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JOINT NSW TAG / SHPA SUBMISSION TO THE EXPERT REVIEW OF MEDICINES AND MEDICAL DEVICES REGULATION

This submission follows two interviews; one telephone interview by Ms Helen Dowling, CEO of The Society of Hospital Pharmacists of Australia (SHPA) with Emeritus Professor LLoyd Sansom on 11th December 2014 and the second by Dr Sasha Bennett, as a representative of SHPA and the NSW Therapeutic Advisory Group (TAG), with the Expert Panel on the 18th December 2014. This submission is made on behalf of NSW TAG and SHPA, and seeks to

- clarify issues identified at these interviews,
- refine responses given greater understanding of the Expert Panel Review, and
- provide solutions that will address issues raised during the interviews for consideration by the Expert Panel.

This submission is provided in 6 sections:

1. Use of a 'trusted regulator' with regard to informing marketing approvals of new chemical entities
2. The role and function of the Poisons Schedule and Scheduling Decisions
3. Issues related to the Special Access Scheme (SAS)
4. Direct-to-consumer advertising of medicines
5. Transparency and accountability of the Therapeutic Goods Administration (TGA)
6. Other 'red tape' issues

Given the expertise of NSW TAG, and that SHPA is committed to facilitating the safe and effective use of medicines, the submission focuses on the use of medicines including biological products and radiopharmaceuticals. Nevertheless many of the issues raised and the solutions proffered apply equally to devices and blood products. Therefore NSW TAG and SHPA consider a consistent approach to medicines, devices and blood products is preferable. It is important that the principles used to evaluate and monitor medicines including the requirements for high level evidence and assessment in the Australian context are applied to all therapeutic goods. Our joint submission supports the goals of the National Medicines Policy in particular the quality use of medicines and a viable pharmaceutical industry. We endorse the removal of unnecessary 'red tape' and increased productivity but note that there is innate risk in the use of medicines and that robust evidence for safety and efficacy and ideally effectiveness is essential prior to marketing approval. Nevertheless

there may be circumstances where such evidence is not (and possibly may never be) available and hence there is a need for rigorous processes by which access to such medicines is made possible and that the Australian regulator has an important role to play in the governance and use of these unmarketed medicines.

1.Use of a 'trusted regulator' with regard to informing marketing approvals of new chemical entities

NSW TAG and SHPA recognise that drug regulation is a global enterprise and that sharing and collaboration would likely be advantageous to Australian regulators, healthcare decision-makers and the general population. Such collaboration and information sharing can be supported by electronic evaluation systems. We note the changes being made by the large regulators to meet the increasing complexity required to ensure that all medicines, whether prescription, over-the-counter, compounded or complementary, are safe, effective and of high quality as well as meeting the public demands for early access to new medicines and unmet medical needs.[1,2,3] The U.S. Food and Drug Administration (FDA) has recently announced organisational, cultural and assessment changes and strengthening of post market surveillance to meet the robust regulatory quality program requirements expected by consumers.[1]

In addition to sharing information relating to marketing approvals, we suggest a similar approach be taken to international harmonisation of underpinning policies, processes and systems for key aspects of drug regulation. Recent major examples from the FDA and EMA include strong enhancements to paediatric drug regulation and to post-marketing surveillance and more proactive pharmacovigilance for this population generally. A recent international review by Hoppu et al[2] provides an informative summary of recent history and current major initiatives relating to paediatric drug regulation from FDA, EMA and other regulators, which we suggest would be helpful to consider in the process of this review. Fundamental to the approach taken by the FDA, EMA and others is the recognition of the need for a range of specialised paediatric expertise to inform all aspects of decision-making, from drug development, initial regulatory evaluation, to all stages of post-marketing surveillance for any medicines intended for use (or likely to be used) in the paediatric population.

Streamlining approval processes: Both NSW TAG and SHPA understand that regulatory processes may be modified in order that data and independent expert reviews obtained from a 'trusted regulator' are included to streamline approval processes. Such a system recognises the current duplication of evidence appraisal and has the potential to share the knowledge, resources and skills of regulatory authorities with broader expertise and a larger workforce enabling timely regulator review and the potential for improved consumer access in Australia; albeit, still ensuring that Australia does not lose the knowledge and skills required to evaluate and approve new chemical entities and associated issues. NSW TAG and SHPA understand that the Australian regulator is a seen as a leader in the Asia-Pacific region.

[1] Yu LX. From our perspective: Patients deserve quality medications. US Food and Drug Administration. http://www.fda.gov/Drugs/NewsEvents/ucm428298.htm

[2] Hoppu K, Anabwani G, Garcia-Bournissen, et al. The status of paediatric medicines initiatives around the world- what has happened and what has not?EurJClinPharm 2012; 68: 1-10.

