafe <www.medsafe.govt.nz>.

168 Email from Susan Martindale, above n 16.

application will likely be declined for reasons of commercial sensitivity.[169] Each request will necessarily have to be decided in its own context and on the balance of all the factors in the OIA. However, the rest of this subsection will provide a general discussion on some specific factors that will feature in this balance and what they indicate about the likelihood of success if a researcher were to request the release of the full clinical study report for an approved medicine from Medsafe.

The underlying principle of the OIA is the presumption that information should be made available unless there is good reason to withhold it.[170] None of the conclusive reasons for withholding information under section 6 apply in the context of information held about medicines. Therefore the only section relevant with regards to justifications for refusing to release information is section 9.

Section 9(2)(a) provides for withholding of information to protect the privacy of natural persons. As discussed in Part IV, section E above, patient confidentiality and protection against release of identifying information in clinical study reports is important. However, the clinical study reports do not generally contain identifying features for individual patients. That information can also be effectively redacted where it is present in clinical study reports and other relevant unpublished documents. Justifying a refusal to provide clinical study reports and other safety information under section 9(2)(a) would generally be unsuccessful.

Section 9(2)(b) of the OIA allows information to be withheld if releasing it would disclose a trade secret or unreasonably prejudice the commercial position of the person who supplied the information - this is a high threshold.[171] The discussion in Part IV, section E above discussed these considerations in a broader context and should be referred to in relation to the OIA discussion below. Clinical study reports may contain commercially sensitive information in the sense that information suggesting the drug does

169 Email from Susan Martindale, above n 17.

170 Official Information Act 1982, s 5.

171 David McGee *Requests for Information Regarding the production of* The Hobbit *and film Production Generally* (31 January 2013) at 12-13.

not have a favourable risk profile or may not be any better than a competitor or generic drug would be likely to negatively affect the manufacturer's commercial position.[172] The Ombudsman has noted that finding information is commercially sensitive alone is not sufficient reason for withholding it under the OIA.[173]

There is precedent in New Zealand in the veterinary context holding that information about the active ingredient and chemical composition of a new medicine will be commercially sensitive and appropriately able to be withheld by the regulator using section 9(2)(b) of the OIA.[174] In the context of veterinary medicines, the Hazardous Substances and New Organisms Act 1996 (HASNO) provides a procedure for dealing with OIA requests and information that might be withheld.[175] The Medicines Act does not have any similar sections apart from possibly section 23B protecting confidential supporting information about innovative medicines for a particular period. This statutory provision slightly colours the consideration of an OIA request and indicates that a greater significance will be placed on protection of confidential information received for approval of innovative medicines. Additionally, because the Medicines Act 1981 expressly prescribes that this information be kept confidential it may not be able to be released in response to an OIA request.

Given that the primary statute will colour OIA considerations, if the ANZTPA Rules and legislation include specific data protection provisions these may well alter the arguments made in this section with regards to the commercial sensitivity of the data received by ANZTPA. If the Rules were enacted with an express procedure for handling OIA requests, similar to that in the HASNO legislation, this would affect the probable outcome of an OIA consideration. It is hoped that, as outlined in sections A and B above, the ANZTPA will take a more transparent and pre-emptively accessible approach to releasing official information.

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172 Interview with Ron Paterson and Leo Donnelly, Ombudsmen (the author, Wellington, 11 September 2013).

173 *Official Information Legislation Guides*, above n 101, at 7 to 8; McGee, above n 171, at 12-13.

174 *Wyeth (NZ) Ltd v Ancare New Zealand Ltd* [2010] NZSC 46.

175 *Wyeth*, above n 174, at [14] and [45]; Hazardous Substances and New Organisms Act 1996, Part 5.

Arguably, information about safety and efficacy does not reach the same commercially sensitive threshold as information about the composition and active ingredient of a medicine. Additionally, as discussed in Part IV, section E clinical study reports do not contain information about long term development strategies or composition and active ingredients of the drug. While some of the content may be considered commercially sensitive, it may not be enough to reach the high threshold of 'unreasonable prejudice' to the commercial position of the manufacturer. Commercial sensitivity may not be made out just by suggesting that the risk profile of the drug may be revealed to be inferior to that of a competitor.

