Review of Pharmacy Remuneration and Regulation
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Response to Pharmacy Remuneration and Regulation Interim Report

SUBMISSION

TGA Licensed Chemotherapy Compounders of Australia

July 2017

This response is written by Baxter Healthcare Pty Ltd, Slade Health Pty Ltd and the Wesley Pharmacy Pty Ltd, on behalf of the TGA Licensed Chemotherapy Compounders of Australia (TLCCA). The TLCCA is an industry group whose functions include communicating with the Commonwealth government, including the Department of Health and the Therapeutic Goods Administration (TGA), on issues that affect the industry.

INTRODUCTION

The TLCCA welcomes the opportunity to provide further input into the Review of Pharmacy Remuneration and Regulation following the release of the Panel's Interim Report.

The purpose of this submission is to address Findings and Options presented in Chapter 10 of the Interim Report concerning payments, standards and practice models for the compounding of chemotherapy.

Specifically, the TLCCA rejects the Panel's Finding 10.2. The submission will also address regulatory matters related to Findings 10.3 and 10.4.

Finding 10.2 The rationale for differential payments for compounding of chemotherapy preparations is not substantiated on the basis of patient risks or health outcomes for medicines that must meet an appropriate level of quality, whether prepared at a Therapeutic Goods Administration (TGA) licensed or non- TGA-licensed facility.

Finding 10.3 The current standards for the compounding of chemotherapy medicines in community pharmacy and other facilities appear to be overly complex. The oversight currently includes legislation, codes and guidelines. The overlap and inconsistency of these across Australia do not provide clear rules or guidance for compounders.

Finding 10.4 There are a number of good practice chemotherapy compounding models that can be leveraged to improve access to existing compounding arrangements.

In its submission in response to the Panel's discussion paper, the TLCAA agreed with the Panel that the differential payments provide recognition of the additional costs to the compounder of holding and complying with a TGA Licence. Furthermore, the fee provides recognition of the superior safety and quality performance and lower risks associated compounding in a TGA licenced facility.

The Panel has subsequently suggested that differential payments cannot be substantiated on the basis of patient risk or health outcomes. The evidence presented in this submission will refute this assertion. Moreover, it must be reiterated that differential payments are not intended to recognise a therapeutic difference in compounded products. The principle of the differential payment appropriately reflects superior quality assurance of a TGA compounded infusion that is subject to a superior regulated environment including regular auditing. The quantum of the payment represents a modest estimate of the cost of complying with this regime.

The submission provides evidence to support both the quality and cost differential of TGA compounded infusions. The remainder of the submission provides further context of the domestic and international regulatory environment in relation to Findings 10.3 and 10.4.

The TLCCA would encourage the Panel to hear further verbal evidence from its member companies should it remain in doubt about any of the matters presented in this submission.

CHEMOTHERAPY COMPOUNDING – PAYMENTS

Finding 10.2 The rationale for differential payments for compounding of chemotherapy preparations is not substantiated on the basis of patient risks or health outcomes for medicines that must meet an appropriate level of quality, whether prepared at a Therapeutic Goods Administration (TGA) licensed or non- TGA-licensed facility.	*Option 10.2 There should be no difference in the remuneration paid by the government for the compounding of chemotherapy medicines in any facility that meets the minimum quality and safety standards. In particular, there should be no additional payment for medicines that are prepared in a facility that exceeds the minimum standards.*

The TLCCA reiterates its consistent position that the difference between chemotherapy medicines provided by TGA licenced compounders and non-TGA licensed compounders is principally one of quality and safety, rather than therapeutic difference. However, it should be noted that if safety and quality is compromised then there is obviously the potential for the therapeutic outcomes to vary.

The notion that the different payments should be substantiated on the basis of patient risk or health outcomes inappropriately applies a new measure and is inconsistent with the original policy intent. The current Pharmaceutical Inspection Co-operation Scheme (PIC/S) for medicinal products recognises only one standard (and in effect, a minimum standard), which is the CGMP currently regulated by the Australian Government's TGA. This standard exists to provide assurance to governments and payers that medicines are being prepared to a suitable standard with safeguards in place to prevent errors and patient harm. The notion that there is a menu of standards to choose from that would that allow for lower quality preparation of sterile medicines is not founded in reality and runs counter to international regulatory trends in healthcare.