Adaptive regulatory framework and the need for augmentation of post-marketing surveillance: Both NSW TAG and SHPA are cognisant of the financial and logistic pressures being placed on the pharmaceutical industry in the development of new drugs and on international regulators' processes including proposed changes to a regulator's evaluation and approval processes such as adaptive licensing. Eichler and colleagues have recognised that adaptive licensing must be an adaptive framework for the life of a chemical entity and that this approach requires significant post-approval monitoring and surveillance.[3] As the Panel is aware, the EMA are currently undertaking an adaptive pathways pilot project.[4] Adoption of such processes by a trusted regulator in the future may have an impact on the ability of the TGA to use such a regulator unless Australia also adopts these adaptive processes. We note a recent editorial by Australian researchers in the Bulletin of the World Health Organisation discussing the need for a global proactive approach to 'balance objectivity of appraisal and equity in access to new products; ensuring that medical advances are affordable, working with a viable pharmaceutical industry that responds to public health needs' and that regulators (and others) have a role to play in the cost of medicines.[5] A useful paper regarding the safety monitoring of medical devices post-approval highlights a number of issues regarding current post marketing surveillance strategies used by the FDA and future directions for post marketing surveillance and is highly recommended.[6]

NSW TAG and SHPA also wish to highlight to the Panel the difficulties faced by hospitals and their patients with regard to access to new medicines when medicines have been available via a clinical trial but become unavailable or unaffordable in the lag time between trial end and TGA approval. Patients previously within the trial often continue to obtain the drug via compassionate access programs. However other patients with the same indications as was required in the trial cannot feasibly access the drug during this lag time. Hence the framework that the TGA may use for the approval of medicines post-trial should take into account such scenarios.

Criteria to be a 'trusted' regulator: NSW TAG and SHPA suggest that the following criteria would be required for a regulator to be considered 'trusted':

- Having a track record with evidence of regulatory effectiveness
- Having similar structures/systems/approaches to regulation. (The Australian regulator would need to recognise differences of other regulators' processes and the limitations that that imposes including recognition of Australian context);
- Having broadly equivalent health systems;
- Requiring high level evidence for approval;
- Having post-marketing programs;
- Having a similar risk tolerance threshold ;
- Having systems in place to detect and resolve problems;
- Aligning with international harmonisation standards; and,

[3] Eichler H, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. Clin Pharm Therap 2014;27. Published online Nov 2014. doi: 10.1002/cpt.59

[4] European Medicines Agency. Status of the adaptive pathways pilot project. 22 Dec 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/12/news_detail_002244.jsp&mid=WC0b01ac058004d5c1

[5] Hill SR, Bero L, McColl G and Roughhead E. Expensive medicines: ensuring objective appraisal and equitable access Bull World Health Organ 2015;93:4-4Adoi: http://dx.doi.org/10.2471/BLT.14.148924

6 Rajan PV, Kramer DB and Kesselheim AS. Medical Device Postapproval Safety Monitoring. Circ Cardiovasc Qual Outcomes 2015.; 8:00-00. doi: 10.1161/CIRCOUTCOMES.114.001460.

- Ensuring transparency with regard to decision-making and access to documentation including clinical trials data, if required. For example, the TGA would be able to obtain access to all information e.g. sponsor's responses when such information is requested. NSW TAG notes the EMA's recent policies with regard to transparency and a recent article regarding the impact of these policies.[7]

Proposed regulatory review framework for marketing approval in Australia: NSW TAG and SHPA understand that there will continue to be a robust review of new medicines/chemical entities by the TGA prior to marketing approval of medicines in Australia. This may take the form of:

1) a *de novo* review where information from other regulatory authorities is not available. This may sometimes be preferred by sponsors; or,

2) a review that takes into account data/recommendations obtained from 'trusted regulator(s)' and would enable a more streamlined approach for sponsors with potential for reduced costs.

Consequences of using a 'trusted' regulator: However as noted by the Chair of the Expert Panel, while the second option may lead to reduced complexity, time, and costs and greater productivity at the 'front end' of the regulatory process, the 'back end' will require augmentation. While use of information from a trusted regulator may help meet the increasing demand for public access to new medicines in a timely manner, post-marketing pharmacovigilance will need to be more rigorous and comprehensive than it currently is in Australia to ensure a positive benefit: harm ratio and protect the Australian consumer, workers and organisations within the health system and the taxpayer. NSW TAG and SHPA note that a slower process of marketing approval for new medicines may, in the past, have enabled Australian consumers to avoid exposure (or led to reduced exposure) to adverse effects that were not identified pre-marketing. We also note that a recent study by Cheng and colleagues investigating boxed warnings of new drug approvals between 1996 and 2012 reported that 35% (180 of 522 new approved medicines) had received boxed warnings with 50 of these receiving boxed warnings during post-marketing and 25 having both pre-market and post-market boxed warnings initiated.[8] Boxed warnings were more common with biological products (affecting approximately half of all approved biological products).

