An Initiative of NSW Clinical Pharmacologists & Pharmacists
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Off-Label Use of Registered Medicines and Use of Medicines under the Personal Importation Scheme in NSW Public Hospitals

A Discussion Paper

Prepared by a Working Group of NSW TAG Inc (See Appendix 1)

September 2003

Executive Summary

This discussion paper has been developed by a Working Party of NSW TAG as a result of a request from member hospitals for guidance concerning the use of medicines for unapproved indications.

The Discussion Paper will consider off-label use of registered medicines and administration in Public Hospitals of unregistered medicines imported by patients for personal use. It also touches briefly on the SAS Scheme. It is intended to assist relevant policy development by Hospital and Area Drug Committees.

The term "off-label use" refers to prescriptions of registered medicines for a use that is not included in the prescribing information or that is disclaimed in the approved information [1]. This includes use outside government approved indication, dosage, age and route. The term does NOT refer to the conditions (if any) imposed on prescription under the Pharmaceutical Benefits Scheme (PBS)-the conditions for PBS subsidy may be more restrictive than the TGA-approved listing. Nor does it refer to the use of medicines not registered in Australia.

Off-label use of medicines has long been recognised as an important issue in teaching hospitals. Such use is extensive and variable, with 60% of all prescriptions in nine paediatric hospitals[1] and 26% of outpatient prescriptions in one Sydney teaching hospital[2] being reported as off-label.

Off-label use of medicines does not appear to be in breach of the Therapeutic Goods Act and the practice is valid where such use is supported by acceptable quality data.

Similarly, use of medicines imported into Australia by individuals for their own personal (or immediate family) use under the *Personal Import Scheme* without prior approval of the Therapeutic Goods Administration (TGA), is legal. Because such medications may not have been approved for supply in Australia there is no guarantee about their safety, efficacy or quality by the TGA.

In hospitals, processes should be set in place to ensure that use of off-label medicines or medicines imported for personal use are used in such a way as to maximize safety and efficacy.

This document outlines a practical approach for systematically evaluating the appropriateness of medicines used in off-label circumstances, and provides guidance to Drug Committees in formulating local policy for the use of medicines used off-label and unregistered medicines imported for personal use and administered in hospitals.

Discussion Paper

Off-Label Use of Registered Medicines and Use of Medicines under the Personal Importation Scheme in NSW Public Hospitals

This discussion paper has been developed as a result of a request from NSWTAG member hospitals for guidance concerning the use of medicines for unapproved indications. It is intended to assist relevant policy development by Hospital and Area Drug Committees.

The Discussion Paper will consider off-label use of registered medicines (including use outside government approved indication, dosage, age and route) and administration in Public Hospitals of unregistered medicines imported by patients for personal use.

It does not deal in any detail with the use of locally available but unregistered medicines under the Special Access Scheme (SAS) (Refer to Therapeutic Goods Administration website - www.health.gov.au/tga/docs/pdf/unapproved/sas.pdf, or as part of a formal clinical trial (CTN or CTX Schemes). All institutions have formal processes to deal with clinical trials through their Institutional Ethics Committees, and many also have such processes for handling requests under the SAS. Where such processes for assessment of SAS medicines do not exist, then the principles outlined in the algorithm (page 12) should be followed, including the evaluation of research evidence concerning safety and efficacy prior to approval by hospital authorities (usually devolved to the Drug and Therapeutic and/or Institutional Ethic Committees).

Section 1: Background

1.1 Regulation:

The Therapeutic Goods Act 1989 sets out the legal requirements for the import, export, manufacture and supply of medicines in Australia. The objective of this Act is to provide a national framework for the regulation of therapeutic goods in Australia so as to ensure their quality, safety, efficacy and timely availability. The Therapeutic Goods Administration (TGA), as part of the Commonwealth Department of Health and Aged Care, has responsibility for administering the Act. Essentially, any product for which therapeutic claims are made must be either listed or registered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia.

All medicines assessed as having a higher level of risk must be registered. The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors (normally pharmaceutical companies) being required to provide comprehensive safety, quality and efficacy data.

The TGA does not regulate the use (including administration) of a medicine once it has been supplied by a product sponsor. Therefore off-label use by a practitioner (who was not a sponsor of the medicines) does not appear to be in breach of the Therapeutics Goods Act. However, it should be noted that this has not been tested in court. (Refer to

Appendix 2 for a detailed analysis.) In some cases practitioners may be regarded as negligent for not using these medicines where such unapproved use is supported by acceptable quality data.

1.2. Definitions:

1.2.1 Off-label (Unlabeled, Unapproved) Medicine Use:

The term "off-label use" refers to prescriptions of registered medicine (see 1.2.2) for a use that is not included in the prescribing information or that is disclaimed in the approved information [1]. [The term does NOT refer to the conditions (if any) imposed on prescription under the Pharmaceutical Benefits Scheme (PBS)-the conditions for PBS subsidy may be more restrictive than the TGA-approved listing. Nor does it refer to the use of medicines not registered in Australia (see 1.2.3)]. Promotion by pharmaceutical companies of off-label use is prohibited by the TGA.

Table 1: Reasons for Off-label Use of Registered medicines [1] (modified from reference 1)

Reason Use is Off-label	Explanation	Examples
Dose	Medicines may be given at doses other than those stated in the approved product information.	▪ calcitriol used at doses greater than those recommended for osteoporosis when treating hypocalcaemia secondary to renal impairment
Age	Medicines may be used outside the approved age range.	▪ valaciclovir – the product information for valaciclovir states that "safety and effectiveness in children has not been established", however it is used in children under 12 years of age
Indication	Medicines may be used for indications other than those stated in the approved product information	▪ clonidine as an analgesic or in the treatment of attention deficit disorder ▪ risperidone used for autism ▪ azithromycin, used for anti-inflammatory effect in cystic fibrosis ▪ indomethacin used for nephrogenic diabetes insipidus ▪ folinic acid used for seizures in neonates
Route	Medicines may be given by an unapproved route	▪ diazepam injection administered rectally in the treatment of status epilepticus ▪ tobramycin injection used as inhalation in cystic fibrosis ▪ acetylcysteine solution for inhalation administered orally for renal protection

1.2.2. Registered medicine:

A registered medicine is one which has been evaluated and approved by the Therapeutic Goods Administration (TGA) and has been entered into the Australian Register of Therapeutic Goods for the treatment of specified medical conditions. All such products carry an "Aust R" or "Aust L" number on the label.

