

Review of the need for further regulation of extemporaneous compounding -

January 2005



Table of Contents

SUMMARY.....	II
LIST OF RECOMMENDATIONS.....	VI
LIST OF ABBREVIATIONS.....	VII
ACKNOWLEDGEMENTS.....	VII
1 INTRODUCTION.....	1
1.1 BACKGROUND TO THE PROJECT.....	1
1.2 TERMS OF REFERENCE.....	2
1.3 METHODOLOGY.....	2
2 THE PRESENT LEGISLATIVE FRAMEWORK IN AUSTRALIA.....	3
2.1 CONSTITUTIONAL LIMITATIONS OF THE THERAPEUTIC GOODS ACT.....	3
3 FINDINGS FROM THE CONSULTATIONS.....	4
3.1 WHAT IS HAPPENING.....	4
3.2 PROBLEMS THAT HAVE BEEN EXPERIENCED OVERSEAS.....	5
3.3 COMPOUNDING IN AUSTRALIA.....	6
3.4 AUSTRALIAN STANDARDS AND GUIDELINES FOR EXTEMPORANEOUS DISPENSING.....	7
3.5 NEW ZEALAND.....	8
3.6 OVERSEAS CONTROLS ON EXTEMPORANEOUS COMPOUNDING.....	9
3.6.1 <i>The United Kingdom</i>	9
3.6.2 <i>The United States</i>	11
4 A RISK BASED APPROACH TO LEGISLATIVE EXEMPTIONS FOR EXTEMPORANEOUS COMPOUNDING.....	13
4.1 WHAT ARE THE DIMENSIONS OF RISK FROM EXTEMPORANEOUS COMPOUNDING.....	14
4.2 UTILISING THESE RISK APPROACHES IN IMPROVING THE SPECIFICITY OF THE EXEMPTIONS.....	15
4.2.1 <i>Exemption from registration of goods</i>	15
4.2.2 <i>Exemption from Part 3.3 of the Therapeutic Goods Act - GMP</i>	16
5 THE EXEMPTIONS FOR HOSPITAL PHARMACIES.....	20
6 ADVERTISING.....	21
6.1 ADVERTISING TO THE PUBLIC.....	21
6.2 ADVERTISING TO PROFESSIONALS.....	22
7 THE APPLICATION OF ANY NEW CONTROLS BEYOND PHARMACISTS.....	23
8 VETERINARY PRODUCTS.....	23
APPENDICES.....	24

Summary

Introduction

Oceania Health Consulting has been contracted by the Therapeutic Goods Administration (TGA) to assess the need for changes (if any) to the current arrangement for extemporaneous compounding of medicines for human use. The review has mainly focussed on discussion with Australian Pharmacy Boards other jurisdictional (State and Territory and New Zealand) representatives on the National Coordinating Committee on Therapeutic Goods (NCCTG) as well as peak pharmacy industry bodies in Australia.

The issue

There are potentially serious public health concerns with the use of the extemporaneous products containing highly actives substances. Exemption from the *Therapeutic Goods Act 1989* (the TG Act) controls was never intended for the practices that have developed. There are key concerns in relation to quality, safety and efficacy. NCCTG has had the practice of extemporaneous compounding under consideration for some time but has not acted, pending publication of the COPRA Guidelines, but there are ongoing concerns even if the COPRA guidelines are fully applied.

The TG Act has the Object, in part, to “...provide for the establishment and maintenance of a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods that are ...used in Australia, whether produced in Australia or elsewhere; or exported from Australia”.

In pursuing this Object, the TG Act establishes controls on standards, advertising, sale or use (through registration) and on manufacturing practices. Specific exemptions are provided from *some* of these activities through provisions in the TG Regulations. In particular Schedules 5 and 5A of the TG Regulations provide exemption from the need to register therapeutic goods under certain circumstances, and Schedule 8 provides exemption from the need to comply with the Code of Good Manufacturing Practice.

These exemptions are irrelevant if the pharmacist (or medical practitioner) involved is an unincorporated body trading within a State and not trading with the Commonwealth, as the Constitution does not provide powers to regulate such persons. The limitations of the Australian Constitution will end once the trans-Tasman regulatory body is formed. This report has taken the approach of assuming that this will occur in July 2005 and that changes can be made to regulate extemporaneous compounding in Australia (or New Zealand) from that date.

Current practice

A small number of Australian pharmacists have become franchisees of the US compounding groups. There is a wide range of preparations made in a number of sectors, e.g. women's health, sports medicine, pain management and veterinary medicines. In addition to those that are franchised, there is reported to be about as many who have set up on their own.

The system of operation relies on email, fax and post to cover a wide population, much wider than the local population around the pharmacy, and sometimes interstate

or internationally, although some of the smaller operators were reported to work much more locally. Particular concern was expressed as to the source of raw materials used and the apparent lack of facilities with material handling systems that are adequate for handling substances that are a risk to operators and to others who may be inadvertently exposed. Another key concern was the compounding of preparations containing coumarin and oral clioquinol, both of which have been removed from the Australian Register of Therapeutic Goods on safety grounds.

The large jurisdictions appear to have a small number of larger specialty pharmacies (probably less than 10 even in the largest jurisdictions) while there are up to around 50 others who have some level of involvement.

Regulatory options – who?

It is clear that there are only two regulatory groups with the capacity to control the present practices under the present (and likely foreseeable future) legislation. They are the jurisdictional Pharmacy Boards and the trans-Tasman successor to the TGA for medicines. Each has different roles. At present the exemptions under the TG Act, even if they applied to natural persons, seem to stop well short of the point at which Pharmacy Boards can regulate effectively. Although there are Australian standards and guidelines that could ensure the quality of compounded preparations met very basic requirements, the application of them to compounding pharmacies seems to be a hit-and-miss process with no rigour or certainty from a national perspective.

Ways forward

Consultations demonstrated that Pharmacy Boards were of the view that the **traditional extemporaneous compounding activity of pharmacists should not be taken away**. It is seen as a necessary part of pharmacy practice. Nevertheless, there is recognition that preparations that have significant systemic effects and/or are used long term, or where the product had to be sterile, the level of risk warranted some further level of regulation.

There are potentially four dimensions that could be regulated to manage risk:

- A. Active pharmaceutical ingredients
- B. Route of administration
- C. High levels of pharmaceutical technology or equipment required
- D. A limit on quantity

Requiring registration of preparations containing some substances

Excluding some substances from the exemption from registration is one way to control risk. The alternatives are: 1) a short list of substances of particular safety concerns; or 2) a quite long list, eg all the substances in S4 and S8; or 3) a more specific list in areas where the compounders are known to be highly active.

The first option has its difficulties but it is recommended as the place to start, as it has the virtue of being workable. Other reforms to the GMP exemption may address other concerns.

There may be other regulatory alternatives that can be applied to these preparations without restricting access. For example it may be appropriate to require the inclusion

of a warning label on any extemporaneous preparation that contains an S4 or S8 substance along the lines of “*This preparation has not been assessed by [the regulator] for safety or efficacy*”.

Requiring some level of GMP assessment

There needs to be a means of ensuring that extemporaneous compounding on any scale – small or large – is undertaken in an appropriate manner. There are two issues to be addressed: what is to be included in any GMP exemptions and the level of regulation of them. Exemption from compliance with the Australian Code of Good Manufacturing Practice for Medicinal Products (ACGMP) need not mean complete exemption from all controls.

In making concessions on quality and safety, a cut-off on a quantity basis is hard to argue for as *the* primary regulatory strategy. *Every* preparation needs to be manufactured in accordance with good manufacturing principles – the extent of the requirement is the key variable. The exemption provided when the TG Regulations were written is, in hindsight, too open-ended.

The recommended approach is to provide a conditional exemption for most extemporaneous preparations, i.e. when prepared in conformity with specifically written Standards for Pharmacy Compounding. These Standards could then have sections applying requirements that are risk-based – a topical cream for local effect having modest requirements, and a preparation that has systemic effects having additional requirements, through to an aseptic preparation requiring a fully validated and monitored facility and elaborate process requirements.

Pharmacy Boards have the role of overseeing pharmacy practice in accordance with various standards now, e.g. the APF and various other professional standards of PSA, or State-specific requirements. Boards should continue to oversight the application of these more stringent Compounding Standards, rather than try to change the status quo by TGA taking on this role.

Total exclusions from the GMP exemption arrangements

Some products are so technically difficult to make that they should not be attempted in a pharmacy that cannot fully comply with the ACGMP. Examples are ‘patches’ and modified release preparations. It is proposed therefore that these products **not** be exempted from the need to comply with ACGMP under Schedule 8 of the TG Regulations.

A quantity limit

In the US some compounding pharmacies now rival small manufacturers. This suggests there does need to be upper limits on the size to which these businesses should be allowed to grow without full GMP compliance and possibly product registration. Setting the quantity limit too low would mean that assessment would be labour-intensive, and it would ensure that compounding pharmacies all stayed small and inefficient. Given that this is not the primary regulatory approach, the limit could be set relatively generously.