A regulator might also be able to use section 9(2)(ba) to justify withholding information. This paragraph protects information which a person has been compelled to provide under an enactment- an applicant is compelled to provide Medsafe with all the information they hold on the safety, efficacy and quality of their drug. Making that information available could be considered likely to prejudice the supply of similar information. There might be a greater incentive for pharmaceutical companies to risk a fine and breach their statutory disclosure obligations if they know that the information that they provide may become publicly available. This would damage the public interest by hindering Medsafe or the ANZTPA's ability to assess new medicines knowing that all necessary information is before them.

There are also natural justice requirements at stake if manufacturers are effectively compelled to disclose clinical information about their products. They are compelled to provide all information to the regulator, including sensitive information that they might not normally wish to disclose, and then would have no option but for this information to be publicly displayed. However, the opportunity for redaction can lessen these risks to companies, as does the requirement that information is only made public after a decision has been made about their application. A manufacturer is not compelled to give Medsafe that information unless they wish to sell their drug to the New Zealand public. Any medicine entering the market must be safe and reasonably effective with benefits that

outweigh its risks. If a manufacturer's drug does not meet those standards, or does not offer more benefits than a competitor the patients consuming it have a right to be fully informed of its shortcomings as much as they do its benefits.

Even if the grounds discussed above are established, information must be disclosed if the justification for withholding it is outweighed by public interest.[176] The Medicines Act itself is relevant in determining what the public interest involves in this context.[177] The 1981 Act does not include a purpose or principles section. However the 2006 Bill has the key objective of safeguarding public health and the safety of New Zealanders.[178] This represents the most recent enunciation of Parliament's intention and involves a primary focus on public health and safety. The primary purpose of the ANZTPA Treaty is also to safeguard public health.

In the area of pharmaceutical drugs and medical devices, there is a high public interest in disclosure. As emphasised in Part IV, hidden data and publication bias have a significant negative impact on public health and can pose real and serious risks for patients. There is substantial evidence that doctors and patients cannot make effective and fully informed health decisions if they do not have access to all the unpublished information about medicines.[179] Additionally, independent researchers would be able to conduct further investigations and meta-analyses which would improve medical understanding and knowledge. These factors create a compelling argument in favour of access to official information in order to protect the public interest. It is arguable that all but the strongest arguments under s 9(2)(a), (b) or (ba) would be overridden by the public interest.

B Ombudsman

The ANZTPA will be subject to the Ombudsmen Act 1975 and the Australian Ombudsmen Act, with both offices co-operating in their investigations.[180] In Europe, the

176 Official Information Act 1982, s 9(1); see also McGee above n 171, at 26.

177 GDS Taylor and JK Gorman *Judicial Review: A New Zealand Perspective* (2nd ed, Lexis Nexis, Wellington, 2010) at 304.

178 Therapeutic Products and Medicines Bill 2006 (103-1), explanatory note.

179 See Part IV above.

180 Therapeutic Products and Medicines Bill 2006 (103-1), cl 154 and 155.

Ombudsman has been a champion for open access to information about drugs and clinical trials in the context of a maladministration complaint against the European Medicines Agency.[181] However it does not appear that the New Zealand Ombudsman has ever been asked to assist with a matter relating to pharmaceutical drugs and information access of the nature discussed in this paper.

The Ombudsman could provide a cost effective avenue for accessing clinical study reports and other unpublished data. Additionally, because the Ombudsman's investigations are carried out in private, there is no danger of premature public disclosure of information that should be kept confidential.[182] The Ombudsman currently has jurisdiction to investigate complaints against Medsafe as it is a part of the Ministry of Health.[183] However in the context of information access it is likely that the most common exercise of the Ombudsman's jurisdiction will be the express function given under the OIA to investigate a refusal to release information.[184]

C Regulations Review Committee

The Regulations Review Committee (RRC) examines all regulations, investigates complaints, and examines proposed regulation-making powers.[185] Six of the eight States of Australia have a Regulatory Review Committee equivalent but no state allows public complaints to be made, as is the practice in New Zealand. This raises the question of whether the ANZTPA will remain subject to RRC oversight and whether, if so, Australian citizens can lay complaints about any Ministerial Council Rules with the RRC. In the absence of any guidance on whether the RRC complaints process will remain in place vis-á-vis the ANZTPA, this paper will assume that it will.