Once registered a medicine is deemed "labeled" for use as outlined in the approved Product Information.

1.2.3. Unregistered (unlicensed) Medicines

A medicine or dosage form of a medicine, which has not been evaluated nor approved in Australia, and hence not entered on the Australian Register of Therapeutic Goods (ARTG).

The Therapeutic Goods Act provides the following mechanisms to allow individuals to gain limited access to therapeutic goods not listed on the ARTG:

1.2.3.1: Unregistered medicines where hospital approval processes are normally defined:

- The Special Access Scheme (SAS), including Authorised Prescribers
- Clinical Trials

1.2.3.2: Unregistered medicines where hospital approval processes are not normally defined:

- Importation for personal use.

Table 2: Examples of Unregistered medicine Use: [1] (modified from reference 1)

Category	Explanation	Examples
Modifications of a registered medicine	1. The preparation of a suspension from capsules or tablets or/and diluent or flavours added 2. Changing a product to one with different pharmacokinetics 3. The preparation of a topical product from an oral preparation	1. sotalol, spironolactone and indomethacin mixtures 2. reformulating methylphenidate (Ritalin) into a long acting preparation 3. tacrolimus capsules reformulated into a topical preparation
Medicines manufactured under a licence to Manufacture Therapeutic Goods	Products may not be suitable because: 1. The adult preparation is not suitable for use in children and there is a need for a smaller dosage form 2. Novel medicines may not be commercially viable to take through the regulatory process 3. A different strength from that commercially available	1. caffeine citrate phenoxybenzamine ampoules 2. "orphan drugs" – refer 1.2.4 3. Clonidine 30mg/2ml injection
Use of "Not for Human Use Chemicals" as medicines	In some rare conditions there may be a need to use non-pharmacopoeial substances as medicines because there is no registered medicine available and no pharmaceutical material of recognised standard	Tween-80 used for meconium ileus Cerium Nitrate for burns
Special Access Scheme (SAS)	Medicines available through the SAS may be: 1. Medicines awaiting registration 2. Medicines registered in other countries but where registration is unlikely to be sought in Australia,	▪ diclofenac suppositories (lower doses available in New Zealand, but not Australia) ▪ idebenone tablets for Friedrich's ataxia available in Europe ▪ carnitine paediatric solution for genetic deficiency available in Europe ▪ thalidomide tablets ▪ dapsone tablets ▪ vasopressin injections ▪ liothyronine injections
The product licence has been abandoned, suspended, revoked or not renewed [2], or where there is no registered product	1. Where there has been a change of manufacturing premises, but where the new premises may not yet be licensed by TGA 2. A sponsor withdraws the product	2. Naprosyn suspension
Clinical Trial Material	Medicines only available through the clinical trial processes	

1.2.4 Orphan Drugs:

An orphan drug is defined as a medicinal product where there is such a small patient group that there is no reasonable expectation that the cost of researching, registering, and making the drug available would be recovered by potential sales [3].

In Australia, orphan drug status can be obtained [3]:

- Where there are no more than 2,000 patients at any one time with the specific disease being treated
- If the sponsor can prove that the product is not commercially viable irrespective of disease prevalence
- For a new indication for an already registered product.

The TGA Orphan Drug Program commenced in January 2001. The Australian Orphan Drugs Program encourages sponsors to market Orphan Drugs in Australia by reducing costs through waiving fees and by providing exclusive approval. As at 9 May 2003, 68 drugs have been designated as orphan drugs by the TGA.

1.2.5 Complementary Medicines:

Refer to the NSW Health Information Bulletin 99/18: "Complementary Medicines in Public Hospitals".

1.3. Extent of off-label Usage

1.3.1 General Population:

In a sample of prescriptions received by 200 outpatients in a Sydney teaching hospital, 26% of marketed prescription medicines prescribed were for off-label indications[4]. A chart review of 500 medicines used during a three month period in a family practice clinic in the USA, showed that 9.2% of medicines prescribed were for indications not included in the FDA approved labeling [5]. Comment was made in the latter that many physicians consult another source of medicine information - American Medical Association (AMA) Drug Evaluations, which reviews and recommends medicines for specific indications irrespective of their FDA-approved labeling status.

1.3.2 Psychiatric Medicine:

A study conducted by Douglas-Hall et al [6] found that, of the 1,387 items prescribed to 266 English psychiatric patients, 103 (7.5%) were prescribed outside the terms of the product licence. Of these, 75% were outside approved indications and 25% were doses which exceeded the maximum permitted. Thirty per cent of patients were prescribed at least one medicine off-licence.

1.3.3 Paediatric Medicine:

Children are subject to the same diseases as adults and by necessity are often treated with the same medicines[7]. However according to the American Academy of Paediatrics only a small fraction of medicines marketed in the United States has been studied in paediatric patients, and a majority of marketed medicines is not labeled, or is insufficiently labeled for use in paediatric patients[7]. Safety and effectiveness information for the youngest paediatric age groups is particularly difficult to find in product labeling. Many medicines commonly used in paediatrics have not been approved for use in children [7].

Furthermore information about the safety and effectiveness in the youngest paediatric age groups (eg neonates) is especially difficult to find [8].

The absence of paediatric testing and labeling poses significant risks for children [7]. Inadequate dosing information exposes paediatric patients to the risk of adverse reactions that could be avoided if such information were provided in product labeling [7]. There is also evidence which suggests that ADRs are more likely with unlicensed and off-label medicines [9]. For example, the deaths of at least 15 children given propofol as a sedative have been attributed to the lack of evidence for this indication in children [10]. The absence of paediatric testing and labeling may also expose paediatric patients to ineffective treatment through underdosing, or may deny paediatric patients the ability to benefit from therapeutic advances because physicians chose to prescribe existing, less effective medications in the face of insufficient paediatric information about a new medication [7]. The failure to produce medicines in dosage forms that can be used by young children (eg liquids and chewable tablets) can also deny them access to important medications[7]. Furthermore it has been suggested that standardised post-marketing surveillance will not occur, spontaneous reporting of ADRs may be less common and the patient information leaflet will confuse parents if it states "not to be used in children" [9].