Other GMP-related issues

One concern that was consistently raised during the consultations was the apparent lack of standardised starting materials. They often did not appear to be labelled BP, USP etc, and identity and purity checks did not always seem to be being carried out

although this has not been assessed first hand. Furthermore, while gloves and masks were reported to be worn, the controls described to prevent environmental contamination and occupational health and safety problems could be insufficient, given the nature of the materials being handled repeatedly.

Hospital pharmacies

The activities of public hospitals are under a different set of exemptions to those of community pharmacists, for both GMP and registration. The exemptions were drafted when the controls were focussed on Australia and took into account factors such as Constitutional reach, which will differ once the regulatory mechanism becomes trans-Tasman. An arrangement that takes the future reach of the legislation and clinical requirements of Australian (and possibly New Zealand) health services needs to be devised.

Advertising of compounded preparations

The proposed trans-Tasman Advertising Code has a much wider definition of advertisement than the current Australian Code. There is, therefore, the opportunity to regulate the advertisement of services that use compounded preparations if it is considered to be in the public interest to do so.

Traditionally all advertising directed at health professionals is exempt from regulation although under the trans-Tasman Advertising Code it will be required to comply with the relevant provisions of the Code. One key feature of the marketing of pharmacy compounding is advertising to generate prescribing. It is very difficult to see why this is necessary. Removal of this practice would go some way to ensure prescribing is more appropriate. Nevertheless, advertising is generally a positive social good and the decision to limit advertising of extemporaneous preparations to professionals should not be taken lightly, even though there seems to be no justification for such advertising.

An intermediate position between doing nothing and prohibiting advertising of compounded preparations to health professionals altogether, is to require a warning in advertising material directed at health professionals that the preparations offered have not been assessed by the regulator for safety and efficacy and informed consent should/must be obtained before they are prescribed. This would remind prescribers of common law duties and ensure they were aware that the preparations have not been assessed in the way a registered product has been.

List of recommendations

1. In the first instance, a relatively small number of substances be excluded from the exemptions provided under Schedule 5 and 5A of the Therapeutic Goods Regulations, including substances that have been removed from or refused inclusion on the ARTG on safety grounds as well as other substances that have restricted access, such as those in Schedule 9 or Appendix C of the SUSDP. 16
 2. The exemption from Schedule 8 of the Therapeutic Goods Regulations for pharmacists be redrafted and made conditional upon preparation in premises that are certified as conforming with the relevant level of professional standards for pharmaceutical compounding. 18
 3. The proposed Standards for Pharmaceutical Compounding be drafted under the auspices of the NCCTG, in partnership with the State and Territory Pharmacy Boards and the TGA, and with input from the other major professional pharmaceutical bodies. 18
 4. Certain technically difficult or high-risk preparations *not* be exempted from the full requirements for licensing and GMP inspection. 18
 5. There be an upper limit to the number of units that can be prepared in a month before the business becomes licensable under Part 3.3 of the *Therapeutic Goods Act 1989*. 18
- Other matters for Consideration:
- a. Consideration be given to the inclusion of a warning label on extemporaneous preparations containing substances in Schedules 2, 3, 4 or 8 of the SUSDP, to the effect of the preparation not having been assessed by the regulator for safety or efficacy..... 16
 - b. Consideration be given to advertisements directed at health professionals for extemporaneously compounded medicines being required to carry a warning that the preparation has not been assessed for safety and efficacy, and that the prescriber is strongly advised to obtain informed consent before prescribing the preparation. 22
 - c. Consider whether the scheme proposed in Appendix 3 works if the cut-off is set high or low? What should the limit be, given the other controls that are proposed in this paper? 28

Abbreviations

NCCTG	National Coordinating Committee for Therapeutic Goods
TGA	Therapeutic Goods Administration
TG Act	<i>Therapeutic Goods Act 1989</i>
TG Regulations	Therapeutic Goods Regulations 1990
APF	Australian Pharmaceutical Formulary and Handbook, 19 th ed. 2004.
COPRA	Council of Pharmacy Registering Authorities Inc.
ARTG	Australian Register of Therapeutic Goods
PCCA	Professional Compounding Chemists of Australia
PSA	Pharmaceutical Society of Australia
SHPA	Society of Hospital Pharmacists of Australia
QCPP	Quality Care Pharmacy Program
GMP	Good Manufacturing Practice
MCA	Medicines Control Agency (now the MHRA)
USP	United States Pharmacopeia (sic)
PCAB	Pharmacy Compounding Accreditation Board
NAPB	National Association of Pharmacy Boards
DHEA	Dehydroepiandrosterone
S2 or 3, etc	Refers to Schedules 2 or 3 etc of the SUSDP
FDA	Food and Drug authority (of the US)
SAS	Special Access Scheme
SUSDP	Standard for Uniform Scheduling of Drugs and Poisons.
ACGMP	Australian Code of Good Manufacturing Practice for Medicinal Products
APVMA	Australian Pesticides and Veterinary Medicines Authority

Acknowledgements

The cooperation of the NCCTG members, Pharmacy Board members, and the many other persons who have given up their time to contribute to this report is gratefully acknowledged.

1 Introduction

Oceania Health Consulting has been contracted by the Therapeutic Goods Administration (TGA) to investigate the need for changes (if any) to the current arrangement for extemporaneous compounding of medicines for human use. The project has mainly focussed on discussion with Australian Pharmacy Boards, other relevant regulatory agencies (State, Territory and New Zealand NCCTG representatives) as well as peak pharmacy industry bodies in Australia.

1.1 Background to the project

The *Therapeutic Goods Act 1989* (TG Act) was established to ensure the quality, safety, efficacy and timely availability of therapeutic goods in Australia. The TG Act generally avoids regulating professional practice, and exemptions for professional practices associated with dispensing and extemporaneous compounding were included in the Therapeutic Goods Regulations 1990 (TG Regulations) to allow this to continue. The legislation is risk-based, and the risk from the level of these practices *as they were occurring at the time of legislative drafting* was considered to be small.

The exemptions were intended to allow, for example, small quantities of APF formulae and dispensing of prescriptions for individualised dermatological formulae to continue to be manufactured by pharmacists without any further controls, provided they met the requirements of the TG Regulations, in particular those of both Schedule 5 and Schedule 8 (see Appendix 2).

Since these regulations were written, however, the practice of extemporaneous compounding has grown out of all proportion in some (a small number of) pharmacies. This is part of an international trend and appears to be accelerating rapidly.

There are potentially serious public health concerns with the growing use of the extemporaneous products containing highly active substances. Exemption from the TG Act for the compounding practices that have developed was never intended. There are concerns in all the key areas of risk from medicines, i.e. in relation to quality, safety and efficacy.

The NCCTG has had the practice of extemporaneous compounding under consideration for some time but has not acted, pending publication of the Council of Pharmacy regulatory Authorities (COPRA) Guidelines. COPRA has recently issued a statement for adoption by pharmacy regulators around the country but ongoing concerns remain among NCCTG members, even if the COPRA guidelines are fully applied.

As the Guidelines as published did not fully address the NCCTG's concerns, this review has been undertaken to assess what (if anything) needs to be done to ensure the necessary level of quality, safety and efficacy in compounded medicines sold in Australia (and ultimately perhaps, in both Australia and New Zealand).

1.2 Terms of reference

The terms of reference for the project are to:

- Review the practices of extemporaneous compounding in Australia;
- Compare the present legislative and practical arrangements in New Zealand and other comparable countries, in consultations with Medsafe (New Zealand) and other overseas regulatory authorities;
- Review the advertising of preparations made pursuant to the present extemporaneous exemptions; and
- Prepare a report on the findings of the review and make recommendations that will preserve the bona fide need for occasional small-scale extemporaneous compounding of medicines, while ensuring the quality, safety and efficacy of therapeutic goods more broadly.

1.3 Methodology

The approach taken has been to consult with the members of the NCCTG in each jurisdiction (including the New Zealand member when he was visiting the TGA). The consultant and the (Australian) NCCTG member then met the Pharmacy Boards in each jurisdiction (except NT where the discussions were by telephone) and discussed the Boards' knowledge of and attitudes towards the practice of extemporaneous compounding, as it has developed in Australia in recent years, and what, if anything, the Boards believed needs to happen.

Consultations with the Pharmacy Guild of Australia, the PSA and with the Chair of the editorial committee of the Australian Pharmaceutical Formulary and Handbook (APF) were to discover what these organisations' views were and what, if any, response they had made to the growing practice of extemporaneous compounding. The consulting process led to further discussions with persons who were suggested as key stakeholders or who heard about the project and requested input.

Consultations have also occurred with key staff within the TGA.

Research into the practices of extemporaneous compounding and the regulatory approaches being pursued overseas has also been undertaken via internet searches and discussions with key informants in the US where the practice appears to be most developed.

The list of persons consulted is given in Appendix 1.

2 The present legislative framework in Australia

The TG Act has the Object, in part, to “...provide for the establishment and maintenance of a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods that are ...used in Australia, whether produced in Australia or elsewhere; or exported from Australia”.

In pursuing this Object, the TG Act establishes controls on standards, advertising, sale or use (through registration) and on manufacturing practice.