From the Panel interviews, we understand that an evaluation of the new drug/product in the context of Australian culture, its health care systems, the genetic variation within the Australian population and between Australia and other countries and the health literacy of its population will be undertaken whether it is a *de novo* process or adopting a recommendation from a 'trusted' regulator. Such a review will include review of the name, presentation, packaging, labelling, consumer and clinician information, the delivery system of the product and its user-friendliness for the indicated patient group. We note two recent local issues that show both the potential good and bad of adopting another regulator's recommendations:

a) Labelling of neuromuscular blocking agents (NMBA) has been changed in the US and Canada due to their regulators' recognition of patients' adverse outcomes occurring because of

[7] Bonini S, Eichler H, Wathion N and Rasi G. Transparency and the European Medicines Agency — Sharing of Clinical Trial Data. N Engl J Med 2014; 371:2452-2455.
[8] Cheng CM, Shin J, Guglielmo BJ. Trends in boxed warnings and withdrawals for novel therapeutic drugs, 1996 through 2012. JAMA Intern Med. 2014 Oct;174(10):1704-5. doi: 10.1001/jamainternmed.2014.4854.

look-alike labelling.[9,10] Despite representation to the TGA and instances of harm in Australia, the TGA has not required manufacturers of NMBA to change their labelling. Adoption of these labelling requirements earlier rather than later is likely to have reduced patient harm.[11]

b) A recent TGA advice regarding ondansetron and the risk of serotonin syndrome, derived from FDA and EMA recommendations based on poor evidence and an implausible mechanism. To our knowledge, no Australian experts on serotonin toxicity, (who are also recognised as world experts), were consulted. Such advice has the potential to cause harm to patients. We are happy to provide further details regarding this issue if you require. It is of concern that the European, US and Canadian regulators did not analyse the issue more thoroughly and critically.

c) TGA approval of changes in the product information of IV paracetamol regarding paediatric dosing recommendations based on incorrect information. We refer the Panel to NSW TAG's IV paracetamol addendum[12] for greater information about this issue, which we subsequently highlighted in Australian Prescriber.[13]

It is unclear what processes within the Australian regulator have allowed the above issues to arise but we would recommend that adoption of new regulatory approval systems would pilot test/model issues such as these before changing the review and approval system.

We also note recent concern[14] regarding a decision by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to recommend a marketing authorization for the combination naltrexone + amfebutamone (also known as bupropion) for use in weight control, despite "uncertainties with regard to cardiovascular outcomes in the longer term". This issue could also act as a test case for TGA's use of a potential 'trusted' regulator's recommendations.

Current gaps in pharmacovigilance: NSW TAG and SHPA are concerned that there is no comprehensive signal detection of unlisted adverse effects for 'non-new'/older medications or medicines that have changed their scheduling status; that TGA post-marketing surveillance is limited to specific drugs; and, that voluntary 'blue card' reporting is low in Australia and internationally and leads to delays in necessary and important decision-making about the safe and rational use of medicines. The flaws of passive surveillance are well known and include the lack of a denominator and missing data. As such, efforts to improve post marketing surveillance include post marketing clinical studies and registries, each of which have their advantages and disadvantages. Incentives would be required to ensure timely accurate data input by time-poor frontline clinicians. This may

[9] Pakenham-Walsh, N and Ana, J, Confusing packaging contributes to death of 15 children. The Lancet Global Health, 2014. 2(11): pp. e634.
[10] FDA. Patient Safety News #54: USP Statement on Preventing Errors with Neuromuscular Blocking Agents. 2006 Accessed 2nd November 2014; Available from:http://www.fda.gov/downloads/Safety/FDAPatientSafetyNews/UCM417834.pdf.
[11] NSW Health, Safety Information 002/11 Neuromuscular Blocking Agents-Minimising Risk. 2011
[12] NSW Therapeutic Advisory Group. Intravenous Paracetamol Use, Dec 2012. [Accessed via http://www.ciap.health.nsw.gov.au/nswtag/reviews/position-statements.html on 7 Jan 2015.
[13] Gazarian M, Drew A and Bennett A. Medicinal mishap- Intravenous paracetamol in paediatrics: cause for caution. Aust Pres 2014; 37: 29-30.
[14] Prescrire press release: Impending approval of a dangerous amphetamine drug for use in weight control? An unacceptable EMA recommendation that must be overturned. 19 Dec 2014. http://www.prescrire.org/Docu/DOCSEUROPE/20141219_ApprovalMysimba.pdf