Trials necessary to gain approval are difficult to undertake given the ethical constraints surrounding the inclusion of children in clinical trials, the structure of such studies and the small number of potential subjects [11]. The medicine may also be required to be used for a condition for which it has not been generally approved, (ie a condition which is not included in the prescribing information or for where such used is disclaimed). There are also many medicines not registered in the Australian market for economic reasons [11].

Moreover, while attempts have been made to use the term "off-label" to imply recklessness in the medical malpractice arena, the American Academy of Paediatrics has also pointed out that failure to use off-label medicines where appropriate under the standard of care may also constitute malpractice [12].

National UK guidelines recommend medicines that are unlicensed for use in children, eg the British Thoracic Society guidelines for treating tuberculosis recommend that pyrazinamide is given, and primaquine is recommended by National guidelines for use in Vivax malaria, although it is this is not an approved indication. [13]

An Italian study which measured the off-label use of medicines in nine general paediatric hospitals, found that 60% of prescriptions (range 44 to 71%) were off-label and involved 89% of children receiving medicines [14].

The following overview of studies on the off-label and unlicensed use of medicines in paediatric hospital wards was tabled in a paper by Pandolfini[14].

Table 1. Overview of studies on the off-label and unlicensed use of drugs in paediatric hospital wards.

Country (year) Reference	Setting	Methodology (design, duration)	Size (population, prescriptions)	Unlicensed and off-label use
USA (1987) Thompson et al. (4)	General paediatrics ward	Retrospective, 19 d	951 prescriptions	Prescriptions: 7%
UK (1996) Turner et al. (5)	Paediatric intensive care ward	Prospective, 4 mo	166 children, 862 prescriptions	Children: 70% Prescriptions: 31%
USA (1997) McKinzie et al. (6)	Paediatric emergency department	Retrospective, 1 mo	359 children	Children: 43%
UK (1998) Turner et al. (7)	General paediatrics and paediatric surgery ward	Prospective, 13 wk	609 children, 2013 prescriptions	Children: 42% Prescriptions: 25%
UK (1999) Turner et al. (8)	Five general paediatrics and paediatric surgery wards	Prospective, 13 wk	1046 children, 4455 prescriptions	Children: 48% Prescriptions: 35%
The Netherlands (2000) 't Jong et al. (9)	Paediatric hospital	Prospective, 5 wk	238 children, 2139 prescriptions	Children: 92% Prescriptions: 66%
Europe (2000) Conroy et al. (10)	Five general paediatrics wards in five European countries	Prospective, 1 mo	624 children, 2262 prescriptions	Children: 67% Prescriptions: 46%
Israel (2000) Gavrilov et al. (11)	General paediatrics ambulatory hospital unit	Prospective, 2 mo	132 children, 222 prescriptions	Children: 42% Prescriptions: 34%
Australia (2000) Turner (12)	Two general paediatrics and paediatric surgery wards	Prospective, 1 mo (general) and 5 wk (surgery)	200 children, 735 prescriptions	Children: 36% Prescriptions: 16%

The lack of approved products also presents an equity of access issue in that children may be prevented access to certain medicines via the Pharmaceutical Benefits Scheme (PBS). In a South Australian study, only 50% of medicines prescribed for paediatric ambulatory patients were listed as PBS benefits [1, 15].

The NSW Government's Committee on Children and Young People inquiry into "The use of prescription drugs and over-the-counter medications in children and young people" released its Issues Paper no 4 in May 2002[16]**.** The paper identifies issues highlighted elsewhere in this document.

1.3.4 During Pregnancy:

Most published experience with drugs prescribed during pregnancy for off-label uses has involved either case reports or small subject numbers. There are few well-controlled large studies[17].

In a study of 731 pregnant women conducted in a US non-private university clinic, 22.6% took one or more (average 1.7) medicines for off-label indications. On no occasion was there documentation that the patient was informed that use of the medicine was outside labeled indications [17].

1.3.5 Oncology:

In a survey of 130 patients conducted at the Peter MacCallum Cancer Institute in Melbourne in January 2001, there were 1351 medication orders of which 17.9% were for off-label uses. Of these, 8.7% were used for off-label indications, 10.3% for off-label dose and 2.8% for off-label route. Ninety two per cent of patients received at least one medicine that was prescribed off-label or that was unlicensed[18].

1.4. Reasons why medicines (including indications/doses/route/age) may remain off-label:

It is the responsibility of the sponsor, normally a pharmaceutical company, to seek initial approval for marketing of medicines. Similarly, any changes to the initial approval, whether it be for indication, dose, dosage form or specific patient population, must be initiated by the sponsor. The TGA cannot compel a sponsor to apply for changes.

- Therapeutic advances are often achieved at a rapid rate while progress through licensing authorities may be slow. For example, the labeled indication may not reflect current knowledge. *Note: The TGA is required by the Therapeutics Goods Act 1989 to complete an evaluation and make a decision on medicine registration within 255 working days after it has decided to accept the application for evaluation.*

- The labeled indication may not include well proven uses of a medicine and may be over restrictive

- There may be changes to the manner or location in which the medicine is manufactured that have not yet been approved by the TGA

Once patents have expired, pharmaceutical companies may not wish to undertake studies for new indications on medicines marketed generically as there is no financial incentive. Potential new indications may be of benefit to such a small number of patients that the financial investment for application of a new indication would not prove to be cost-effective.