Specific exemptions are provided from *some* of these activities through provisions in the TG Regulations. In particular Schedules 5 and 5A of the TG Regulations provide exemption from the need to register therapeutic goods under certain circumstances, and Schedule 8 provides, in effect, exemption from the need to comply with the Code of Good Manufacturing Practice under certain circumstances.

The detail of the exemptions provided in these Schedules of the TG Regulations is set out in Appendix 2.

2.1 Constitutional limitations of the Therapeutic Goods Act

The above exemptions are, however, irrelevant if the pharmacist (or medical practitioner) engaging in the practice of extemporaneous compounding is an unincorporated body trading within a State and not trading with the Commonwealth, as the Australian Constitution does not provide powers to regulate such persons at all (see section 6 of the TG Act).

Some States, notably NSW and Tasmania, have passed complementary legislation that applies the TG Act as if it were a law of the State, and Victoria adopted the TG Act in total, although over time the amendments to the TG Act have not been picked up in full so the legislation in Victoria now differs. Even in these jurisdictions, however, there have been difficulties in covering natural persons trading intrastate.

In South Australia a great many pharmacies are incorporated bodies, which means the Commonwealth would have jurisdiction over them but in any case, as a policy issue, the TGA wants to leave the regulation of pharmacies to the Pharmacy Boards and not to become involved in the regulation of pharmacy practice. If there was a complaint, however, with evidence of practices are in breach of the TG Act, TGA could act where the pharmacy is incorporated.

The limitations of the Australian Constitution will end once the trans-Tasman regulatory body is formed. The Treaty forming it will invoke the foreign affairs powers of the Constitution, which will then enable the regulation of natural persons in Australia. This report has taken the approach of assuming that this will occur in July 2005 and that changes can be made to the provision of the new legislation that parallels those in Schedules 5, 5A and 8 to regulate to the extent that is necessary, extemporaneous compounding by any person in Australia or New Zealand from that date.

It should be emphasised, however, that some of the practices reported to be currently happening appear to be in breach of the TG Act as it stands.

3 Findings from the consultations

3.1 What is happening

It was not the purpose of this project to research in detail what the current practice of extemporaneous compounding entails, other than by discussion with other regulators. Nevertheless, some background information provided during those discussions is helpful.

The practice of extemporaneous compounding on a large scale developed first in the US¹. Pharmacies in the US were being taken over by chains, and independent pharmacists were finding it particularly hard to compete. Compounding offered them a profitable niche. Medicines were compounded that were “personalised” for the client. A franchised arrangement evolved, based on the legislative exemptions that were made for quite different purposes.

Franchisors typically provide a few days training in compounding. Franchisees are provided with a wide range of ingredients and bases not generally available to pharmacists and a range of formulae may be advertised to doctors with the name of the nearest franchisee. The franchisor is able to provide the necessary equipment. Basically the pharmacist involved paid up an initial fee, which included the basic equipment and ingredients and an annual fee to maintain membership.

A small number of Australian pharmacists, visiting the United States on various study tours, were made aware of such franchises and Australian pharmacists became franchisees. Since then the franchises have expanded considerably and the training can be undertaken in Australia.

There is a wide range of preparations made (up to 15 different sectors according to one interviewee) covering, for example women’s health, sports medicine, pain management, veterinary medicines, etc, involving hundreds of different starting materials and thousands of preparations.

In addition to those who are franchised, there is reported to be about as many compounding pharmacists who have set up on their own. These pharmacists may not have the support and access to raw materials intended for human use that the franchisee pharmacists have, so their products may be even high risk than those who are franchised, but there is no information to allow objective assessment of this one way or the other.

The system of operation utilises email, fax and post to cover a wide population, much wider than the local population around the pharmacy, and sometimes interstate or internationally, although some of the smaller operators were reported to work much more locally.

The consultant was told that the scale of operation in some of the pharmacies was very large, with filing cabinets full of incomplete and completed prescriptions on hand, and large stocks of raw materials, including some highly active substances such as progesterone and testosterone. Concern was expressed as to the source of these raw

¹ I am indebted to Mr G McInerney, a NSW Pharmacy Board member, for some of this information, as well as for other assistance.

materials and the apparent lack of evidence of quality of some of them. Often facilities were reported to be very modern, but not invariably so. There are also concerns that the material handling systems may not be adequate for handling hormones and other substances that represent a risk to operators and to others who may be inadvertently exposed, particularly if they are exposed regularly.

Furthermore, officers of the TGA and others advised of supply of preparations containing oral clioquinol and topical coumarin, both substances that have been removed from the Australian Register of Therapeutic Goods (ARTG) on safety grounds. Clearly, such preparations should not be available in Australia.

3.2 Problems that have been experienced overseas

The US has had a number of incidents related to pharmacy compounding that indicate what can go wrong in an area with inadequate standards and without external auditing against those standards. Three brief case histories are given in the box below. A search of the internet will readily identify others.

Case 1: Deliberate dilution of anti-cancer drugs

Kansas City pharmacist Robert Courtney pleaded guilty in February 2002 to diluting 158 chemotherapy doses for 34 patients from March 2001 through June 2001. But he admitted that greed drove him to dilute drugs since 1992, affecting as many as 4,200 patients, 400 doctors and 98,000 prescriptions.

Case 2: Injectable betamethasone causing meningitis

The California State Board of Pharmacy on July 17, 2001 suspended the interim license of a pharmacist from "Docs Pharmacy", linked to three deaths from meningitis in the bacteria contamination of a compounded drug. The Pharmacist, Robert Horwitz has been ordered to stop work and his pharmacy has been ordered to stop dispensing any compounded drugs until the next hearing date. Betamethasone, a steroid used to treat inflammation, was prepared at Docs Pharmacy and distributed to 6 different health care facilities in Contra Costa County. Tests proved the drug compound was contaminated with the bacteria *Serratia*. A total of 38 patients received the contaminated injections. Three of the patients died.

Docs Pharmacy and its principal owner and Pharmacist-in-Charge, Robert Horwitz, were charged with violating an interim order issued on July 6 to stop the compounding or mixing of any drugs until a court hearing. That order limited the pharmacy dispense only prescription medications that it purchased from a drug manufacturer. The order was ignored. Docs Pharmacy continued to dispense compounded medication after the court order was issued.

Horwitz had been named pharmacist of the year in 1997 by Professional Compounding Centers of America.

Case 3 – Incorrect dose of thyroid hormone

Four patients were hospitalized in Atlanta - two in a coma - after they swallowed a compounded thyroid drug that was as much as 1,000 times the prescribed strength. The pharmacist, John Marzullo, surrendered his license in February 2002.

Most recently the FDA has taken action to prevent the supply of domperidone for increasing lactation, an indication that is not approved in any country. The FDA press release states (see <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01292.html>):

“The [FDA] is concerned with the potential public health risks associated with domperidone. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from marketing in a number of countries. In several countries where the oral form of domperidone continues to be marketed, labels for the product contain specific warnings against use of domperidone by breastfeeding women and note that the drug is excreted in breast milk that could expose a breastfeeding infant to unknown risks.”

These events highlights the danger of ill-informed and ill-judged medical and pharmacy practices being allowed to continue without proper checks and balances.

3.3 Compounding in Australia

Most jurisdictions have a significant number of pharmacies who are making a specialty of extemporaneous compounding and undertaking it on a substantial scale. While accurate data on numbers are not available, it would appear the large jurisdictions have a small number of larger specialty pharmacies (probably less than 10 even in the largest jurisdictions) while there are up to 50 others who have some level of involvement². The smaller jurisdictions seem to have disproportionately fewer pharmacies that are specialising in this way.

The level of activity by either health agency staff or Pharmacy Board staff in investigating the activities appears to depend upon the extent to which it has been brought to the attention of the agency and their legislative capacity to actually do anything about it, if they see a need.

The Pharmacy Board in some jurisdictions, Victoria for example, has frequently publicised its concerns about many of the practices, but it is very difficult to assess the impact this has had. Possibly there are fewer new entrants to this field in Victoria, but there are at least some new ones. Action over modified release preparations has also been undertaken in NSW, and other Boards have sent circulars out advising on compounding standards, essentially re-iterating the requirements of the APF.

NCCTG has expressed particular concern about:

- The increasing importation of substances for use in extemporaneous compounding that are prohibited imports under Schedule 4 or 8 of the Customs (Prohibited Imports) Regulations, such as dexamphetamine and anabolic or androgenic substances;
- The lack of demonstrated justification for the therapeutic claims that are being made;
- The quality and safety of the compounded products; and

² The Professional Compounding Chemists of Australia (PCCA) lists the member pharmacies on their website (www.pccarx.com.au). The numbers in each jurisdiction are: ACT 2; NSW 36; Qld 18; SA 4; Vic 15; WA 7; NZ 1. None is listed for Tasmania or the NT. It is not known if this is all of those who are engaged in pharmacy compounding but it is likely to be the majority.

- The exploitation of provisions under the Therapeutic Goods Act 1989 that enable the traditional practice of pharmacy.