include linking with hospital accreditation, individual professional development and/or treatment reimbursement. Interoperability with datasets containing clinical information that allow automatic signalling of adverse events, ensuring harmonisation and sharing between state and national databases, enabling real time evaluation to identify problems rapidly and use of a unique medicines identifier are some considerations for future post-marketing surveillance systems. As regulators such as the FDA and the EMA are actively progressing post-marketing surveillance systems, this Expert Review is timely. Australia can learn from and then develop complementary registry surveillance systems to progress globalised distributed data systems in the future as well as participate in international post-marketing clinical studies. The article by Rajan and colleagues details the future directions for post approval safety monitoring.[15]

Given the proposed extended pharmacovigilant role the Australian regulator will have with the enhancement of the 'back end' of the regulatory process and the ability to add to the evidence base, methods by which non-pharmaceutical sponsorship of applications to update registration of medicines may be required; that is, organisations that do not manufacture but have an interest in the down- or up-scheduling of products based on new evidence should be able to make submissions to the TGA. There is also concern amongst NSW TAG and SHPA members that product information is often not current and that updating of product information of registered medicines is not timely. There is also strong evidence that consumers overestimate the benefit of an intervention and underestimate harm[16] and hence regulators are best to take a 'defensive' position with regard to medication safety. In addition, TGA has a role ensuring that clinicians understand the potential benefits and harms of treatments and that, the clinicians, in turn, ensure that consumers have realistic expectations and can make informed decisions.

Oversight of non-approved medicines: As administrators of the SAS it is clear that the Australian regulator not only has a role in the evaluation of medicines approved for marketing in Australia but also has a regulatory role for medicines for which no application is made for marketing within Australia, those medicines that do not gain approval, those medicines that are withdrawn from the market after approval and those medicines that are marketed but are used in an off-label manner. Hence it has a role and responsibility in developing education and training tools for prescribers and other decision-makers to ensure quality use of both registered, unregistered and off –label medicines and promoting uptake of the knowledge and skills these tools seek to disseminate. NSW TAG and SHPA welcome the recent online learning modules for pharmacovigilance developed by the TGA and NPS MedicineWise. NSW TAG and SHPA note that the increasing preponderance of online learning modules are competing for the attention of time-poor clinicians and that application of the modules' messages is best enhanced when it is applied routinely and in an on-going manner within the workplace.

[15] Rajan PV, Kramer DB and Kesselheim AS. Medical Device Postapproval Safety Monitoring. Circ Cardiovasc Qual Outcomes 2015.; 8:00-00. doi: 10.1161/CIRCOUTCOMES.114.001460

[16] Hoffman TC and Del Mar C. Patients' Expectations of the Benefits and Harms of Treatments, Screening and Tests: A Systematic review. JAMA Intern Med. Published online 22 Dec 2014. http://archinte.jamanetwork.com/article.aspx?articleid=2038981

Recommendations:

- Any new chemical entity, or new off- label use of any chemical entity or any product that has had changes to its scheduling must be evaluated using a post-marketing surveillance scheme and that such a scheme be upgraded to ensure it is comprehensive and rigorous. It is suggested that options for online reporting mechanisms be explored.
- The TGA imposes post-authorisation safety and/or efficacy studies and greater collaboration between regulators and payers, decision-makers, and/or health technology assessment organisations in order to achieve appropriate levels of safety and effectiveness.
- A similar approach be adopted to that employed by the FDA and EMA regarding the use of specialised paediatric expertise for optimising the outcomes of any process that involves sharing information from 'trusted regulators' or undertaking any 'de novo' evaluations (including in the post-marketing phase) for paediatric use medicines
- Consumers and frontline practitioners including hospital pharmacists and nurses be a part of the review process for the Australian context so that look-alike, sound-alike issues do not arise.
- The TGA be aware of international regulatory recommendations and their basis and consults with Australian clinical experts prior to non-adoption or adoption of requirements for labelling and packaging or advices regarding potential drug interactions or other information/warnings being published.
- Genetic variations that influence a chemical entity's efficacy and safety be assessed for relevance in the Australian population by experts in the field.
- Modelling of issues (such as above) prior to adoption of any new regulatory approval system.
- If the above modelling shows benefit, the Australian regulator adopt a staged and cautious approach to using a 'trusted' regulator's information/recommendations.
- The Australia regulator (or similar expert Australian organisation) undertakes a review of current post-marketing surveillance and other pharmacovigilance processes examines the international literature and undertakes a consultation process to ensure that a feasible, rigorous and comprehensive system can be implemented within Australia. Barriers, enablers/incentives and drivers for such a system should be explored. The use of electronic systems should be explored pro-actively.
- If a system using more than one trusted regulator is adopted and these regulators do not provide a consistent recommendation, the Australian regulator should be required to undertake an evaluation process as if the application was *de novo* with the additional information provided by the trusted regulators so as to ensure an objective result
- Although the regulator has no forcing function by which to monitor off-label use of medicines, we recommend that a review of off-label medicines use particularly the monitoring of off-label use of approved new drugs and the consequences of such use should be included in this Expert Panel Review. For example by considering the creation of an off-label use of medicines registry or support for another organisation to develop and maintain such a registry[17]. A minimum dataset of off-label use of a medicine would be collected in