The Interim Report also presents an option to apply no additional payment for medicines that exceed "the minimum standards". This option is counterintuitive and conflicts with the finding concerning TGA standards. The fact is that the only minimum standard currently in place is the TGA standard – that being the PIC/S Current Good Manufacturing Practice (CGMP) for sterile medicines in healthcare establishments as recognised by the TGA, FDA and other international bodies. This is effectively a minimum standard as no lower standard exists. However, there are lower levels of regulatory compliance and audit for non-TGA licensed facilities.

Non-TGA licensed sterile compounding pharmacies are not subject to the same level of external audit. Nevertheless, they are required to comply with Australian Pharmacy Board and relevant Society of Hospital Pharmacists of Australia (SHPA) guidelines for the preparation of sterile medicines. While in theory there should not be a therapeutic difference in compounded medicines where the guidelines are adhered to, given the absence of a regular external auditing regime it is difficult to assess the level of compliance.

The Panel has not disputed that there are certain additional costs associated with operating within a TGA licensed environment. In practice, these costs are substantial and if payment for chemotherapy compounding was made uniform across all compounders, there would be financial incentive for high volumes of compounding to move to the lower cost non-TGA compounding environment.

This would result in more medicines being prepared in an environment without the quality assurance safeguards of regular, rigorous and independent compliance audit.

A sample of some of the unique costs associated with maintaining a TGA licensed chemotherapy compounding facility is provided in Appendix 1.

Before providing a detailed response to specific comments made in the Interim Report, it can be noted that the basis of the TLCCA's response to this section of the report is that:

- While there are multiple and varied references relating to standards for preparing compounded medicines, there is only one that involves routine testing of compliance through independent audit. Adherence to another alternative standard is not quantifiable;

- There is no accepted minimum compounding standard outside of CGMP. The Panel has not provided any reference as to how a lower minimum standard would be developed, implemented, funded, administered or audited.

- The TGA and United States Food and Drug Administration (FDA) have been unequivocal that CGMP provide are the best available standards to minimise the risk of patient harm. [1]

The FDA has been explicit in relation to the consequences of medicines being prepared with standards inferior to CGMP, noting in its 2016 Guidance for Industry:

> Extract of FDA Commentary on non-CGMP (503a) compounding of human drugs
>
> *"FDA has also identified **many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health**, and that shipped, sometimes in large amounts, the compounded drug products made under these conditions to patients and health care providers across the country. The longer a compounded sterile drug product that has been contaminated is held by a pharmacist or physician before distribution, or held in inventory in a health care facility before administration, the greater the **likelihood of microbial proliferation and increased patient harm.**"*
>
> *Source: FDA Guidance for Industry 2016, Compounding and Related Documents 2016* [2]

Consideration of this broader international context provides a powerful case as to the dangers of implementing, encouraging or endorsing a lower standard or level of compliance for sterile compounding of chemotherapy medicines in Australia.

[1] FDA Guidance for Industry: Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry. Compounding and Related Documents 2016.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf
[2] *Ibid* – see page 4 of FDA Guidance.

The following table provides a direct response from the TLCCA to some of specific comments made in the Panel's Interim Report.

Interim Report	TLCCA Response
"Throughout the Panel's national consultations, the majority of stakeholders considered that there is no therapeutic difference between products produced in a TGA-licensed or appropriate non-licensed facility."	The CCPS was not offered or implemented on the basis of a therapeutic difference. It recognises the additional cost of complying with measures the TGA deems necessary, and provides additional reimbursement to cover these costs. This payment ensures there is not a disincentive for entities to compound products with superior quality standards and regular auditing.
"A number of local compounding facilities that were not TGA licensed emphasised that they were required to comply with multiple sets of standards and were producing products that were 'identical' to those compounded in TGA facilities"	The local compounding facilities described commit to adhering to guidelines that contain some standards that are similar to those required of TGA licensed facilities. However, compliance to these standards is self-assessed. If it were the case that products produced in non-TGA licensed facilities were in fact identical to those produced in TGA licensed facilities, it would seem contradictory that that the TGA and FDA mandate adherence to CGMP when identical results can be achieved in the absence of this standard. The TGA 2017 Guide to GMP for compounded medicinal products provides a useful illustration of the associated higher quality assurance and costs. For example, the costly requirement for additional microbiological and sterility testing of work areas and products.[3] While some non-TGA compounding facilities may contend that products are 'identical', this is not the view of many private and public hospitals which have mandated a TGA licence as the minimum requirement to participate in tender processes. This behaviour demonstrates that the users of compounded products do not support