The concerns of NCCTG and the TGA in regard to extemporaneous compounding relate to the fact that the exemptions were never intended to cover such a wide range of products, e.g. active constituents with potent systemic effects for long term use. At the time of the drafting of the TG Act, the practice of extemporaneous compounding (dispensing and small scale batch preparation of well recognised products) was at a low level and was dwindling. It mostly related to dermal preparations for local effect, other than in hospitals where a much wider range of preparations was made, for obvious reasons. Comparison of the editions of the APF over that time shows the falling emphasis on non-proprietary formulae and decreasing emphasis of extemporaneous compounding. This has been mirrored in pharmacy student training. They spend much less time in this area as modern, evidence-based pharmaceutical practice has developed.

In relation to the import of certain of the active substances, attempts by the TGA to have these imports followed up have not led to what it regards as satisfactory outcomes. The importers have had State licences or permits to purchase, possess and either use or sell/supply the materials, and so the State health authorities have not been able to provide an effective check on these imports, even when the quantities have been surprisingly large.

There are only two regulatory groups with the capacity to control the present practices under the present (and likely foreseeable future) legislation. They are the Pharmacy Boards and the trans-Tasman successor to the TGA for medicines. Each will have different roles. At present the exemptions under the TG Act, even if they applied to natural persons, seem to stop well short of the point at which Pharmacy Boards can regulate effectively, so there is a gap even if the Boards act as effectively as they can under present arrangements. This gap seems to be mirrored in other jurisdictions, notably the US.

3.4 Australian standards and guidelines for extemporaneous dispensing

As outlined above, Victoria has undertaken more than any other jurisdiction in trying to regulate this area of practice, to ensure quality safety and efficacy of the products that are being prepared. It has prepared a policy statement which it has taken to COPRA for adoption by other Pharmacy Boards. Unfortunately, that process seemed to lead to a “lowest common denominator” approach being taken (nothing in the statement could go further than the jurisdiction with the weakest set of controls could apply).

One benefit from the process, however, was the upgrading of some of the provisions of the APF in regard to compounding, and the APF 19 (published February 2004) has a useful suite of principles and guidelines for non-sterile extemporaneous compounding that, if rigorously applied, would go some way to addressing the quality concerns. It also emphasises that a commercially available product should be used wherever possible, but this is not enforceable in any practical way.

The other relevant document in regard to compounding is the PSA’s Competency Standards. Functional area 5.2 of these standards deals with the preparation of

pharmaceutical products extemporaneously. While the elements, performance criteria and evidence guides included in the Competency Standards are appropriate, it is not clear that the pharmacists are likely to fully comprehend the implications of some aspects. For example, under 5.2 *Compound Pharmaceutical Products*, the first element is “*Consider relevant legislative and policy requirements*”. One of the Performance Criteria for this point is “*Understands specific codes and regulations that apply...*” and the Evidence Guide is “*Demonstrated understanding of relevant codes (eg the Australian Code of Good Manufacturing Practice for Medicinal Products)*”

In fact the ACGMP is a very complex document and it is doubtful that many pharmacists can interpret its requirements accurately, i.e. the problem is that pharmacists may not know what they don't know. This is critical when substances such as sex hormones are being manipulated on a regular basis: e.g. the need to control cross-contamination and exposure of the workers through appropriate ventilation and protective equipment. Persons interviewed in the course of this project who had been to these facilities did not report that the facilities were highly sophisticated in this regard.

Documents such as the APF and the PSA's Professional Practice Standards and Competency Standards are applied, in the main, through the Quality Care Pharmacy Program (QCPP). This is designed to ensure a quality approach in the pharmacies. But given the highly potent nature of the compounding that is occurring, that is not a sufficiently robust approach.

The Pharmacy Guild is seeking to review the QCPP Standards this year, but some informants indicated that it is unlikely that the PSA's professional standards will be part of this review, due to timing issues. In any case, it should be the Boards with the PSA (rather than the Guild) that set such standards, although the Guild is clearly a key stakeholder.

Even Pharmacy Boards usually do not have staff that have backgrounds in GMP and so they may not find it easy to critically assess these activities. To complicate matters, the competition reforms have removed the need to register premises in some jurisdictions, making assessment of these premises even more difficult.

In summary, there are Australian standards and guidelines that could ensure the quality of compounded preparations met very basic requirements, but the application of them to compounding pharmacies seems to be a hit-and-miss process with no rigour or certainty from a national perspective.

3.5 New Zealand

New Zealand has a special part of its Code of GMP that relates to compounding and dispensing (Part 3). This part also has an annex that relates to compounding of sterile preparations. It was published in 1995.

Part 3 apparently has no legal force but it is generally complied with. The Application section of the Code states:

“Part 3 applies to the preparation of a medicine for an individual person. Part 3 also applies to the small scale batch preparation and/or repacking of a medicine by a pharmacist in a pharmacy, for retail sale or dispensing from that pharmacy, where:

- i) *The size of the batch does not exceed:*
- *2.5 litres of an oral or topical liquid*
 - *2 kilograms of a cream, ointment or powder;*
 - *100 capsules, suppositories, or other single solid dose forms;*
 - *50 repackaged units.*

and

- ii) *The medicine is not required to be sterile;*

and

- iii) *A batch of the medicine is prepared not more than once a week, unless the previous batch has been used in that period.*

Repacking requires the same documentation as small scale compounding.

Any preparation of a larger size batches than those specified above or any size batches required to be sterile, other than for an individual person, should be done in compliance with Part 1 of the New Zealand Code [of GMP].”

At the commencement of this project this approach was commended as warranting careful thought as a way forward. However, consultations revealed that few people thought the application provision would be a workable and enforceable solution to the issue in the Australian context. First, it is noted that it has not prevented the opening of specialist compounding pharmacies in New Zealand. Second, given the scale of operation so some of the Australian pharmacies, and the number of unfilled prescriptions they have on hand, it would be impossible to discriminate between making a batch and making several dispensed items at once. Third, it is hard to see how one could readily assess compliance. Finally it may address the quality issue to some extent but does nothing to address efficacy and safety issue inherent in some of these preparations. It is not a comprehensive solution.

Nevertheless, specific standards for compounding modest quantities of relatively low risk products are required and will be discussed in section 4.2.2. In that section a quantity limit is proposed, but setting the quantity limit too low may mean that many pharmacies would need to fully comply with the ACGMP, which has inherent difficulties that may not be readily surmountable. The precise level of the cut-off needs to be determined after discussion with industry.

3.6 Overseas controls on extemporaneous compounding

3.6.1 The United Kingdom

Searching the UK Medicines and the National Health Service websites did not find any reference to the practice of compounding. It is known that the MCA used to issue special licenses to NHS hospitals in relation to certain aspects of manufacture in the past, but this appears to have ceased. No further effort was made in this regard as all the evidence points to the centre of this practice as being the US.

The Council of the Royal Pharmaceutical Society includes a section on extemporaneous preparation/compounding in its Code of Ethics, which was published in its Pharmaceutical Journal on 10 March 2001. The relevant section is provided in Box 1.

Box 1 Extract from the Code of Ethics of the Royal Pharmaceutical Society – specifications for extemporaneous preparation/compounding

21. Extemporaneous preparation/compounding

This service specification is not intended to cover the reconstitution of dry powders with water or other diluents.

The public is entitled to expect that products extemporaneously prepared in a pharmacy will be prepared accurately, suitable for use and meet the accepted standards for quality assurance.

Pharmacists wishing to be involved in extemporaneous preparation must ensure that they, and any other staff involved, are competent to undertake the tasks to be performed and that the requisite facilities and equipment are available.

(a) A product should only be extemporaneously prepared when there is no product with a marketing authorisation available and where the pharmacist is able to prepare the product in compliance with accepted standards.

(b) Equipment must be maintained in good order to ensure that performance is unimpaired.

(c) Pharmacists must be satisfied as to the safety and appropriateness of the formula for the product.

(d) Ingredients must be of acceptable pharmaceutical quality, all calculations and, where possible, measurements should be checked. Pharmacists must pay particular attention to substances which may be hazardous and require special handling techniques.

(e) The product must be labelled with the necessary particulars, including any special requirements for the safe handling or storage of the product, and an expiry date.

(f) Records must be kept for a minimum of two years but if possible for five years. The records must include the formula, the ingredients and the quantities used, their source, batch number and expiry date. Where the preparation is dispensed in response to a prescription the records must also include the patient's and prescription details and the date of dispensing. A record must be kept of personnel involved including the identity of the pharmacist taking overall responsibility.

3.6.2 The United States

The United States Pharmacopeia

The current United States Pharmacopeia (USP) 2004 First Supplement includes two key monographs in relation to pharmaceutical compounding, 795 relating to nonsterile preparations and 797 relating to sterile preparations. These are mandatory in that they are intended to be adopted by State Pharmacy Boards. There is a further advisory monograph (1075) entitled '*Good Compounding Practices*', which is for guidance only and is not intended to be mandated by the Boards.

The standards and guidance provided in the USP First Supplement are analogous to a mini-code of GMP (particularly in the case of sterile preparations) intended to be applied by the State Boards. They go much further than the compounding guidelines presently published in the APF and the relevant Competency Guidelines.

The National Association of Pharmacy Boards' Compounding Accreditation

The National Association of Pharmacy Boards (NAPB) is establishing a Pharmacy Compounding Accreditation Board (PCAB), a coalition of national pharmacy professional and regulatory organisations. This group is implementing an accreditation program for compounding pharmacies, with the aim of enhancing the quality of compounding practices and raising awareness of compounding.