Section 2: Local Policy Development

2.1 Off-label Use of Registered medicines:

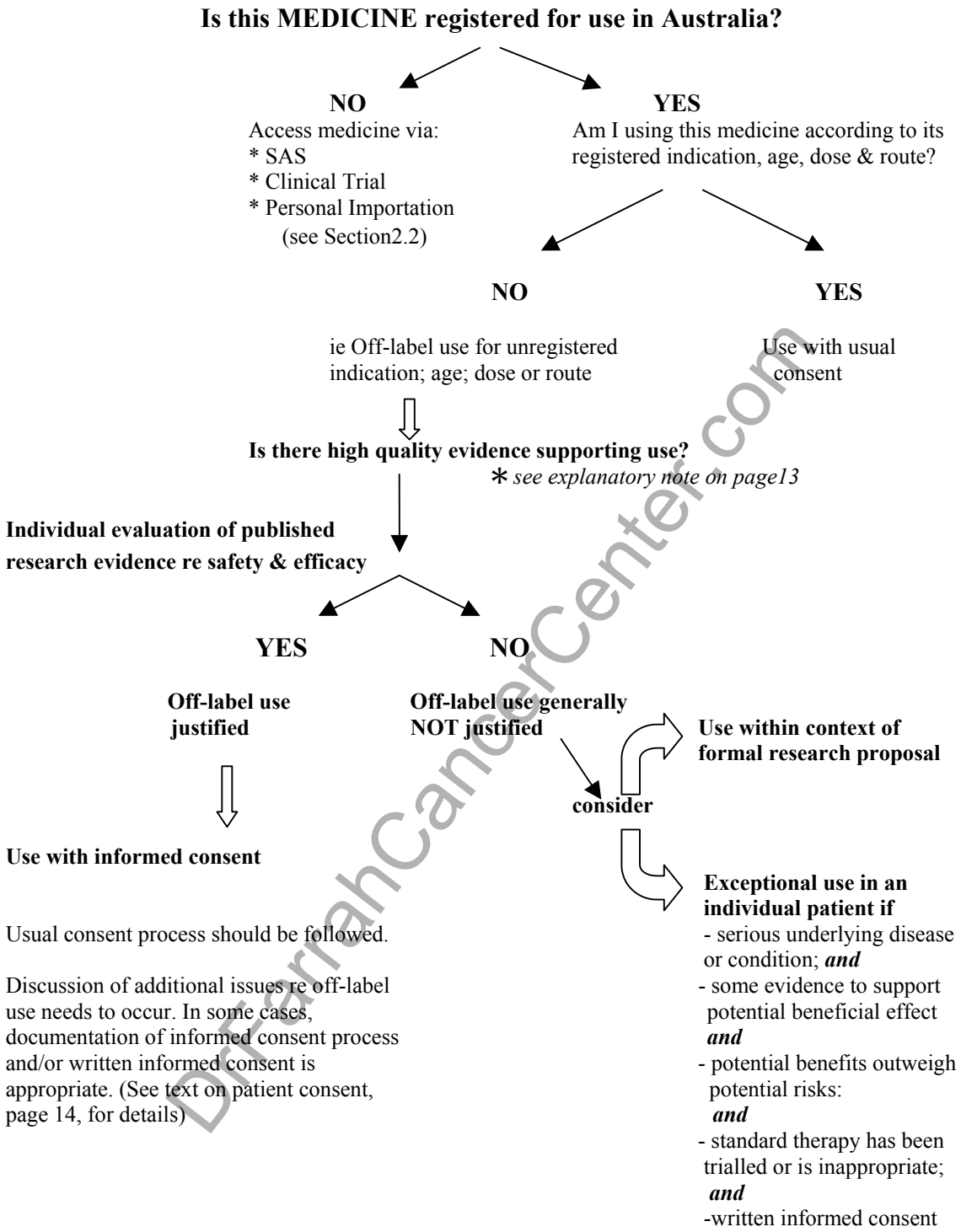
The issue of off-label use of medicines is of particular importance to teaching hospitals as:

- these institutions are at the leading edge of care and of research
- suitable licensed products may not be available
- these products may be the treatment of last resort

The following points are highlighted for consideration when developing local policy on the use of these agents.

2.1.1 Evidence Supporting Use

The following chart may be used in considering the level of evidence supporting use.



Note: *Answering* ***YES*** *to the question* ***"is there high quality evidence supporting use?"*** *would mean that the drug* ***may*** *be used, not necessarily that it* ***should*** *be used in a particular way. This is particularly so when the dimension of duration of use is considered. Even if high quality studies support use of a medicine in the short term, evidence about efficacy/safety in the longer term is needed if the medicine is likely to be used indefinitely.*

The people or groups who are involved in the decision making process as outlined above may be different in different hospitals. (Refer to Appendix 3 for an example of how this process might work in a teaching hospital setting)

⁕ Is there high quality evidence supporting use: (Explanatory note for algorithm on page 12)

(a) In general, the answer to this question should be derived from a critical evaluation of the best available patient-based **research evidence** regarding both efficacy and safety. Individual clinicians (or designated groups of clinicians who may be undertaking this task) should exercise a similar level of rigour as applies to the TGA evaluation of medicines submitted for registration approval. Accepted guidelines for critical appraisal of therapeutic studies[19-22]; for grading of "strength of evidence[23, 24]; and for deciding about applicability of research evidence to individual patient circumstances[25, 26] can be used in answering this question. Various bodies, such as the NSW Therapeutic Assessment Group (TAG) or the National Prescribing Service (NPS), may be able to assist hospitals with the task of evaluating the published literature.

Routine off label use can be justified if there is:

- high quality evidence supporting **efficacy** or effectiveness; and
- sufficient evidence regarding the **safety** spectrum of the medicine to allow a reasonable evaluation of the **benefit:risk** ratio for any given clinical context (especially pertinent with regard to newly marketed medicines). The available efficacy and safety data should be weighed against the seriousness of the underlying condition. As a general rule, the less serious the clinical need, the higher the level of evidence needed to support use of the medicine. Individual patient values and preferences should also be considered[27]

It should be noted that most of the existing guidelines and systems for ranking evidence are focused on efficacy evaluation. The types of studies that should be sought with regard to evaluating the full spectrum of safety of a particular medicine are broader. In many instances only observational studies (eg cohort or case-control studies) from post-marketing surveillance (rather than randomised controlled trials, or meta-analyses) will provide the necessary data, particularly with regard to rare, but potentially serious, adverse effects (eg serious sepsis and death associated with anti-TNF therapy) or those manifest following prolonged exposure (eg hepatotoxicity with low dose weekly methotrexate for RA) or following a long latent period (eg infertility following cancer chemotherapy in childhood).

(b) In some instances, high quality research evidence supporting the use of a particular drug may not be available (and may be unlikely to ever become available). However, there may be data available regarding ***extensive experience*** supporting the efficacy and safety of a particular medicine. Although such data (or "expert opinion" regarding the appropriateness of such use) is considered to be of lower quality than high quality research evidence, there are examples where such data may be used to inform decisions regarding whether a medicine can be considered for off-label use. There are several "authoritative" medicines' compendia which make recommendations for appropriate use supported either by research evidence and/or consensus opinion based on extensive experience with various medicines (eg Australian Medicines Handbook; Therapeutic Guidelines (Australia); Medicines in Children (UK); Royal Children's Hospital Pharmacopoeia, (Melbourne). Other "authoritative" sources may include, for example, recommendations from professional societies (although the quality and validity of some of these can be quite variable). Less formal sources of "experience" or "opinion" based support are less acceptable and caution is recommended when considering this level of support for off-label use.[23, 28] It should be clearly acknowledged that this category of support for off-label use needs to be systematically reviewed as new research evidence becomes available.