A regulation cannot be reviewed on its merits. However a complaint can be based on several grounds relating broadly to the relationship between regulation and the relevant

181 *Decision of the European Ombudsman*, above n 102.
182 Ombudsmen Act 1975, ss 18 and 21.
183 Ombudsmen Act 1975, Schedule 1, Part 1.
184 Official Information Act 1982, s 28.
185 Cabinet Office *Cabinet Manual 2008*, at [7.79]-[7.78]; Standing Orders of the House of Representatives 2011, SO314.

Act, or on procedural grounds.[186] If, for example, the Ministerial Council declines to make Rules which provide for information access or clinical trial registration, as described in Sections A and B above, it may be possible to complain to the RRC about such Rules and claim that they breach the public safety mandate described in the Treaty and empowering legislation.

The most relevant ground for challenging a Rule in this context would be that it is not in accordance with the general objects and intentions of the statute under which it is made.[187] All Rules made by the Ministerial Council or Managing Director to constitute the regulatory framework must give effect to the objectives of the Treaty.[188] The objective is first and foremost to facilitate public health and create a scheme for regulating medicines according to international best practice. Arguably, a clinical trials register and better public access to information is current international best practice. Furthermore, public health is better facilitated by allowing doctors and researchers to access unpublished data, as was explored in Part IV above.

There may therefore be grounds for complaint if any future Rules hinder such public information access and publication of clinical trial data. However this is predicated on the assumption that the RRC oversight and complaints process remain applicable to the ANZTPA. It would be highly unsatisfactory if the ANZTPA were to be immune from the regulations complaints process, especially because it is a body with legal personality in Australia only and because the regulation of medicines and medical devices is such a crucial part of the public health system in New Zealand and Australia. Given this significance full public scrutiny of the decision-making body is important, especially given the extensive powers to create delegated legislation that have been given to the Ministerial Council and Managing Director.

In addition to complaints, public participation in regulatory decision-making is possible via participation in things like patient interest groups. However, there is a risk that only

186 Standing Orders of the House of Representatives 2011, SO315(2).
187 Standing Orders of the House of Representatives 2011, SO315(2)(a).
188 Joint Therapeutic Agency Treaty, above n 28, art 9.

larger industry players will have a significant lobby voice, given the comparative power and resources available to most large pharmaceutical companies operating in the Australasian market.[189] This may 'drown out' the impact of patient groups to some extent, making the more formal complaints process more important in the context of pharmaceutical regulation. There may also be a role for a consumer or patient advocacy group more generally, which can gather information and be consulted on Rules made by the Ministerial Council on behalf of consumers in Australia and New Zealand.[190]

VIII Conclusion

This paper has provided an overview of the current and proposed future legislative structures that regulate medicines and medical devices in New Zealand. It has done so in light of the deficit in information relating to safety and efficacy data for medicines and medical devices. While this analysis is relevant to Medsafe, especially the administrative law discussion, most of its application will be in the context of the ANZTPA scheme. The ANZTPA project is an opportunity to implement substantial changes in the way that medicines are regulated in New Zealand and Australia to remedy the information deficit and protect public health and welfare.

The key propositions in this paper are:

- That the ANZCTR should become a mandatory clinical trials registry for all trials done in Australia and New Zealand, with ethics committees and trial sponsors holding responsibility for populating the register. Sufficient enforcement powers and resourcing should be provided for in legislation or Rules to ensure the efficacy of this scheme.

189 Discussed in the context of electricity regulation in Mark Bennett and Joel Colon-Rios "Public Participation in New Zealand's Regulatory Processes" in Susy Frankel and Deborah Ryder (eds) *Recalibrating Behaviour: Smarter Regulation in a Global World* (LexisNexis, Wellington, 2013) 181 from 214.

190 Discussed in Bennet and Colon-Rios, above n 189, at 217 and 260.

- That a statutory duty should be imposed on the ANZTPA to make all the unpublished information it holds about medicines that pass through the approval process publicly available.
- That, generally speaking, the arguments for preventing disclosure of official information containing clinical study reports and other unpublished raw data would not outweigh the significant public interest in disclosure.
- That administrative law 'tools' such as OIA requests, Regulations Review Committee complaints, and use of the Ombudsman may assist in facilitating disclosure of trial data and clinical study reports held by Medsafe or the ANZTPA.