A PCAB Standards Task Force has been created with the aim of setting standards for a voluntary site accreditation process for compounding pharmacies. The Task Force is preparing a quality compounding standards document, to be used as a foundation for an accreditation program for compounding pharmacies. Other components include the application and accreditation processes as well as marketing and education programs. Trained surveyors will be appointed for the accreditation process.

The standards will be based on the USP monographs and the USP is represented on the NAPB and the Task Force. It is at least possible that a number of US States will mandate the PCAB standards and accreditation, although it is early days yet. Furthermore, it is understood that insurance companies may not cover activities conducted outside the guidelines and standards.

Actions by the Federal Drug Administration

The FDA, like the TGA, relies, in the main, on the activities of the State Pharmacy Boards to control compounding activities in pharmacies. Unlike Australia, however, this is regulatory enforcement discretion; technically all compounded medicines are unapproved under the federal legislation and the activities only occur because of the exercise of enforcement discretion by FDA officials.

Where product quality problems have been identified, or where complaints of serious adverse drug reactions have been received, the FDA may step in and, in concert with the relevant State officials, conduct inspections and take further action as required. On the whole, however, the day-to-day regulation of pharmacy compounding is left to the States.

In 1992 the FDA produced a compliance policy guidance (CPG) documentⁱ that listed factors that FDA considered in determining whether a practice was compounding or manufacturing, but a CPG is not a legislative instrument.

In 1997 the FDAMA addressed pharmacy compounding in section 503A. This provided a law specifying certain conditions under which compounded drugs could be exempt from new drug requirements, good manufacturing requirements, and adequate directions for use in labelling requirements, as set forth in the Federal Food Drug and Cosmetic Act. It also restricted certain types of advertising and promotion of compounded preparations; it was this that led to the legal challenge in the US Supreme Court, which eventually saw the whole section struck down in 2002.

Since then, a revised CPG on pharmacy compounding was issued in May 2002. FDA has received comments on the revised CPG and is considering these comments. Currently, FDA uses the factors delineated in the May 2002 CPG in determining whether its exercise of enforcement discretion with regard to compounded drug products is warranted.

Primary public policy concerns to the FDA include (1) the risk to public health when large amounts of drugs have not gone through FDA's drug approval process and are prepared without rigorous application of GMP, and (2) the issue of maintaining a level playing field between regulated manufacturers and pharmacy compounders.

The volume of compounding conducted by a pharmacy is one important factor (among others) that FDA considers in determining whether that firm is engaged in extemporaneous pharmacy compounding or is operating in a manner more consistent with that of a drug manufacturer.

4 A risk based approach to legislative exemptions for extemporaneous compounding

As discussed already, when the TG Act was drafted the level of compounding was low, at least in community pharmacy. The products were generally topical for local effect, or time-honoured formulae for the relief of symptoms of self limiting diseases, eg coughs and colds. The risk to public health was very low.

However, the development of a system of compounding franchises based on the broadly drafted exemptions has raised the level of public health risk considerably. The use of the exemption to provide a marketing advantage for a wide range of products with potent systemic effects and that are used over a long period of time, without assessment of safety, means a much higher level of public health risk. Furthermore, the process is being used to ‘work around’ the controls exerted by other means. For example, if someone tries to access dehydroepiandrosterone (DHEA) by the Special Access Scheme (SAS) they are almost certain to be refused. If they go to a compounding pharmacy, they will have no difficulty in accessing a DHEA preparation. In the case of DHEA this is more of an annoying inconsistency than a major risk to health, but in the case of e.g. oral clioquinol or topical coumarin, it is a much more serious matter.

Consultations suggested that Pharmacy Boards are universally of the view that the **traditional extemporaneous compounding activity of pharmacists should not be taken away**. It is seen as a necessary part of pharmacy practice. Nevertheless, there is recognition that preparations that have significant systemic effects and/or are used long term, or where the preparation has to be sterile, the level of risk warranted some further level of regulation, i.e. that the present total exemptions from the TG Act go too far.

The means of controlling the activities of compounding pharmacists are, to some extent, matters for judgement – how far does one go? The US is also having difficulty in getting the balance right. For that reason the draft report offers Recommendations, where the action seems to be necessary on the basis of the firm evidence, but these alone will not address all the concerns. Therefore, the draft report also offers some further ideas for *Consideration*. These tend to be more ground-breaking in their nature, and may be either discarded or included in the final report as recommendations if further debate suggests they may be viable options. Alternatively the debate about them may stimulate thinking in other new directions.

4.1 What are the dimensions of risk from extemporaneous compounding

In essence there are four dimensions of risk to public health that could be used to improve the regulatory scheme and narrow the exemptions to reflect their original intent.

A. Active pharmaceutical ingredients as a source of risk

Examples of substances that pose a high level of risk include:

1. Substances that have been refused registration or removed from the ARTG on ground of safety, eg oral clioquinol, coumarin.
2. Poor quality starting materials.
3. Extremely potent substances (see C below).

B. Route of administration

Risk depends upon the type of product that is being manufactured, for example (in order of ascending risk):

1. Dermal or mucous membranes for local effect – intended for unbroken areas.
3. Topical or mucous membranes or oral – systemic effect, or broken skin.
4. Ophthalmic.
5. Injectable.

The route, and consideration of whether the effect is local or systemic, could be used to establish the degree of regulation of the compounding process³.

C. High levels of pharmaceutical technology or equipment required

Examples of products that require highly specialised equipment and might be grounds for high level GMP compliance include:

1. Sterile preparations, especially aseptically prepared injections.
2. Metered dose aerosols, dry powders for inhalation.
3. Low dose solid dose forms – less than 2 mg⁴ (or 2%) of a potent (S3, S4, S8 or S9) substance but not those exempt from uniformity testing in the TGO-56 (i.e. medicines that are homoeopathic, or herbals not included in the SUSDP Schedules; or are unscheduled multivitamins and/or minerals).
4. Modified release preparations.

D. A limit on quantity

A limit on quantity provides a limit to the number of persons who could be exposed to a particular faulty batch or series of batches that went undetected.

³ It is worth noting that the USP Monograph “*Good Compounding Practices*” (1075) outlines a nine level scale based mainly on route of administration.

⁴ The European Pharmacopoeia (and hence the British Pharmacopoeia) uses this cut-off as the determining requirement for the most stringent uniformity of content testing.

4.2 Utilising these risk approaches in improving the specificity of the exemptions

4.2.1 Exemption from registration of goods

The greater control of substances could be achieved by excluding some substances from the exempt status in Appendices 5 and 5A of the TG Regulations (or the eventual trans-Tasman equivalent). Substances that have been refused registration or removed from the ARTG (or the New Zealand equivalent) are an obvious starting point. The US FDA has a similar provision.

Whether other substances should be excluded is a matter of judgement. It should be borne in mind that removal from the exemption in Schedule 5 does not mean the substances are banned altogether. The medical practitioner would, however, have to apply under the Special Access Scheme to gain access.

On the other hand, TGA does not want to be handling hundreds of SAS applications unnecessarily. Furthermore, there is a real demand for some of these products (the progesterone creams for women for example) and if these were suddenly unavailable, it could be quite disruptive both to the users and the smooth functioning of the TGA.

In summary the alternatives are to exclude from the exemption from registration:

1. a short list of substances of particular safety concerns; or
2. a quite long list, eg all the substances in S4 and S8; or
3. a more specific list in areas where the compounders are known to be highly active, eg preparations for impotence, sex hormones, products containing DHEA, etc.

The second alternative increases the administrative burden on the SAS process, and would catch e.g. a dermatologist writing a prescription to dilute a proprietary steroid cream. The net is too wide to be readily manageable.

The third alternative would address the major areas of concern, but it is not risk-based. It is soundly based given the potent nature of the active constituents in the products, but there would be many just-as-risky substances that were not regulated, and there is not a lot of first hand evidence of harm (but this not surprising as surveillance is not strong).

The first alternative will be regarded by some as too lax and inconsistent with the overall regulatory scheme. It is, however, a place to start and has the virtue of being workable. Other reforms to the GMP exemption (see below) may address key remaining concerns if the first option is taken.

There may be other regulatory alternatives that can be applied to these preparations without restricting access to a wide range of substances. At present it is clear that the users think these preparations are as safe (and often safer) than a commercial product. The reverse may be the case, and so it may be appropriate to require the inclusion of a warning label on any extemporaneous preparation that contains an S4 or S8 substance along the lines of “*This preparation has not been assessed by [the regulator] for safety or efficacy*”.

If that is too broad it might only be applied to preparations containing certain S4 and S8 substances, eg including hormones. This list could be quite long, without causing the disruption that requirement for full registration would cause.