If there is no high quality evidence supporting use of a particular medicine, and it is not suitable for "exceptional" or "research" indications, use of the medicine is generally not recommended.

2.1.2 Patient Consent:

(Refer to Appendix 4 - Consent and Off-Label Prescription and Administration of Medicines)

- **Where there is high quality evidence supporting off-label use:**

The usual process of consent used for labelled use will need to be followed. This would include a discussion on the reason for using the medicine, alternative therapies and side effects. Because the medicine is being used off-label additional information may need to be supplied about any uncertainties associated with such use and in some cases patients may require additional information because of concerns that they may express. In some cases, documentation of the consent process and/or written consent may be appropriate.

- **Where there is no high quality evidence supporting off-label use and the medicine has been approved by the hospital drug committee for individual exceptional use or within the context of a formal research proposal:**

Documented written informed consent is required.

- **Where a hospital administers a medicine imported by a patient for personal use:**

(Refer to Section 2.2: Medicines Imported for Personal Use)

Documented written informed consent is required. If the hospital is responsible for the administration of an imported medicine, it is important that the patient is aware of risks that may be associated with taking that medicine, as it has not been through the normal evaluation and approval processes undertaken for registered medicines.
These risks include:

- unknown risks associated with quality, safety and efficacy of the imported medicine
- unknown interactions with other medications the patient may be taking.

If the patient has their own supply of imported medicines and uses them against the advice of the attending medical officer, then the patient needs to acknowledge that they understand the risks of doing so. Hospital staff must ensure that the advice and patient acknowledgement are recorded in writing. Whether this requires a specific consent form will depend upon the circumstances and the frequency of occurrence of these circumstances.

(Refer Appendix 5 – St Vincent's Hospital, Sydney, Consent Form – an example of a consent form for medicines imported by patients for personal use)

2.1.3 Information to Consumers:

Whenever supplying consumer medicines information (CMI) leaflets or other printed information to patients for medicines which are used off-label, it is important to ensure that patients are counseled about any inconsistencies which may appear in the CMI's or other printed information. This may prevent unnecessary confusion or concerns in patients. This issue is highlighted by a recent report in the ISMP Medication Safety Alert, where an elderly patient who had been prescribed amitriptyline for his neck pain, became angry with his physician for "misdiagnosing" his condition, as the leaflet did not mention that the medicine might be used to treat neuropathic pain[29]. Lack of awareness by patients of the indication for a medicine, has also resulted in diagnostic errors. Two patients who had been prescribed anticonvulsants for reasons other than epilepsy went on to develop blackouts. These blackouts were erroneously diagnosed as epilepsy. Misinterpretation of their anticonvulsant therapy treatment as evidence for epilepsy was a crucial factor in their misdiagnosis[30].

2.1.4 Adverse Drug Reactions:

Adverse drug reactions or interactions involving medicines used off-label and those imported under the Personal Import Scheme, should be reported to ADRAC using the blue cards or the on-line facility in the usual manner.

2.1.5 Implications Post Hospital Discharge:

As medicines are only available on the PBS for labeled uses (approved indication, dosage, age and route), patients may be considerably disadvantaged financially if they have been prescribed medicines for off-label use. Wherever possible, implications should be discussed with patients prior to initiation of the medication.

2 2. Medicines Imported for Personal Use

Under the *Personal Import Scheme* individuals can legally import medicines into Australia for their personal (or immediate family) use without prior approval of the Therapeutic Goods Administration (TGA). This scheme does not allow the importation of medicines prohibited by Customs legislation or injectable medicines that contain material of human or animal origin (except insulin), unless an import permit has been obtained. Because such medications may not have been approved for supply in Australia there is no guarantee about their safety, efficacy or quality by the TGA.

The issues raised when patients request to use these imported medicines while admitted into hospital have some common features with the use by patients of complementary medicines and reference has been made to NSW Health Information Bulletin No 98/18 - *Complementary Medicines in Public Hospitals*

Hospitals may wish to include the use and administration of medicines which have been imported by patients under the *Personal Import Scheme,* in their local policy. The following points are offered as guidance:

2.2.1 Medication History - the use of medicines imported by the patient should be noted in the patient's medication history.

2.2.2 Documentation – document any discussion with the patient about the potential for adverse outcomes with the use of medicines whose safety, efficacy or quality has not been subject to the oversight of the Therapeutic Goods Administration or Australian research.

2.2.3 Supply - all therapeutic substances used in hospital are generally dispensed and supplied by the Pharmacy Department. This will not be the case where the patient has imported a substance not generally available or approved for use within Australia. Where the medicines are not listed on the Australian Register of Therapeutic Goods they cannot be provided by a hospital unless they are made available under one of the schemes authorised by sections 19 or 19A of the *Therapeutic Goods Act.*

2.2.4 Administration - there is no obligation on a hospital to facilitate or participate in the administration of a medicine imported by the patient if it is considered that such use is inappropriate. Advice must be provided to the patient about concerns held for the use of the imported medicine. This must be documented.

If the hospital decides to proceed with administration, then the hospital should be reasonably assured of the content and pharmacological effect of the medicine. It should also assure itself that the medicine has been stored appropriately and that all relevant prescription and administration procedures are in accordance with hospital policies.

2.2.5 Patient Consent – Refer to Section 2.1.2, on Patient Consent above.

2.2.6 Storage – Medicines imported by the patient must be stored appropriately to prevent injury to others. This is necessary to meet the standard of care owed by both the hospital and the patient. Ideally the storage should be under the control of the patient.

Where the pharmaceutical company has delivered the medicine directly to the pharmacy or where it is necessary for the hospital to take custody of the medicine from the patient, because of, for example, special storage or administration requirements; or where the patient is an inpatient, the medicine should be stored according to routine pharmacy procedures.

It is highly desirable that the issues raised above are addressed prior to the patient proceeding to import the medicine.

