Options for reform of the regulatory framework for pharmacy compounding

Submission by APHS in response to the Consultation Regulation Impact Statement relating to Options for reform of the regulatory framework for pharmacy compounding.

APHS Pharmacy Group

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APHS Pharmacy welcomes the opportunity to provide this submission in response to the Consultation Regulation Impact Statement (RIS) relating to Options for reform of the regulatory framework for pharmacy compounding.

About APHS

The APHS Pharmacy Group operates in Queensland, New South Wales, Victoria, South Australia, Western Australia and, the Australian Capital Territory. APHS pharmacies specialise in the provision of pharmaceutical care to inpatients of private, public and day treatment hospitals. The majority of our pharmacies provide extemporaneous compounding of medicines, particularly the preparation and dispensing of chemotherapy items.

APHS Pharmacy supports the introduction of a balanced, risk-based regulatory framework for pharmacy compounding. This framework contributes to the quality of medicines compounded and dispensed by pharmacies, while enabling the continued capacity of pharmacies to provide medicines in a safe, timely, cost-effective, and sustainable manner.

Summary of observations and recommendations in relation to the RIS

1. APHS supports regulation of compounding aligned with the level of patient risk associated with the use of individual compounded preparations. Any framework used to delineate the level of or type of regulation should be based on specific factors that contribute to the risk, namely the characteristics of the ingredients, complexity of the process, and the number of individuals potentially exposed.

2. Greater clarity and differentiation are required regarding the concepts and definitions used in the RIS if they are to be the basis of determining the application of differing levels of regulation.

3. The regulation of pharmacists’ professional practice and of pharmacy facilities should primarily be the responsibility of the Pharmacy Board of Australia (PBA) in conjunction with state and territory pharmacy regulating agencies. Regulation should be based on standards for Good Pharmacy Practice,¹ practice standards, codes, and professional guidelines prepared by the professional organisations.²

4. As basic extemporaneous compounding is a traditional role of pharmacists and should be considered normal professional practice, it should be regulated by the profession using professional guidelines and practice standards.

5. Pharmacists should only be permitted to extemporaneously compound a medicine under the principles of normal professional practice if there is no suitable and available medicine on the ARTG.

¹ Joint FIP/WHO Guidelines on GPP: Standards for Good Pharmacy Practice.
² Examples include PSA’s Professional Practice Standards Version 4, 2010 and SHPA’s Practice Standards.
6. The RIS and pending PBA document on manufacturing in pharmacy should be considered jointly and submissions in relation to the RIS should be considered provisional until the profession has had the opportunity to consider the PBA’s statement.

7. Any regulation, whether by the profession or by TGA, of the compounding of medicines in pharmacies should be applicable in a consistent manner in all jurisdictions and in all pharmacy practice settings.

8. The TGA may need to consider establishing a regulation framework and process for all compounding (including simple compounding procedures) that occurs outside of pharmacy facilities and practices regulated by the PBA.

9. The current regulatory framework should be the basis for the regulation of extemporaneous compounding which occurs within a pharmacy practice for a small number of patients on an individual patient basis and includes minimal complexity using standard formulations.

10. Enhanced profession-based regulation and updated legislation should be the basis for regulation of complex and high volume compounding which occurs in a pharmacy practice on an individual patient basis, for single units, for immediate use.

11. A manufacturing licence and associated inspection should be the basis for regulation of any compounding that entails the preparation of batches of products that will be used for multiple patients, or over extended periods of time. It should also be the basis for regulation of compounding from first principles of specified dose forms including: ophthalmic and parenteral preparations, terminally sterilised preparations, implants, micro-dose formulations, penicillins, and modified release dose forms.
Submission detail

The need for regulation

1. APHS supports regulation of compounding aligned with the level of patient risk associated with the use of individual compounded preparations. Any framework used to delineate the level of or type of regulation should be based on specific factors that contribute to the risk, namely the characteristics of the ingredients, complexity of the process, and the number of individuals potentially exposed.

The introduction section of the TGA Consultation Regulation Impact Statement (RIS), Options for reform of the regulatory framework for pharmacy compounding refers to concerns regarding the complexity and scale of manufacturing in pharmacies.