Recommendation:

- 1. In the first instance, a relatively small number of substances be excluded from the exemptions provided under Schedule 5 and 5A of the Therapeutic Goods Regulations, including substances that have been removed from or refused inclusion on the ARTG on safety grounds as well as other substances that have restricted access, such as those in Schedule 9 or Appendix C of the SUSDP.**

For consideration:

- a. Consideration be given to the inclusion of a warning label on extemporaneous preparations containing substances in Schedules 2, 3, 4 or 8 of the SUSDP, to the effect of the preparation not having been assessed by the regulator for safety or efficacy.*

4.2.2 Exemption from Part 3.3 of the Therapeutic Goods Act - GMP

As outlined in section 3.4, there are standards and guidelines that apply to pharmacists, but their application and enforcement is piecemeal. Only the Pharmacy Boards have the power to do so and they usually do not have a field workforce that is large enough or specialised enough to assess compounding activities adequately. Furthermore, Boards tend to be complaint-driven, particularly now premises are not registered in every jurisdiction⁵.

However, there needs to be a means of ensuring that extemporaneous compounding on any scale is undertaken in an appropriate manner. There are two issues to be addressed: what is to be included in any GMP exemptions and the level of regulation of them. Exemption from full compliance with the ACGMP need not mean complete exemption from responsibility to ensure appropriate standards of preparation.

A cut-off on a quantity as the *primary* regulatory strategy is hard to argue for as the best basis for concessions to quality and safety standards⁶. Everything needs to be manufactured in accordance with good manufacturing principles, whether it is a small quantity of a topical product for local effect, or an injectable preparation. The extent of the requirement is the key variable.

The exemption provided when the TG Act was written was, in hindsight, too open-ended. An obvious approach is to provide a conditional exemption for most extemporaneous preparations when prepared in conformity with specifically written Standards for Pharmacy Compounding. These Compounding Standards could then

⁵ Registration of premises was removed as a result of a competition review. Surveillance of pharmacies is handicapped by the removal of the requirement to register premises.

⁶ There is an argument about minimising the overall level of public exposure through controls on quantity. It is discussed later in this report.

have sections applying requirements that are risk based – a topical cream for local effect having modest requirements, and a preparation that has systemic effects having additional requirements, through to an aseptic preparation requiring a fully validated and monitored facility and elaborate process requirements. The obvious model in the case of sterile injectables is the USP. Ideally, publications such as the APF and other PSA Standards would be consistent with the requirements of the Compounding Standards. One forerunner of such a document is the (now ten year old) “*Standards for the Preparation of Pharmaceuticals in Australian Hospital Pharmacy Departments*”ⁱⁱ.

Certification of facilities need not (and probably should not) be done by the TGA. There are other regulating bodies, not least the Pharmacy Boards. A good alternative may be an arrangement parallel to that being set up by the NAPB in the US. Initially the task would be to prepare the Standards themselves. Both the US and Canada are undertaking similar activity and it would be relatively easy to modify their requirements to fit Australian circumstances as well as build on the existing Australian models (ii). Nevertheless, drafting it would be a big task that would need to be undertaken collaboratively by the TGA⁷ with at least the Pharmacy Guild, PSA (including representation of the APF Editorial Committee) and SHPA.

Facilities in which only e.g. topical preparations for local effect and standard formulary non-sterile preparations were made, could simply self-certify. Others may require inspection and certification by an independent, skilled auditor.

It is emphasised that this proposal does not use quantity as a determinant of whether something is required to conform to Compounding Standards or not. The requirements proposed are based solely on the level of risk inherent in the product. Using a quantity cut-off is superficially attractive, but is hard to administer and is limited by the logic – all products should be of the same quality as far as possible, although it has to be said, the less there is, the less the public is exposed.

The requirements for all sterile injectable preparations would need to be stringent, along the lines of those in the USPⁱⁱⁱ.

Exclusions from the exemption arrangements

Some products are so technically difficult to make that they should not be attempted in a pharmacy that cannot fully comply with the ACGMP. It is proposed therefore that these products not be included in the extemporaneous exemption at all. Such preparations would include, for example:

1. Aseptically prepared sterile preparations, other than those for use within 24 hours (or for such a period as specifically generated chemical and microbiological stability data supports, but in any case no longer than a few days).
2. Any multidose injectable preparation.
3. Metered dose aerosols, dry powder inhalers.
4. Transdermal delivery systems (‘patches’).

⁷ TGA should take the lead on standard setting given the level of expertise that they have, which is greater than any other group in Australia.

5. Oral solid dosage forms with a dose per unit less than, say, 2 mg⁴ of at least those substances included in Schedules 2, 3, 4 or 8 in any quantity.
6. Modified release preparations.

A limit on quantity

As outlined in section 3, there is little enthusiasm for the approach of setting quantity limits for compounding. Reasons for this include: pharmacists have been compounding all of history and the profession wants to see its roots retained; *all* preparations should be manufactured to an appropriate standard and a quantity cut-off does not ensure this; and it will be very difficult for regulators to demonstrate that any quantity threshold is exceeded.

Nevertheless, in the US some compounding pharmacies rival small manufacturers. This suggests that there does need to be upper limits on the size to which these businesses should be allowed to grow without full GMP compliance, both because the public exposure becomes so great (and hence the risk) and because the ‘playing field’ between manufacturers and compounders should be as level as possible.

Setting the quantity limit too low would mean that many pharmacies will have to fully comply with ACGMP, which has a number of problems, including the workforce required to audit them all, as well as the inappropriateness of the ACGMP for one-off preparations. On the other hand, the pharmacists should not be able to compete unfairly with the TGA-regulated medicines industry.

Given the difficulties with assessment workload and enforcement, and given that this is **not** the primary regulatory approach, the limit above which activities become licensable could be set relatively generously. A scheme for this is set out in Appendix 3 *as an example* of how it might be applied. Clearly the final arrangements would be arrived at after discussion with industry.

Recommendations:

- 2. The exemption from Schedule 8 of the Therapeutic Goods Regulations for pharmacists be redrafted and made conditional upon preparation in premises that are certified as conforming with the relevant level of a professional standards for pharmaceutical compounding.**
- 3. The proposed Standards for Pharmaceutical Compounding be drafted under the auspices of the NCCTG, in partnership with the State and Territory Pharmacy Boards and the TGA, and with input from the other major professional pharmaceutical bodies.**
- 4. Certain technically difficult or high-risk preparations *not* be exempted from the full requirements for licensing and GMP inspection.**
- 5. There be an upper limit to the number of units that can be prepared in a month before the business become licensable under Part 3.3 of the *Therapeutic Goods Act 1989*.**

Drafting the Standards for Pharmacy Compounding

Drafting the new Compounding Standards could be quite a large task and require considerable consultation. It is likely that the TGA would have difficulty in doing this internally given the workload of the relevant personnel, particularly in the run up to the commissioning of the trans-Tasman arrangements. It is suggested that the task of developing the initial draft Compounding Standards could be contracted out. This would require funding but it is a key task that must be completed in a timely manner.

The content of the Compounding Standards and related guidelines would need to cover the wide range of types of preparation. It may therefore be in parts, at least divided into sterile and non-sterile products. Possibly very low risk products such as dermal preparations for *local* effect, and non-sterile preparations made in accordance with official formulae (i.e. of the various editions of the APF, BP etc) could be excluded altogether or subject to self-certification.

The Compounding Standards would necessarily be principle-based, but given the nature of the activities covered by them, they should be very explicit in what they require, or come with extensive guidance on the specifics of how to comply.

The relevant sections of the USP, the soon to be published NAPB document, the 1993 Australian hospital pharmacy guidelines, the APF and the current ACGMP would all be key starting materials in the Code's development, as well as any documents that industry can provide.

Proprietary products that require re-constitution or other manipulation, when used in accordance with their registered use should be exempt.

Specific wording of the exemption

The wording of a new exemption to clause 6 of Schedule 5 of the TG Regulations could be along the lines of:

6(a) Except as provided for under 6(b), medicines (other than medicines used for gene therapy) that are dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person are exempt when preparation is conducted in a premises certified as meeting the requirements of the Code of Good Manufacturing Practice for Compounding for that class of preparation.

6(b) This exemption does not apply to:

- i. Aseptically prepared sterile preparations, other than
 - * those for use within 24 hours, or
 - * total parenteral nutrition solutions prepared in a hospital for use by that hospital.
- ii. Multi-dose injectable preparations.
- iii. Metered dose aerosols, dry powder inhalers.
- iv. Transdermal delivery systems ('patches').
- v. Solid dosage forms with a dose per unit less than 2 mg of a substance included in Schedules 3, 4 or 8 in any amount or concentration.
- vi. Modified release preparations.

Who would undertake the certification?

The certification of compliance with the Compounding Standards would best be undertaken by the body that has responsibility for overseeing pharmacies now, i.e. the Pharmacy Board in each jurisdiction. Pharmacy Boards could undertake this collectively through COPRA, or by one State Board sponsoring the system for the nation. Each Board attempting it on its own may not be practical. If this initiative is not willingly taken up by the Boards, it may fall back to the TGA to undertake it. Either way, it should be undertaken on a cost-recovery basis.

Other issues

Starting material standards

One concern that was raised during the consultations was the apparent lack of standardised raw materials. They often did not appear to be labelled BP, USP, etc, and the source may be from a supplier that was possibly not a quality producer. Identity and purity checks did not seem to be being carried out. Clearly, the purity of raw materials is critical and the Compounding Standards would need to spell out very clearly the need for starting materials to be certified as complying with pharmacopoeial or other appropriate standards, or the pharmacist would have to undertake identity, purity and such other tests as were appropriate for that substance.