Appendix 1

Working Party members:

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The Working Party acknowledges comments made on the paper by Dr Debra Kennedy and members of NSW TAG.

Appendix 2

Does Off-Label Prescription and Administration of Registered medicines Meet the Requirements of the *Therapeutic Goods Act* (Cth) 1989?

The Issue

Concern has been expressed by some hospitals that "the prescription and administration of registered drugs for an unapproved indication is potentially an offence under s20 of the *Therapeutic Goods Act* 1989 (Cth) (henceforth "*TG Act")*". This concern also reflects issues raised in correspondence in the letters pages of the *Australian Journal of Hospital Pharmacy* in 1993 and 1994 between Mr Stuart Gibb, Chief Pharmacist, Royal Perth Hospital and Dr Geoffrey Vaughan, National Manager, Therapeutic Goods Administration.

The doubts expressed rely upon provisions of the *TG Act* and implications raised thus:

- Any product for which therapeutic claims are made must be either listed or registered in the Australian Register of Therapeutic Goods before it can be supplied in Australia (s17)
- Separate registration is required for each indication or specific therapeutic use of a drug (s16(1)(e))
- Each clinical indication for the use of a particular drug makes the drug a separate good for that indication s16(1)(f).
- Particular therapeutic goods are approved under the *TG Act* for marketing and supply for specific uses.
- The goods can be lawfully marketed and supplied only for those specific uses.
- It is an offence to supply therapeutic goods which are not registered or exempted from the *TG Act* (s20)
- "Supply" is defined in s 3 of the *TG Act* to include "supply by way of administration to, or application in the treatment of, a person".

The correspondence in the pages of the *Australian Journal of Hospital Pharmacy* included concern expressed by Mr Gibb that:

> "The Act [*TG Act*] is not intended to apply to off-label use, then it should specifically exclude such use instead of leaving us in limbo where the Act says one thing but the TGA interprets another. Unfortunately, I do not believe we can assume protection from that. Surely, all it requires is an amendment to the Act or Regulations to:
>
> 1. specifically exclude off-label use from its provisions; or
> 2. delegate to institutional ethics committees and/or drug and therapeutics committees the authority to approve consensus guidelines for off-label use; or
> 3. redefine supply as only applying to sponsors."[1]

In reply to Mr Gibb, Dr Vaughan wrote:

> "As I explained in my last letter to the *Journal*, 'Unless the hospital is the sponsor of the drug … (it)is not subject to control under the Act in respect of the indications for which the drug is to be used within the hospital'. Similarly, prescribers working outside hospitals are not subject to such control.

[1] Gibb SM Non-Approved Consensus Indications for Drugs [letter]. *Aust J Hosp Pharm* 1994; 24:280-1

…
Uses other than those for which sponsors have been granted approval in the registration process could be described as 'off-label' uses. The Act neither prohibits nor sanctions off-label use of drugs by non-sponsors. Rather, prescribers must accept responsibility for such use."[2]

Discussion

The *TG Act* has the object of providing for the establishment and maintenance of a national system of controls relating to the quality, safety, efficiency and timely availability of therapeutic goods, including medicines and regulates the import of therapeutic goods and their supply in Australia. The prescription and administration of drugs is subject to State legislation (in NSW the *Poisons and Therapeutic Goods Act* 1966).

While it could be argued that the administration of a registered medicine for an off-label purpose could be a "supply" and *prima facie* a breach of s 20 of the TG Act, unless it was carried out by the sponsor of the drug, a defence is available under s 20 (1A):

> "It is a defence to a prosecution under subsection (1) if the defendant proves that the defendant was not the sponsor of the goods at the time of the importation, export, manufacture or supply, as the case may be."

A "sponsor" is defined in the Act as follows:

> ***sponsor***, in relation to therapeutic goods, means:
> (a) a person who exports, or arranges the exportation of, the goods from Australia; or
> (b) a person who imports, or arranges the importation of, the goods into Australia; or
> (c) a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);
> but does not include a person who:
> (d) exports, imports or manufactures the goods; or
> (e) arranges the exportation, importation or manufacture of the goods;
> on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.

Sponsors are limited to those who export, import or manufacture the therapeutic good.

Section 20 was amended in 1996 (after the correspondence in the *Australian Journal of Hospital Pharmacy*) by the *Therapeutic Goods Amendment Act* 1996. This amending legislation was intended to:

> "[P]rovide a system for temporarily approving unevaluated drugs as substitute products for existing registered drugs that are either unavailable or in short supply; provide limits and safeguards to ensure that this is only used in limited circumstances; and establish a

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2 Vaughan GN. Non-Approved Indications for Drugs [letter]. *Aust J Hosp Pharm* 1994; 24: 356-7

new procedure for listing simple over-the-counter drugs on the Australian Register of Therapeutic Goods."[3]

The amended s20 included s20(1A). There is only limited information within the Parliamentary record to explain the legislative purpose of this provision:

> "… introduces an offence of intentionally or recklessly importing, exporting, manufacturing or supplying therapeutic goods for use in humans that are not authorized by the Act or exempted from it. If the person can prove that they were not the sponsor of the goods at the time of the importation, exportation, manufacture or supply then they have a defence."[4]

Section 20(1A) would seem to address Mr Gibb's concerns (item 3 of his recommendation).

Thus, in most situations where off-label medicines are prescribed or administered, s20(1A) would be a defence against any claim of a breach of section 20 of the *TG Act*.

Case Law

The issue had a brief airing in the Federal Court judgment of Sackville J in *Commonwealth of Australia v Human Rights & Equal Opportunity Commission* [1997] 147 ALR 469). This was a case involving a claim of sex discrimination in the availability for men of Calcitriol under the PBS. Part of the judgment says:

> "For the purposes of Part 3 of the *Therapeutic Goods Act* (which includes s 17), therapeutic goods are to be taken to be separate and distinct from other therapeutic goods if they have different "indications" or "directions for use": s 16(1)(e), (f). "Indications", in relation to therapeutic goods means the specific therapeutic uses of the goods: s 3. Although the point was not argued, it would seem to follow, as the Commissioner was prepared to accept, that a drug which has several specific therapeutic uses constitutes, for the purposes of Part 3 of the *Therapeutic Goods Act*, several separate and distinct "therapeutic goods".