[3] TGA - Compounded medicines and good manufacturing practice (GMP) Guide to the interpretation of the PIC/S Guide to GMP for compounded medicinal products Version 2.0, May 2017. Available: https://www.tga.gov.au/sites/default/files/compounded-medicines-and-good-manufacturing-practice-gmp.pdf

	the view that there no difference between non-TGA and TGA licensed products.
"The Panel also notes concerns relating to the impact of the two-tiered remuneration structure on the viability of local facilities, which often play an important role in rural and remote communities. *The Panel agrees that these types of local facilities play a vital role in supplying chemotherapy services in many areas of Australia and should receive equality in remuneration for their services, subject to meeting minimum quality and safety standards."*	The panel refers to the Northern Territory and Tasmania as examples of areas in need of viable local facilities to ensure timely access to quality compounded chemotherapy. Currently in each of these locations the Public Hospital sector is the major provider of Chemotherapy infusions. Departments of Health in both jurisdictions have released purchasing RFPs in the past 12 months for compounding services. These RFPs specified a TGA licence as the required minimum standard for prospective respondents, as they have done RFPs prior to the introduction of the CCPS. TGA licensed compounders incur additional costs to meet CGMP requirements. These costs are incorporated into commercial arrangements-costs the facilities in Tasmania and the Northern Territory have been willing to voluntarily pay to ensure the highest quality product available. Removal of the CCPS payment will not remove increase costs of complying with CGMP, rather it will simply remove the funding and recognition of this cost.
"Arguments made in favour of the additional $20 for TGA-licensed facilities were generally based on recognition of the additional costs to the compounder of holding and complying with a TGA licence. The Panel is not satisfied of there being sufficient evidence to demonstrate these additional costs or that they should be valued at $20 per claim."	The TLCCA contends that the $20 payment is a modest estimate of the costs of complying with the TGA licence. However, to ensure the value of this fee is retained in real terms over time, an indexation arrangement should be applied. This indexation should be commensurate with cost inflation in the healthcare sector. Appendix 1 provides a sample of the some of the unique costs associated with TGA licensed chemotherapy compounding.
"Furthermore, the Panel does not consider it appropriate to apply differential remuneration levels for products prepared in TGA-licensed versus non-TGA-licensed facilities, as this would appear to imply a difference in quality or safety which has not been borne out in practice."	The Panel's assertion that no difference in quality or safety has been borne out in practice is not supported by the evidence. In particular there are widely accepted differences in relation to non-TGA facilities: • Inability to apply extended shelf life, leading to potential wastage where the patient delays therapy; and

	• Inability to supply bulk manufacturing and achieve associated efficiencies such as a Ready To Use inventory of medications. The Panel's Interim Report quotes from the SHPA submission that: *"The difference in medicines compounded by TGA licensed compounders is in the quality of the product, and the certification of its development process. Due to the standards of the manufacturing facility, their products have longer shelf lives and expiry dates. For example, an infusion compounded by TGA licensed compounders may not 'expire' for several months, whereas a similar infusion compounded by a non-TGA licensed compounder, may have an expiry of 48 hours or not more than 7 days. As such, TGA licensed compounding facilities are able to compound batch preparations of medicines and distribute to pharmacies and health services who do not have compounding facilities. Due to the cost of certification most hospital pharmacies are not TGA licensed, and therefore only compound medicines for individual patients."* The FDA note in their hospital compounding guidance for industry: *"However, a health system pharmacy that compounds drug products without patient-specific prescriptions for facilities within its health system across a broader geographic area could function as a large manufacturing operation, but without the necessary standards to assure drug quality. If such a pharmacy contaminates or otherwise adulterates or misbrands a compounded drug, the drug has the potential to harm many patients."* Both of these statements refer to the

	appropriateness of local pharmacy or hospital compounders providing compounded products for patients being treated by their own facilities, but not distributing these products to large numbers of patients due to the lack of certifiable standards.