These conclusions should be considered and implemented in the context of the ANZTPA scheme in order to create a more transparent system which is aligned with the emerging international best practice. Additionally, use of the administrative law tools discussed could be done effectively under the current Medicines Act regime. Australia and New Zealand are constrained to follow the larger European and North American markets with regards to disclosure requirements and transparency or risk creating a regulatory environment that is seen by the industry as overly burdensome and therefore unviable. However, this does not mean that any attempt to improve transparency and disclosure in the Australasian market should be abandoned. The ANZTPA scheme is scheduled to come into force in 2016, by which time there will have been further progress made internationally which Australasia should ensure it remains consistent with.

Bitter experience has shown that the information deficit in relation to medicines and medical devices has real and significant impacts, as illustrated by the appendices attached below. This is not something that patients are generally aware of yet it directly impacts their right to be fully informed before making a treatment decision. Additionally, it affects decisions to publicly fund medicines and distorts the medical literature on which doctors rely when evaluating treatment options in the context of an individual patient. Legislative change is one aspect that is required to remedy this situation. It is important to

create a culture of transparency and openness amongst government regulators that facilitates better informed treatment decisions and improved public health and safety.

IX Appendix One

This is an anecdote taken from *Bad Pharma* by Ben Goldacre.[191]

> "Reboxetine is a drug I myself have prescribed. Other drugs had done nothing for this patient, so we wanted to try something new. I'd read the trial data before I wrote the prescription, and found only well-designed, fair tests, with overwhelmingly positive results. Reboxetine was better than placebo, as good as any other antidepressant in head-to-head comparisons. It's approved for use by the Medicines and Healthcare products Regulatory Agency (MHRA), which governs all drugs in the UK. Millions of doses are prescribed every year, around the world. Reboxetine was clearly a safe and effective treatment. The patient and I discussed the evidence briefly, and agreed it was the right treatment to try next. I signed a piece of paper, a prescription, saying I wanted my patient to have this drug.
>
> But we had both been misled. In October 2010 a group of researchers were finally able to bring together all the trials that had ever been conducted on reboxetine.[192] Through a long process of investigation- searching on academic journals but also arduously requesting data from the manufacturers and gathering documents from regulators- they were able to assemble all the data, both from trials that were published, and from those that had never appeared in academic papers.
>
> When all this trial data was put together it produced a shocking picture. Seven trials had been conducted comparing reboxetine against placebo. Only one, conducted in 254 patients, had a neat positive result, and that one was published in an academic journal, for doctors and researchers to read. But six more trials were conducted, in almost ten times as

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191 Ben Goldacre *Bad Pharma: How drug companies mislead doctors and harm patients* (Fourth Estate, London, 2012) at 5.

192 Dirk Eyding, Monika Lelgemann, Ulrich Grouven, Martin Harter, Mandy Kromp, Thomas Kaiser, Michaela F Kerekes, Martin Gerken, Beate Wieseler,"Reboxetine for Acute Depression: Systematic Review and Meta-Analysis of Published and Unpublished Placebo and Selective Serotonin Reuptake Inhibitor Controlled Trials" (2010) 341 BMJ c4737; Sarah Boseley "Antidepressant Reboxetine No Better than a Placebo, Study Finds" *The Guardian* (online ed, United Kingdom, 13 October 2010).

> many patients. All of them showed that reboxetine was no better than a dummy sugar pill. None of these trials was published. I had no idea they existed.
>
> It got worse. The trials comparing reboxetine against other drugs showed exactly the same picture: three small studies, 507 patients in total, showed that reboxetine was just as good as any other drug. They were all published. But 1,657 patients' worth of data was left unpublished, and this unpublished data showed that patients on reboxetine did worse than those on other drugs. If all this wasn't bad enough, there was also the side-effects data. The drug looked fine in trials which appeared in academic literature: but when we saw the unpublished studies, it turned out that patients were more likely to have side effects, more likely to drop out of taking the drug, and more likely to withdraw from the trial because of side effects, if they were taking reboxetine rather than one of its competitors.
>
> …
>
> I did everything a doctor was supposed to do. I read all the papers, I critically appraised them, I understood them, I discussed them with my patient, and we made a decision together, based on the evidence. In the published data, reboxetine was a safe and effective drug. In reality, it was no better than a sugar pill, and worse, it does more harm than good. As a doctor I did something which, on the balance of the evidence, harmed my patient, simply because unflattering data was left unpublished."