The judge concluded:

> " . . . I do not think that on the material before me I can or should determine that the non-registration of Calcitriol under the *Therapeutic Goods Act* for use in the treatment of osteoporosis in males necessarily makes the circumstances of the complainants different from those of women generally, for the purposes of s 5(1) of the *SD Act*. Mr Hilton's [counsel for the Commonwealth] construction of the legislation [above] appears on the face of it to be plausible, but the point was not argued in any depth and, because of the course the proceedings took before the Commissioner, could not be based on detailed factual findings by HREOC. Perhaps more importantly, the agreed facts make it clear that at least one complainant has been prescribed Calcitriol by a doctor and has received the drug for the treatment of his osteoporosis, albeit not under the PBS. The evidence does not address the circumstance in which the drug was prescribed or dispensed. It may be that the evidence will provide an explanation as to how the medicine came to be prescribed and dispensed for this purpose without infringing the *Therapeutic Goods Act*.

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3 Bills Digest No 73 1995-96 "Therapeutic Goods Amendment Bill 1996"

4 Bills Digest No 73 1995-96 "Therapeutic Goods Amendment Bill 1996"

The incompleteness of the factual material is reinforced by the fact that Mr Robertson informed me, without objection from Mr Hilton, that the complainants are now receiving Calcitriol free of charge. Again, the evidence does not address how this state of affairs has come about and how it can be reconciled with the apparent effect of the *Therapeutic Goods Act*.

In all the circumstances, I think the appropriate course is for HREOC to make findings on any facts that may be necessary to determine the effect of the *Therapeutic Goods Act* on the prescription and dispensing of drugs for uses not placed on the register under the *Therapeutic Goods Act*. Any such findings would need to be taken into account with the other factors that I have mentioned elsewhere in this judgment in order to determine whether the relevant circumstances are "materially different" for the purposes of s 5(1) of the *SD Act*."

Conclusion

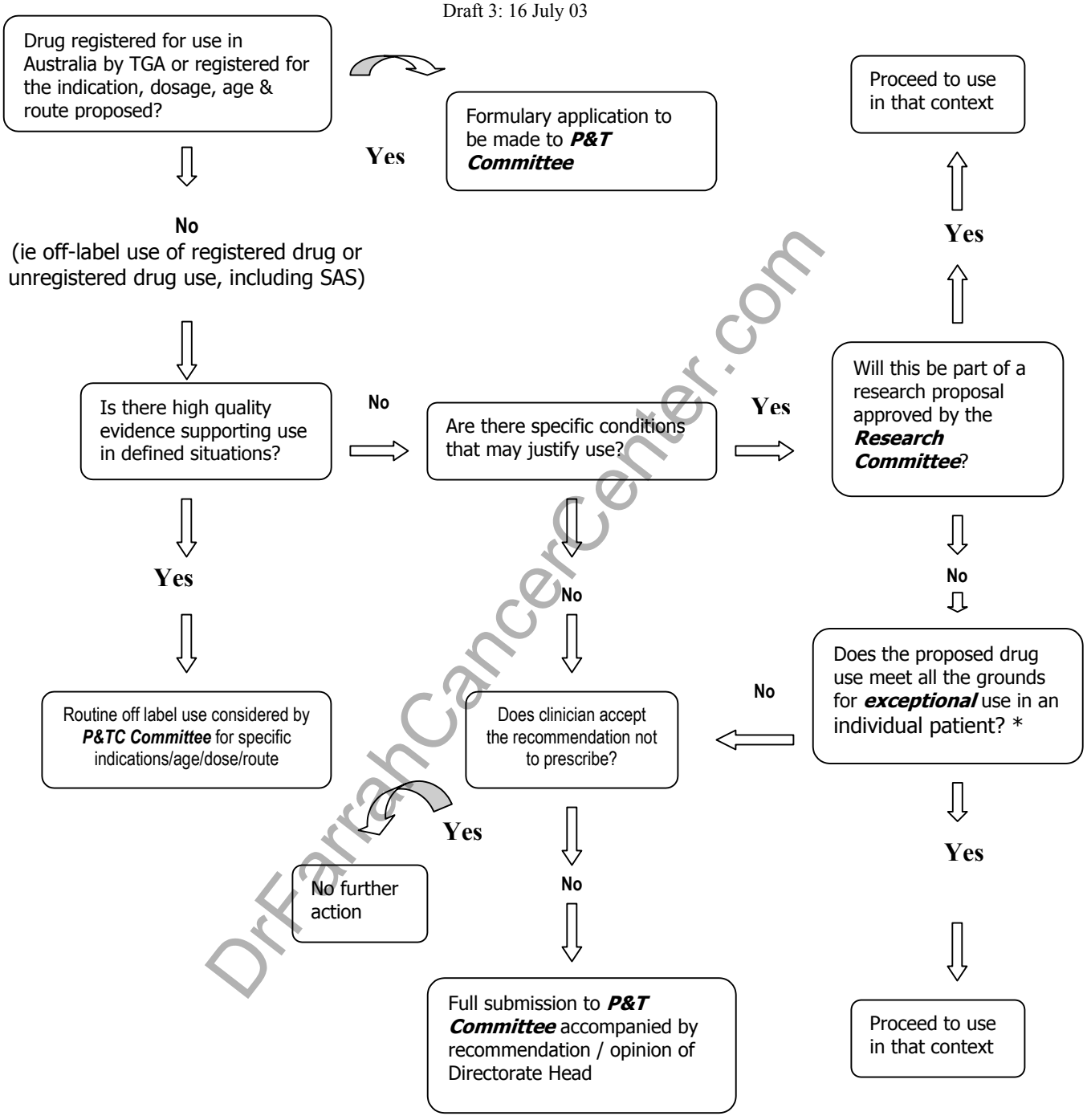
The off-label prescription and administration of medicines registered under the *Therapeutic Goods Act* 1989 would not appear to be in breach of the Act as long as the prescription or administration was not authorised or carried out by a sponsor of the medicine. To simply prescribe or dispense a medicine off-label does not constitute being the sponsor. Note should be made that issues pertaining to the *National Health Act* 1953 and the Pharmaceutical Benefits Scheme have not been addressed.