CHEMOTHERAPY COMPOUNDING STANDARDS

<u>Finding 10.3</u> The current standards for the compounding of chemotherapy medicines in community pharmacy and other facilities appear to be overly complex. The oversight currently includes legislation, codes and guidelines. The overlap and inconsistency of these across Australia do not provide clear rules or guidance for compounders.	*<u>Option 10.3</u> Uniform Minimum Standards* *There should be a clear, uniform set of minimum quality standards for all approved chemotherapy compounding facilities based in a hospital, a community pharmacy or elsewhere. These minimum standards should:* *a. not require that a compounding facility be Therapeutic Goods Administration (TGA) licensed to meet the minimum requirements* *b. mean that a TGA-licensed facility clearly satisfies the minimum standards* *c. reflect the variety of settings that are appropriate for the preparation of chemotherapy medicines, including 'urgent' preparation in a hospital setting or a community pharmacy setting.*

The TLCCA agrees that beyond of CGMP requirements our members are required to abide by, there is no clearly defined minimum standard for chemotherapy compounding.

The Interim Report advances the merits for developing minimum standards. However, it overlooks that critical point that without an independent auditing and thorough compliance regime the implementation of such standards will be ineffective.

The current Pharmaceutical Inspection Co-operation Scheme (PIC/S) for medicinal products recognises only one standard (and in effect, a minimum standard), which is the CGMP currently regulated by the Australian Government's TGA. It would be perverse for the Government to subsequently implement a secondary and inferior regulatory standard. This would also see Australia move away from world's best practice, while other jurisdictions globally are striving to comply and obtain this coveted standard.[4]

The TLCCA is concerned about the Panel's interpretation of FDA guidance on compounding standards. The Panel has stated that:

"With this in mind, the Panel has been generally concerned about the standards applied at certain facilities it has observed.

The Panel notes that there are examples of uniform minimum standards being applied in overseas countries. For example, the United States applies additional standards for chemotherapy compounding pharmacies. In particular, the Drug Quality and Security Act 2013, introduced after a meningitis outbreak in 2012 was traced to a compounding pharmacy, exempts compounded

[4] There are now more than 50 participating authorities globally, with many other authorities seeking membership. https://www.picscheme.org/en/members

medicines from certain requirements of the Federal Food, Drug, and Cosmetic Act 1938 where the medicine is compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility meeting applicable requirements."

The TLCCA contends that the panel has misinterpreted the FDA guidance on compounding standards, particularly by implying that facilities that meet a minimum standard (known as 503a in the FDA guidance), should be free to sell compounded products to other facilities. In fact, the guidance makes clear that products compounded under the minimum standard should only be prepared taking into account the restrictions below:

Extract of FDA Guidance for Industry 2016

However, FDA does not intend to take action if a hospital pharmacy distributes compounded drug products without first receiving a patient-specific prescription or order provided that:

(1) The drug products are distributed only to healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a 1 mile radius of the compounding pharmacy;

(2) The drug products are only administered within the healthcare facilities to patients within the healthcare facilities, pursuant to a patient specific prescription or order; and

(3) The drug products are compounded in accordance with all other provisions of section 503A, and any other applicable requirements of the FD&C Act and FDA regulations (e.g., the drug products are not made under insanitary conditions (section 501(a)(2)(A)) or misbranded (e.g., section 502(g)).

The 1-mile radius in our policy is intended to distinguish a hospital campus from a larger health system. As explained in section II.B of this guidance, certain characteristics of hospital pharmacies distinguish them from conventional manufacturers. ***However, a health system pharmacy that compounds drug products without patient-specific prescriptions for facilities within its health system across a broader geographic area could function as a large manufacturing operation, but without the necessary standards to assure drug quality. If such a pharmacy contaminates or otherwise adulterates or misbrands a compounded drug, the drug has the potential to harm many patients.*** *Outsourcing facilities, which are subject to CGMP requirements and other conditions that help to assure drug quality, can compound and distribute drug products to healthcare facilities nationwide without first receiving prescriptions for identified individual patients.*

Source: FDA Guidance for Industry 2016, Compounding and Related Documents 2016 [5]