NB: Reboxetine is an antidepressant manufactured by Pfizer sometimes referred to by the trade name Edronax.

X Appendix Two: SSRIs in children and adolescents

This case study is a summary of an investigation by the Medicines and Health Products Regulatory Authority in the United Kingdom (MHRA): [193] Selective Serotonin Reuptake Inhibitors (SSRIs) are drugs that have approval in New Zealand and several other countries for treatment of depression in adults. Examples of SSRIs include fluoxetine (commonly referred to by its trade name, Prozac) and paroxetine (also known as Seroxat). Medsafe issued a warning to health practitioners following the revelations about the use of SSRIs in children and has since undertaken further studies on SSRIs in children.[194]

GlaxoSmithKline (GSK) developed Seroxat and it was approved for the market in the late 1980s. Between 1994 and 2009 GSK conducted nine trials on the safety and efficacy of SSRIs in children. None of these found that SSRIs were effective in treating paediatric depression; additionally there was evidence of a risk of increased suicidal behaviour caused by Seroxat, meaning that the risks of its use in children far outweighed the benefits.[195] Because Seroxat was not legally approved for use in children, GSK were not required to share this information with regulators, including Medsafe.[196] However Seroxat was being prescribed to thousands of children in the UK and in New Zealand as an unapproved medicine. It was not until 2003, when GSK handed out briefing documents to the MHRA about a proposed application to extend the approval of SSRIs to children that the safety issues were brought to the attention of regulators around the world.[197]

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193 *MHRA Investigation into Glaxosmithkline/ Seroxat* (Medicines and Healthcare Products Regulatory Agency UK, summary, 6 March 2008).

194 Letter from Dr Stewart Jessamine (Principal Technical Specialist, Medsafe) to health professionals regarding the use of SSRI antidepressants in children and adolescents (22 March 2004); Medsafe "Selective Serotonin Reuptake Inhibitors (SSRIs) In children and adolescents" (2009) 30 Prescriber Update 1 at 1.

195 *MHRA Investigation into Glaxosmithkline/ Seroxat* (Medicines and Healthcare Products Regulatory Agency UK, summary, 6 March 2008) at [2] and [13].

196 Letter from Dr Stewart Jessamine (Principal Technical Specialist, Medsafe) to health professionals regarding the use of SSRI antidepressants in children and adolescents (22 March 2004).

197 *MHRA Investigation into Glaxosmithkline/ Seroxat* (Medicines and Healthcare Products Regulatory Agency UK, summary, 6 March 2008) at [10] to [12].

XI Appendix Three: Vioxx

The following is an excerpt from an article in *The Listener* (17 November 2012) written by Mark Broatch:[198]

> "In 2004 a popular anti-inflammatory drug known as Vioxx (rofecoxib) was withdrawn worldwide by Merck Sharp & Dohme after years in the market and having made billions of dollars for the company. A study had found using it for longer than 18 months could measurably increase the risk of heart attack and stroke. Medical journal the *Lancet* said unacceptable risks were apparent years earlier. At the time, about 15,000 New Zealanders were using Vioxx for pain relief and inflammation.
>
> Subsequent studies, including a Swiss study that combined 31 randomised, controlled trials in various countries involving more than 100,000 patients, have since confirmed the high level of risk of many popular painkillers, known as non-steroidal anti-inflammatory drugs (NSAIDs), when taken long-term. Brands still sold in New Zealand include Naprosyn (naproxen), Nurofen (ibuprofen) and Voltaren (diclofenac).
>
> And in 2007, another anti-inflammatory, Prexige, was withdrawn from sale following reports of severe liver damage in people taking more than 200mg a day. At the time, more than 1000 New Zealanders were reported to be taking twice that dose."

198 Mark Broatch "Bitter Pills" *The Listener* (New Zealand, 17 November 2012) at 16.

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