The risks associated with compounding activities are multi-factorial and may include the toxicity of the ingredients, purity and quality assessment of the ingredients, the number and nature of manipulations involved, the extent of dilution and accuracy of the resultant concentration of active ingredients, the validation of the technique, equipment and environment, the stability of the final product and the lag time and storage conditions between compounding and use, and the overall number of units prepared and patients supplied the product. In summary, these factors can be grouped as the characteristics of the ingredients, the complexity of the process, and the number of individuals potentially exposed.

In quantifying the risk associated with the complexity of compounding medicines, it should be noted that the scope of compounding in pharmacies ranges through a risk gradient from common simple low-risk procedures such as reconstitution of antibiotic powders to prepare oral syrups, historical tasks such as extemporaneous preparation of topical and oral pharmacopoeia based formulations, specific compounding functions such as aseptic reconstitution of TGA-approved cytotoxic products, through to the higher-risk, but uncommon, manufacture of complex non-pharmacopoeia formulations from raw ingredients.

The RIS states that the majority of pharmacies in Australia compound on average only three products each week and extemporaneously compounded PBS medicines account for just 0.15% of all PBS prescriptions. Of the 195 million PBS prescriptions processed annually, only 300,000 are compounded medicines. This number equates to approximately one extemporaneously compounded PBS medicine per pharmacy, per week.

Less than 10% of pharmacies claim to specialise in compounding and prepare, on average, 25 items per week. There are a small number of pharmacies that are 'compounding only' pharmacies and only approximately 50 pharmacies (including APHS pharmacies) that reconstitute chemotherapy medicines. In effect, the majority of pharmacies in Australia compound very few medicines and few pharmacies in Australia compound large volumes, or complex medicines.
Concern in Australia regarding the risk associated with compounded medicines has been reinforced by reports of the morbidity and mortality associated with contaminated injectable products compounded by the New England Compounding Centre pharmacy in the United States. APHS is not aware of any pharmacies in Australia, other than TGA-approved premises, which compound injectable products in bulk.

Terms used in the RIS

2. Greater clarity and differentiation are required regarding the concepts and definitions used in the RIS if they are to be the basis of determining the application of differing levels of regulation.

There is inconsistency between the statement that this RIS does not apply to “the traditional role of a pharmacist” and the use of the terms “complex compounding” (as defined in the RIS) as a basis for considering greater levels of regulation.

The most common compounding activity undertaken in APHS pharmacies is the extemporaneous aseptic reconstitution of a TGA-registered cytotoxic pharmaceutical product. This is done in accordance with the applicable TGA-approved Product Information, producing a single dose of medicine for immediate administration to a specified patient in accordance with a medical practitioner’s prescription. As individual tasks, these compounding activities can range from simple procedures of dilution, dose measure, and transfer between two containers, to complex procedures involving multiple steps and multiple containers. While in all cases the processes are undertaken by specially trained staff in monitored facilities using protective equipment and following procedures and techniques in accordance with professional guidelines, in many ways it is simply a highly developed form of the traditional role of a pharmacist performing extemporaneous compounding. As such, it should be regulated as being an aspect of a pharmacists’ professional practice however, in this RIS the activity is captured by the definition of ‘complex compounding’ and according to appendix 4, would require a manufacturing licence.

The glossary provided at appendix 1 in the RIS provides a definition of complex compounding which captures the preparation of “…a single ‘unit of issue’ of... sterile products, cytotoxics, hormones, micro-dose forms and sustained release products.” This definition fails to differentiate between extemporaneous compounding such as aseptic reconstitution using TGA-registered ingredients and prepared in accordance with TGA-approved procedures, and higher-risk compounding activities such as the preparation of products utilising materials, techniques or formulations that are not approved or endorsed.