Appendix 3:

Formulary decision making algorithm: , Sydney Children's Hospital

Please read with accompanying generic algorithm(page 12) and explanatory text (page 13)

Draft 3: 16 July 03



* Meets criteria for exceptional use as per "generic algorithm" (Page 12); **and**

- **Independent expert** concurs with use; **and**
- **Directorate Head** or their nominated delegate (eg independent Department Head) has approved use; **and**
- **Pharmacy and Therapeutic (P&T) Committee** has approved use
  (**P&TC Executive** may give interim approval between meetings if the clinical condition warrants that urgency)

Appendix 4

Consent and Off-Label Prescription and Administration of Medicines

Consent Generally

In law, consent to the administration of a medicine is necessary for two reasons:

- In order to avoid a claim of trespass to the person (in a civil action) or assault and battery (in a criminal action). The law requires that a person must understand the "nature and effect" of what is to take place and then they must voluntarily agree[5]. There is a legal presumption that all adults are competent to consent, although this is a rebuttable presumption[6]. In New South Wales there is a statutory presumption that minors over the age of fourteen years are competent to consent[7] and competent parents or guardians may consent to medical and dental treatment where the child is less than sixteen years of age[8].

- In gaining consent it is also necessary, in order to meet an appropriate standard of care owed to the patient, to provide the patient with information about their diagnosis and treatment. If this standard of care is not met, and the patient suffers some harm then an action in the tort of negligence may be successful.

Trespass to the Person (and assault and battery)

There is no reason to believe that the fact that a medicine was prescribed or administered "off-label" would mean that the patient had not validly consented - understanding the "nature and effect" of what was being done. It is the administration of a medicine that is important, the registration status of the medicine would not usually affect the validity of any consent gained. This would not apply however where, for example, the purpose of the administration of the medicine was misrepresented.

Negligence

The standard of care owed when giving information to a patient has been considered by the High Court of Australia in a number of recent cases; notably *Rogers v. Whitaker* (1992) 175 CLR 479 and *Rosenberg v. Percival* (2001) 205 CLR 434.

In *Rogers v Whitaker* the majority of the High Court said:

> "The law should recognize that a doctor has a duty to warn a patient of a material risk inherent in the proposed treatment; a risk is material if, in the circumstances of the particular case, a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it or if the medical practitioner is

5 *Chatterton v Gerson* [1981] 1 QB 432
6 *Re C (adult: refusal of medical treatment*) [1994] 1 WLR 290
7 *Minors (Property and Contracts) Act* 1970 (NSW), s49(2)
8 *Minors (Property and Contracts) Act* 1970 (NSW), s49(1)

> or should reasonably be aware that the particular patient, if warned of the risk, would be likely to attach significance to it." (at 490)

Whilst the *Rogers v Whitaker* case concerned those *risks* that a patient should be warned of the High Court also affirmed statements by King CJ in the South Australian Court of Appeal judgment in *F v R* (1983) 33 SASR 189 (at 192):

> "The relevant circumstances include the nature of the matter to be disclosed, the nature of the treatment, the desire of the patient for information, the temperament and health of the patient, and the general surrounding circumstances.
>
> …
>
> The purpose of disclosure is to provide the patient with the information necessary to enable him to make informed decisions concerning his future and, in particular, whether to undergo proposed treatment. The duty extends therefore only to matters which might influence the decisions of a reasonable person in the situation of the patient."

The question of interest is whether a patient must be informed that a proposed usage of a medicine is off-label. No blanket answer can be given to this question. Any advice will depend upon the circumstances of each case. Given the widespread use of medicines off-label it may well be the case that this information will not be material to most patients. That is, it is not something to which many people will attach significance. **The fact that a medicine is being prescribed or administered off-label** may not be significant to most patients, but it must be remembered that any **inherent risk** of the particular medicine or class of medicines may still be significant to the patient – and appropriate information must be given.

There will be situations, however, for example where the proposed off-label use of a medicine is not well known, unusual or of "last resort", where such information may need to be supplied to a patient. This will be a matter of judgment especially if there is something known about the patient that would provide some warning that a particular patient may attach some significance to the fact that a medicine being prescribed or administered is for an off-label indication.

Even if a patient suffers injury following the administration of a medicine for an off-label indication it may be difficult for them to prove that if they had known that it was being prescribed off-label that they would not have consented to its use. Nothing in this discussion has addressed the standard of care involved in the decision to use an off-label medicine.

Appendix 5

St Vincent's Hospital Consent Form for Drugs Imported by Patients for Personal Use:

DRUG NAME:_____

SPONSOR / MANUFACTURER:_____

CONDITION TO BE TREATED:_____

Advice to Patient
The above drug is not registered in Australia for use in your condition by the Therapeutic Goods Administration of the Australian Department of Health and Ageing. Currently, it is an investigational agent which you have imported at your own expense for your personal use.
As this drug is not registered, there may be side effects of which your doctors are not yet aware. You should discuss the known side effects with your doctor before the commencement of treatment. If you have not done this, please ask your doctor now to discuss this with you. In addition, should your treatment be ongoing, you should ask your doctor whether any new and significant information that may affect you has become available.

Acknowledgement of risk and waiver of liability by patient
By signing this form, I acknowledge that I have agreed to take the experimental drug ……knowing that it is not approved for treatment by the Australian regulatory authorities and that it may have side effects and risks which may cause me serious harm. I voluntarily accept these risks.
I agree that St Vincent's Hospital, St Vincents and Mater Health Sydney Ltd, the Sisters of Charity Health Service and their officers, employees, contractors and agents will not be liable for any injuries, damage or other loss that I may suffer or incur through the use of this drug.

Acknowledgement that all costs of the drug are a personal responsibility of the patient
By signing this form I acknowledge that I am personally responsible for paying for ongoing supplies of ……..and that neither St Vincent's Hospital nor the Sisters of Charity Health Service is able to contribute to these costs now or in the future.
Statement of Consent by Patient
I have read the above information and statements of personal responsibility and liability. I understand that by signing this form I am agreeing to accept this responsibility and liability. I acknowledge that the nature, reason for use, and possible risks of the treatment and cost to me have been explained to my satisfaction. Before signing this document I have been given the opportunity to ask questions relating to any possible harm I might suffer as a result of the treatment and I have received a satisfactory answer.

_____ _____ _____
Date Signature of patient

I have fully explained to _____ *(patient's name)* the nature, purpose and risks of the drug treatment to be employed.

_____ _____
Date Signature of authorised prescriber

_____ _____ _____
Date Signature of Witness Name of Witness (Printed)

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