[5] Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act: Guidance for Industry. April 2016 Available:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496287.pdf

CHEMOTHERAPY COMPOUNDING PRACTICE MODELS

<u>Finding 10.4</u> There are a number of good practice chemotherapy compounding models that can be leveraged to improve access to existing compounding arrangements.	*<u>Option 10.4</u> Practice Models* *Existing practice models in place in public hospitals for limited trade of medicines prepared onsite, such as radio pharmaceuticals, should be considered for providing greater access to chemotherapy arrangements.*

The TLCCA supports the objective of providing greater access to chemotherapy treatments, provided it can be achieved without increased risk of patient harm. However, the Panel has not established that current arrangements do not provide adequate access and that the expansion of compounding trade by public hospitals could be achieved without compromising quality and safety.

The Panel's Interim report Finding/Option 10.4 relies upon the SHPA's submission, which commented that:

> *"The difference in medicines compounded by TGA licensed compounders is in the quality of the product, and the certification of its development process. Due to the standards of the manufacturing facility, their products have longer shelf lives and expiry dates. For example, an infusion compounded by TGA licensed compounders may not 'expire' for several months, whereas a similar infusion compounded by a non-TGA licensed compounder, may have an expiry of 48 hours or not more than 7 days. As such, TGA licensed compounding facilities are able to compound batch preparations of medicines and distribute to pharmacies and health services who do not have compounding facilities. Due to the cost of certification most hospital pharmacies are not TGA licensed, and therefore only compound medicines for individual patients."*

The Panel appears to suggest this comment is supportive of expanding public hospital compound trade. This would be a misinterpretation, given that the SHPA evidence also supports the contention that there is a quality difference when the TGA CGMP standard is applied. Current practice models in TGA licensed facilities are already equipped for distribution across wide geographical areas.

FURTHER REFERENCES

The following references are provided to support the TLCCA submission and the development of the Panel's Final Report and Recommendations.

1. **The Pew Charitable Trust - U.S. Illnesses and Deaths Associated With Compounded Medications or Repackaged Medications**. Available: http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/us-illnesses-and-deaths-associated-with-compounded-medications

2. **Society of Hospital Pharmacists of Australia (SHPA) Manufacturing Guidelines**. Available: https://www.shpa.org.au/resources/shpa-guidelines-for-medicines-prepared-in-australian-hospital-pharmacy-departments

3. **Therapeutic Goods Act 1989**. Available: https://www.legislation.gov.au/Series/C2004A03952

4. **PIC/S Guide to Good Practices for the Preparation of Medical Products in Healthcare Establishments**. Available: https://www.picscheme.org/en/publications

5. **Potential Risks of Pharmacy Compounding**. There is a significant volume of US literature that concludes that unenforced compounding standards can cause additional patient harm. For example, Gudeman et al (2013) conclude that:

   > *"A comprehensive body of regulations governing every aspect of drug manufacture and testing—enforced through regular FDA inspections—is required to achieve consistent high quality. Setting aside these controls and creating a new class of pharmaceutical manufacturing, done without FDA oversight, is not in the best interests of patients."*

   Gudeman, J., Jozwiakowski, M., Chollet, J. and Randell, M. (2013). Potential Risks of Pharmacy Compounding. *Drugs in R&D*, 13(1), pp.1-8.

APPENDIX 1 – EXAMPLE OF COSTS ASSOCIATIED WITH TGA LICENSED CHEMOTHERAPY COMPOUNDING

The following costs are representative of those incurred per TGA licensed facility, unique to complying with cGMP. This is an illustrative rather than an exhaustive list. TLCCA members may provide further details in separate submissions.

Component	Cost
Continuous Particle Monitoring (CPM) Installation	$220,000
CPM Maintenance p.a.	$15,000
Daily Media Fills and micro p.a.	$93,000
Product Samples held p.a.	$27,000
Gowns p.a.	$93,000
Drug/Container/Packaging stability p.a.	$280,000
IT System licensing and maintenance p.a.	$120,000
Equipment Certification costs p.a.	$65,000
Quality Assurance Specialist p.a.	$140,000
TGA License p.a.	$12,200
TGA Audit ($660/hr/inspector for 1 day every 2 years) p.a.	$15,840