The extent of the application of the RIS

3. The regulation of pharmacists’ professional practice and of pharmacy facilities should primarily be the responsibility of the Pharmacy Board of Australia (PBA) in conjunction with state and territory pharmacy regulating agencies. Regulation should be based on standards for Good Pharmacy Practice,³ practice standards, codes, and professional guidelines prepared by the professional organisations.⁴

³ Joint FIP/WHO Guidelines on GPP: Standards for Good Pharmacy Practice.
⁴ Examples include PSA’s Professional Practice Standards Version 4, 2010 and SHPA’s Practice Standards.
The RIS states that the scope of the regulation “does not extend to the traditional role of a pharmacist in preparing medicine for a known particular patient ... For clarity, this includes the reconstitution of a TGA-approved medicine in accordance with the directions in the TGA-approved Product Information document.”

While there may be concern regarding elevated risk associated with manufacturing involving the use of formulations that are not derived from pharmacopeias or approved formularies, procedures that are not in accordance with professional standards, and the production of batch quantities for use over extended periods and multiple patients, the response to this concern should not lead to excessive regulation of compounding undertaken on an individual patient basis, including extemporaneous aseptic reconstitution. Excessive regulation would result in an unjustifiable increase in costs and a reduction in access by the public to extemporaneously compounded medicines prepared within normal professional pharmacy practice.

**Regulation of professional practice**

4. As basic extemporaneous compounding is a traditional role of pharmacists and should be considered normal professional practice, it should be regulated by the profession using professional guidelines and practice standards.

An extensive range of professional guidelines and practice standards exist in relation to the handling of chemotherapy medicines. A list of the guidelines applied by APHS in relation to extemporaneous reconstitution includes:

- International Society of Oncology Pharmacy Practitioners (ISOPP): Standards of Practice 2007
- ISOPP: Pharmacy Practice Oncology Guidelines Audit Tool
- Society of Hospital Pharmacists of Australia (SHPA): Standards of Practice for the Safe Handling of Cytotoxic Drugs in Pharmacy Departments, 2005
- Pharmaceutical Society of Australia: Professional Practice Standards Standard 11: Compounding of sterile preparations
- Worksafe Victoria: Handling cytotoxic drugs in the workplace 2003
- Safe Handling of Cytotoxic Drugs and Related Wastes: Guidelines for South Australian Health Services 2012
- Australian Standard AS 4273-1999: Design, installation and use of pharmaceutical isolators
- Australian Standard AS 2567-2002: Laminar flow cytotoxic drug safety cabinets
- Australian Standard AS 2639: Laminar flow cytotoxic drug safety cabinets- Installation and use
- Australia Standard AS 1386.3-1989: Cleanrooms and clean workstations
- PIC/S Guide to good practices for the preparation of medical products in healthcare establishment (PE 010-3) 2008

Professional guidelines of this nature should form the basis of profession-based regulation of pharmacists’ normal professional practice.

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5 Approved formularies include references such as the Australian Pharmaceutical Formulary.
5. Pharmacists should only be permitted to extemporaneously compound a medicine under the principles of normal professional practice if there is no suitable and available medicine on the ARTG.

Extemporaneous compounding of a product should not be undertaken by a pharmacist where there is available a commercial TGA-approved product manufactured under TGA-approved conditions which would satisfy the requirements of the prescription.

6. The RIS and pending PBA document on manufacturing in pharmacy should be considered jointly and submissions in relation to the RIS should be considered provisional until the profession has had the opportunity to consider the PBA’s statement.

As the PBA is currently undertaking a review of manufacturing in pharmacy, it is unclear as to the likely extent of any future profession-based regulation of compounding in pharmacy. Being unaware at present as to how extensive the PBA’s proposed regulation may be (the nature of preparations that Board may seek to regulate, the need for credentialing or accreditation, etc), limits the capacity to respond to the RIS.

Scope of regulation

7. Any regulation, whether by the profession or by TGA, of the compounding of medicines in pharmacies should be applicable in a consistent manner in all jurisdictions and in all pharmacy practice settings.

The development of a regulatory framework that is applicable in some states or territories and not others; applicable in some types of hospital and not others or; applicable to some professions and not others would be inequitable and create opportunities for avoidance.

Compounding in sites other than approved pharmacies

8. The TGA may need to consider establishing a regulation framework and process for all compounding (including simple compounding procedures) that occurs outside of pharmacy facilities and practices regulated by the PBA.