Occupational health and safety and environmental controls

While gloves and masks were reported to be worn, the controls described to prevent environmental contamination and occupational health and safety problems could be insufficient, given the nature of the materials being handled repeatedly. This is a matter that would need to be referred to in the Standards, even though the occupational health and safety legislation is administered by other agencies, not Pharmacy Boards.

5 The exemptions for hospital pharmacies

The activities of public hospitals are under a different set of exemptions to those of community pharmacists for both sets of exemptions – from GMP and from registration. The exemptions were drafted when the controls were focussed on Australia and took into account factors such as Constitutional reach, which will differ once the regulatory mechanism becomes trans-Tasman. An arrangement that takes the future reach of the legislation and clinical requirements of Australian and New Zealand health services needs to be devised.

It needs to be emphasised, however, that there is a genuine clinical need for hospital pharmacy manufacture, and risks must be balanced against the benefit of having access to the extemporaneously compounded medicines. Concerns about present hospital pharmacy manufacturing did not underlie the commissioning of this project, but it is timely to think through whether there are changes that ought to be made. This should follow the arrangements for pharmacy compounding but until these are agreed then there is little point in considering the hospital pharmacy exemption issues further.

6 Advertising

6.1 Advertising to the public

The advertising to the public of exempt goods that contain medicines in Schedule 4 or 8 of the SUSDP is prohibited by the TG Regulations now, only because of the S4 or S8 substances, not because they are unevaluated preparations. Otherwise compounded preparations can be advertised. In practice, the advertisements are often for a service that requires the use of these preparations, but not for the preparation itself.

Advertising of services that use substances in S4 of the SUSDP is currently allowed, as the definition of advertisement in the TG Act is not wide enough to cover such advertisements. In the past the view has been that the advertising of services utilising S4 medicines lies beyond the intended scope of therapeutic goods legislation. This has been regarded as the province of pharmacy and medical boards, but they have generally been unable to address the concerns about advertising of some services. For that reason, the view has changed.

The proposed trans-Tasman Advertising Code has a much wider definition of advertisement. The current draft wording is:

Advertisement: means any communication which promotes or discourages the use, sale or supply of products (whether or not in conjunction with the supply of services, and whether or not the communication identifies particular products or services).

The draft outlines, in relation to this definition:

The definition of “advertisement”, in relation to therapeutic products, is broad and includes any form of communication that either directly or indirectly promotes or discourages the use, sale or supply of a therapeutic product. For example, an advertisement about a health service or treatment program that includes a reference to the use, sale or supply of a medicine or medical device is also an advertisement for that medicine or medical device. However, an advertisement for a service, which only incidentally references a type of therapeutic product, is not covered by this definition (e.g. laser hair clinic).

Bona fide news, bona fide editorial, bona fide public interest programs and bona fide entertainment programs, or bona fide education, research and professional advice are not covered by the Code.

There is, therefore, the opportunity to regulate the advertisement of services that use compounded preparations if it is considered to be in the public interest to do so.

One approach would be to require advertisements for services relying on the use of goods that are not registered goods to carry a warning that the service entails that use of preparations the safety and efficacy of which have not been demonstrated. It would be argued by the advertisers, however, that the use of unregistered goods could not be anticipated until the examination of the patient, etc.

Thus, this alternative is not easy or certain. Discussion with some NCCTG members suggest that they would find such an uncertain measure hard to support.

6.2 Advertising to professionals

Traditionally all advertising directed at health professionals is exempt from regulation but this will now be picked up under the trans-Tasman Advertising Code. One key aspect of the pharmacy compounding process is advertising directed at medical practitioners to generate prescribing. Under the Code as proposed, this would be permitted subject to certain requirements. These are summarised in Appendix 4, and the full trans-Tasman Code can be obtained from <http://www.tga.gov.au/tta/advtt.htm>.

It is very difficult to see why advertising of extemporaneously compounded preparations to health practitioners is necessary. Removal of this practice would go some way to limit the level of prescribing.

Nevertheless, advertising is a positive social good, in advising both prescribers and the public of new products and services that, in the case of medicines, provide relief from illness and disease. The decision to further limit advertising of extemporaneous preparations to professionals should not be taken lightly, even though there seems to be no justification for such advertising.

An intermediate position between doing nothing and prohibiting advertising of compounded preparations to health professionals altogether, which would be fiercely resisted, is to require a warning in advertising material directed at health professionals, that the preparations offered have not been assessed by the regulator for safety and efficacy and informed consent should/must be obtained before they are prescribed. This would remind prescribers of common law duties and ensure they were aware that the preparations have not been assessed in the way a registered product has been.

The measure would be enforced by the Code Council (or its successor) as at present, but would need to be underpinned by legislative power if the usual process failed, given that it is a pharmacist, not a pharmaceutical company that would be the target of any sanctions.

For consideration:

- b. Consideration be given to advertisements directed at health professionals for extemporaneously compounded medicines being required to carry a warning that the preparation has not been assessed for safety and efficacy, and that the prescriber is strongly advised to obtain informed consent before prescribing the preparation.*

7 The application of any new controls beyond pharmacists

The TG Act provides essentially the same exemptions for medical practitioners as it does for pharmacists. It is clear that if the exemption for pharmacists alone was tightened, it would not be very long before medical practitioners or dentists or anyone else that was exempt would be employed to supervise the activity. Therefore, it is essential that the controls apply to uniformly across health professionals, not just pharmacists.

8 Veterinary products

The regulation of veterinary medicines is not under the control of the TG Act, but it is apparent that compounding of veterinary medicines is also occurring to get around the controls applied by the relevant regulatory scheme. This issue has not been considered but is mentioned for completeness. The TGA may wish to advise the Australian Pesticides and Veterinary Medicines Agency of the practice so that it can consider what, if any, action is required.

Appendix 1 – Organisations consulted during the project

Date	Organisation
19 July	Secretary NCCTG
19 July	Surveillance Section, TGA
19 July	Non-Prescription Medicines Branch, TGA
19 July	Drug Safety and Evaluation Branch, TGA
19 July	Department of Human Services, Victoria ☎
22 July	Medsafe New Zealand
23 July	Treaties and Monitoring section TGA
23 July	Legal section TGA
13 Aug	ACT Health; ACT Pharmacy Board.
16 Aug	Pharmaceutical Services, NSW Health
16 Aug	NSW Pharmacy Board
17 Aug	Queensland Health Department
17 Aug	Queensland Pharmacy Board
23 Aug	Pharmaceutical Services, Tasmanian Department Health and Human Services
23 Aug	Tasmanian Pharmacy Board
24 Aug	Department of Human Services, Victoria
24 Aug	Pharmacy Board of Victoria
1 Sept	Pharmacy Guild of Australia
2 Sept	Pharmaceutical Society of Australia
2 Sept	Surveillance Section, TGA
5 Sept	Society of Hospital Pharmacists of Australia
6 Sept	Pharmaceutical Services, WA Department of Health
6 Sept	Pharmaceutical Council of Western Australia
6 Sept	Chief Pharmacist, Princess Margaret Hospital WA
7 Sept	Pharmaceutical Services, SA Department Human Services
7 Sept	SA Pharmacy Board
8 Sept	United States Pharmacopeia Commission ☎
26 Sept	Chair, AMA Therapeutics Committee ☎
27 Sept	Professional Compounding Chemists of Australia
28 Sept	Medical Advisor, TGA
1 Oct	US Federal Drug Administration ☎

☎ Denotes telephone interview.

Appendix 2 – Exemptions provided in the Schedules to the regulations relevant to this project.

The relevant exemptions are as follows:

Exemption from inclusion of the goods on the ARTG

First exemption: Therapeutic Goods Regulations, Schedule 5 item 6:

- 6 Medicines (other than medicines used for gene therapy) that are dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person.

Second exemption – for hospitals and institutions - Therapeutic Goods Regulations Schedule 5A, item 5:

Item	Therapeutic goods	Conditions
5	<p>Therapeutic goods, other than goods referred to in item 3, that are:</p> <p>(a) manufactured by a person:</p> <p>(i) under a contract between the person and a private hospital; and</p> <p>(ii) in accordance with a formulation specified by the private hospital; and</p> <p>(iii) for use by, or in connection with, a patient of the private hospital; or</p> <p>(b) manufactured by a person:</p> <p>(i) under a contract between the person and a public hospital in a State or Territory; and</p> <p>(ii) in accordance with a formulation specified by the public hospital; and</p> <p>(iii) for use by, or in connection with, a patient of a public hospital in the same State or Territory; or</p> <p>(c) manufactured by a person:</p> <p>(i) under a contract between the person and a public institution; and</p> <p>(ii) in accordance with a formulation specified by the public institution; and</p> <p>(iii) for use by, or in connection with, a patient of the public institution</p>	<p>(a) there are no listed goods or registered goods that, in all relevant respects, are substantially similar to the goods; and</p> <p>(b) the person:</p> <p>(i) manufactures the goods at premises in Australia; and</p> <p>(ii) holds a licence, required by the Act, that authorises the manufacture, or a step in the manufacture, of the goods at those premises; and</p> <p>(c) the person notifies the Secretary, in accordance with a form approved by the Secretary and within 15 days of the end of a quarter, of:</p> <p>(i) the goods manufactured under the contract during that quarter; and</p> <p>(ii) the private hospital, public hospital or public institution that entered the contract</p>

Exemption from Schedule 8, ie persons exempt from the operation of Part 3.3 of the Act

Part 3.3 of the Act relates to the requirement to comply with (in particular in this case) the Code of Good Manufacturing Practice.