The RIS has been written in respect to compounding in pharmacies. A number of other registered health professionals and other groups have the capacity to compound medicines including medical practitioners, veterinary surgeons, Chinese medicine practitioners, and herbalists. As these groups are not within the jurisdiction of the PBA, alternate regulatory framework and processes should be considered.
Options presented in the RIS

The following responses to the options presented in the RIS are based on previous discussion in this document, particularly the principle that the risk and therefore, the level of regulation required, should be determined by, and in accordance with, the characteristics of the ingredients, the complexity of the compounding process, and the volume of production which has a bearing on the number and level of patient or operator exposure.

Option A - status quo

9. The current regulatory framework should be the basis for the regulation of extemporaneous compounding which occurs within a pharmacy practice for a small number of patients on an individual patient basis and includes minimal complexity using standard formulations.

- Regulation should involve profession-based assessment of facilities, evidence of documentation of procedures, competence demonstrated through completion of satisfactory continuing professional education, and compliance with professional practice standards.

- Examples of extemporaneous compounding that would be captured by this level of regulation includes the occasional extemporaneous compounding of formulations in approved pharmacopoeias and compounding (reconstitution) of non-parenteral TGA-approved products using TGA-approved procedures (e.g. oral antibiotic syrups, eye drops).

- A higher level of regulation would be necessary for compounding involving the aseptic reconstitution of sterile TGA-approved products including: cytotoxic medicines, the preparation of parenteral nutrition solutions, compounding of complex formulations and dose forms, and for large volume, batch production.

- Extemporaneously compounded products prepared under this level of regulation should be identified as such on their label and should carry both manufacture and expiration dates.

Option B – enhanced co-regulation and update legislation

10. Enhanced profession-based regulation and updated legislation should be the basis for regulation of complex and high volume compounding which occurs in a pharmacy practice on an individual patient basis, for single units, for immediate use.

- Regulation should involve enhanced profession-based assessment of dedicated and specialised facilities that are in compliance with national guidelines, evidence of documentation of protocols and procedures, operator competence demonstrated through completion of continuing professional education with certification, and compliance with professional practice standards.

- The detail of regulation and monitoring performed by PBA, jurisdictional pharmacy authorities, and other
professional bodies should be graded in a nationally-consistent manner in relation to the nature and volume of compounding undertaken.

- This option would enable the continued existence in regional centres of pharmacies with the capacity to compound cytotoxic medicines by aseptic reconstitution in a viable, timely manner, and in the limited quantities required to enable people from the surrounding rural area who are being treated for cancer to obtain treatment locally and not need to travel to urban centres.

- This option would enable pharmacies that elect to access from large-scale TGA-licensed facilities doses of cytotoxic medicines which can be pre-planned and have adequate shelf-life, to still locally compound by aseptic reconstitution doses of cytotoxic medicines when the patient's medical condition or schedule warrants immediate preparation, or when the medicine has such a short half-life that it could not be provided from a distant facility due to transit time.

- The capacity to claim the status as a specialised compounding pharmacy for oral and topical preparations of both pharmacopoeia and non-pharmacopeia basis, or to undertake aseptic reconstitution of sterile TGA-approved products including cytotoxic medicines and the preparation of parenteral nutrition solutions, all on an individual patient basis, for immediate use, would be provided under this option.

- A higher level of regulation would be necessary for compounding of batches of product, or for compounding from first principles of specified dose forms including ophthalmic and parenteral preparations, terminally sterilised preparations, implants, micro-dose formulations, penicillins, and modified release dose forms.

- Extemporaneously compounded products prepared under this level of regulation should be identified as such on their label and should carry both manufacture and expiration dates.

**Option C – manufacturing licence for specified manufacture in pharmacies**

11. A manufacturing licence and associated inspection should be the basis for regulation of any compounding that entails the preparation of batches of products that will be used for multiple patients, or over extended periods of time. It should also be the basis for regulation of compounding from first principles of specified dose forms including: ophthalmic and parenteral preparations, terminally sterilised preparations, implants, micro-dose formulations, penicillins, and modified release dose forms.

- A pharmacy facility undertaking compounding of these products would require a manufacturing licence.

- Extemporaneously compounded products prepared under this level of regulation should be identified as such on their label and should carry both manufacture and expiration dates.