Schedule 8 is made pursuant to regulation 18 of the Therapeutic Goods Regulations.

Schedule 8, items 2 – 4 state:

Item	Persons	Matter in relation to which person exempted
2	pharmacists	<p>the manufacture of therapeutic goods produced by the pharmacist:</p> <p>(a) in a pharmacy where the pharmacist practices and the pharmacy is open to the public; or</p> <p>(b) on the premises of a dispensary conducted by a Friendly Society; or</p> <p>(c) on the premises of a private hospital;</p> <p>for supply (other than by wholesale) on or from those premises</p>
3	biomedical engineers, radiochemists and pharmacists in public hospitals	<p>the manufacture of therapeutic goods by the person when employed by a public hospital or a public institution and produced by that person for supply in hospitals or public institutions in the same State or Territory</p>
4	herbalists, nutritionists, naturopaths, practitioners of traditional Chinese medicine or homoeopathic practitioners engaged in the manufacture of any herbal, homoeopathic or nutritional supplement preparation	<p>where the preparation is for use in the course of his or her business and:</p> <p>(a) the preparations are manufactured on premises that the person carrying on the business occupies and that he or she is able to close so as to exclude the public; and</p> <p>(b) the person carrying on the business:</p> <p>(i) supplies the preparation for administration to a particular person after consulting with that person; and</p> <p>(ii) uses his or her own judgment as to the treatment required</p>

Appendix 3 A scheme for limiting the overall level of production at a compounding pharmacy before full compliance with Part 3.3 of the *Therapeutic Goods Act* is required.

In order to ensure that the scale of exempt manufacture of compounded preparations does not become so great that the public health risk is substantial, limits are proposed on the number of doses that can be prepared without application of the full ACGMP.

The doses can be calculated by defining what a typical dosage unit will be, and then setting a limit for the number of doses that can be made in a specific time period, e.g. on month. A possible scheme is given in the Table following:

Product type	Unit	Unit measure
Solid dose form	1	each
Cream, ointment, topical liquid	2.5	gram
oral liquid	10	mL
eye or nose drops/spray	0.1	mL
injection - single use	1	each

It is proposed that a pharmacy, other than a public hospital pharmacy, that prepares more than a certain number of units per month, measured as outlined below, be required to fully comply with the provisions of Part 3.3 of the TG Act, i.e. the business needs to apply for licensing and fully comply with the ACGMP. The number of units defined could be in the range of 5,000 to 20,000 units of production per month. The lower level is around that for New Zealand now (see below). The upper level represents quite a large throughput of compounded preparations. The chosen level is likely to lie somewhere within this range.

The first month in which the defined level is exceeded is the sentinel month. If the sentinel month exceeds this amount by more than e.g. 10% or if any month in the succeeding six months exceeds the specified number of units, then the business ceases to be exempt from ACGMP. It remains licensable so long as in any month in 12 months exceeds the specified number of units.

A separate much smaller number of units should be specified for sterile products.

Supply within or to an acute general hospital might be exempt for the purpose of this arrangement⁸, so that hospital pharmacy supplies are not compromised. It is not, in any case, the source of the problem and the hospital itself should exercise duty of care and/or due diligence. It is in the position to be able to make its own risk assessment.

⁸ Perhaps the exemption should apply only when there is a written acknowledgement between the hospital and the pharmacy, when ownership is separate, indicating that the hospital has taken steps to ensure the quality of the preparations it receives from the pharmacy that supplies it.

The New Zealand limits, if converted to units by the above table, equal around 1,150 units. The calculation is given in the Table below.

Product type	Unit	Unit measure	NZ Amounts	Total units
Solid dose form	1	each	100	100
Cream, ointment, topical liquid etc	2.5	gram	2000G	800
Oral liquid	10	mL	2500mL	250
Total units				1150

For consideration:

- c. Consider whether the scheme proposed in Appendix 3 will work best if the cut-off is set high or low? What should the limit be, given the other controls that are proposed in this paper?*

Appendix 4 Key Sections of the Trans-Tasman Advertising Code relevant to Compounded Preparations

trans-Tasman Advertising Code – page 7, Section A3.2: Application of the Code to specific types of advertisements

Unbranded advertising

An unbranded advertisement promotes the use or supply of product by inviting the consumer to seek further information about symptoms or conditions and their treatment or management while not referring overtly to any particular branded product. Unbranded advertisements must comply with Advertising Requirements 1, 3, 4, 5, 6 and 8 of the Code.

[Explanatory note] A typical example of an unbranded advertisement:

"Did you know that there is a new product available for controlling {medical condition}? If you are suffering from {symptoms / conditions} ask your medical practitioner about appropriate treatment options."

Generic advertising

A generic advertisement promotes the benefits of a particular category of therapeutic products, substance, ingredient or medical device component and is not related to any particular branded product. Generic advertisements must comply with Advertising Requirements 1, 3, 4, 5, 6 and 8 of the Code.

[Explanatory note] A typical example of a generic advertisement:

"Have you considered the benefits of {substance}. Recent research has shown that {substance} in combination with exercise reduces oxidative stress and blood pressure in older adults. Call (phone number) for more information on products which contain this substance."

Note: the requirements 1, 3, 4, 5, 6 and 8 of the TT Code are:

- 1 Advertisements must not encourage, or be likely to encourage, inappropriate or excessive use.
- 3 Advertisements must contain the mandatory information to ensure responsible use.
- 4 Advertisements must contain truthful and balanced representations and claims that are valid and have been substantiated, and:
 - [a) and b) not relevant]
 - c) for exempt therapeutic products: must be compliant with the Australia New Zealand Therapeutic Products Advertising Code.

Advertisements must not directly nor by implication, omission, ambiguity or comparison mislead or deceive, or be likely to mislead or deceive. Claims and representations made in advertisements must be truthful and have been substantiated.
- 5 Advertisements must not unduly glamorize products or services.

- 6 Advertisements may include reference to sponsorship of any government agency, hospital or other facility providing healthcare services, provided that sponsorship is explicitly acknowledged and cannot be misconstrued as an endorsement of a product.
- Advertisements may contain or imply an endorsement by individual, or individual groups of, healthcare practitioners in their professional capacity, bodies or associations representing the interests of the health of consumers, conducting or funding medical research or representing health practitioners, provided that the endorsement does not in any way imply endorsement by any government agency, hospital or other facility providing healthcare services. However, such endorsements must have prior consent from the endorser, be authenticated and the advertisement must contain, prominently displayed, the name of the endorser and acknowledgement of any valuable consideration.
- 7 Testimonials in advertisements, where not prohibited by law, must comply with the Code, be authenticated, genuine, current, typical and acknowledge any valuable consideration.
- 8 Advertisements directed to consumers must not refer directly or by implication to serious diseases, conditions, ailments or defects without approval from the Trans Tasman Therapeutic Products Agency. [Note this requirement does not apply to advertising to health professionals.]

trans-Tasman Advertising Code – page 35, Section B3: Advertising to health care Practitioners – additional requirement:

Requirement 9 (medicines)

All communications made by company representatives must comply with the Code. Where the product being advertised is a finished product, therapeutic claims for unlicensed products and unapproved indications must not be made, unless the product is exempt from product licensing. Whenever a therapeutic claim is made for a product for which the sponsor is required to hold a product licence, a company representative must offer the approved PI, or other data used by the sponsor as the basis for obtaining the product licence for the product.

Whenever a therapeutic claim is made for:

- an active ingredient that may be used to manufacture of therapeutic products; or
- a product which is exempt from product licensing;

the data used by the supplier to verify the claim must be offered by the company representative.

Advertisements directed to healthcare practitioners for extemporaneously compounded therapeutic products (as finished goods which are exempt from product licensing) are required to comply with the Code.

[Explanatory note] Active ingredients are exempt from product licensing but may be advertised to healthcare practitioners to be used in extemporaneous compounding of finished products. Any factual new information on the benefits of a particular active ingredient can be provided as educational material or bona fide research, which is exempt from the Code.

References

- i Federal Drug Administration. May 2002, Compliance Policy Guide Number 460.200 – Pharmacy compounding. (see http://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf). Note this was originally published in 1992 and a revised version was republished under the above reference number in 2002.
- ii National Coordinating Committee for Therapeutic Goods. 1993. *Standards for the Preparation of Pharmaceuticals in Australian Hospital Pharmacy Departments*. Published in the Australian Journal of Hospital Pharmacy, Vol 24, No 2, 1994.
- iii United States Pharmacopoeia. 2004. First Supplement (2004, monograph 797).