[17] Council of Australian Therapeutic Groups. Rethinking medicines decision-making in Australian Hospitals: Guiding principles for the quality use of off-label medicines; CATAG 2013.

order to enhance pharmacovigilance and assist development of new information and research in order to inform product information and quality use of medicines.

- Consider further development of online learning modules (or collaboration with developers of such modules) that assist clinicians in their evidence-based evaluation of and decision-making about medicines use as well as ways these lessons may be routinely applied in practice to ensure their uptake and value.
- Consider methods by which non-pharmaceutical sponsorship of applications to update registration of medicines may be required. This will likely require further consultation with bodies such as the National Institute of Health and exploration of other regulators' processes.

2.The role and function of the Poisons Schedule and Scheduling Decisions

Scheduling is predicated on assessment of harm: benefit relationship with a fundamental responsibility to protect the Australian public. The Australian public needs to be assured that there is a robust scheduling systems that:

- fully evaluates the harm: benefit ratio,
- is based on evidence (local and international),
- is in the public domain
- is a transparent decision-making process; and
- is pre-emptive as well as responsive.

Current perceived gaps in scheduling evaluations: We note the current system changes to the scheduling decision-making that increase its transparency, flexibility and ability to act in urgent situations. However it is unclear to NSW TAG and SHPA whether scheduling is always a data driven process and how much Australian and international surveillance occurs that may impact on scheduling issues. Is evidence reviewed prior to consultation or does the TGA rely on those making submissions to produce the evidence? How does the TGA recognise the conflicts of interest that might arise in submissions? For example, it was unclear to NSW TAG and SHPA whether the TGA had undertaken a review of the evidence prior to a call for submissions regarding the rescheduling of alprazolam (to S8). The TGA issues paper did not suggest that a literature search had been undertaken. Hence NSW TAG undertook a search and appraisal of the literature with regard to this issue. NSW TAG was unsure whether individuals/organisations were duplicating a similar literature search and evaluation or not. The process could have been made easier by knowing that the TGA were aware of and had appraised the literature regarding this scheduling change so that submitters could have addressed the issues raised. This same issue arose with the recent invitation for public comment for the November 2014 joint Advisory Committees on Medicines and Chemical Scheduling (ACCS/ACMS) meeting. NSW TAG did not have the supporting documentation and evidence-base on which the rescheduling proposals had been based. The comments made in our submission were based on general QUM principles and search of relevant literature. This was in contrast to the Review of cardiovascular safety of non-steroidal anti-inflammatory drugs and Safety review of diclofenac, where there was extensive background material provided in the November 2014 Call for Submissions.

National and state jurisdictional scheduling considerations: Individual state jurisdictions are often the first to act with respect to scheduling issues because of an identified local issue (e.g. from state

police) and their systems are such that they can usually act fairly quickly to address local issues incorporating the assistance of other state departments such as the Attorney-General and the Department of Fair Trading. Local legislation or scheduling changes have occurred in the past in NSW in relation to unscheduled psychoactive substance (substances touted as 'legal highs') and the rescheduling of pseudoephedrine from S2 to S3; and we understand, in Victoria with Chinese medicines and in Western Australia with various cannabinoid substances. However given that it is unlikely that these issues will remain local, NSW TAG and SHPA recommend that the TGA takes a pro-active surveillance and facilitator role to ensure that there is a national approach to such issues and that no gaps can be exploited by 'entrepreneurs'.

Further, rather than a new chemical entity being considered unscheduled (when it does not clearly belong in Schedules 2, 3 or 4), consideration should be given to scheduling it in another schedule category, for example, Schedule X where manufacture, supply and use is prohibited, and hence potential harm reduced until further consideration and post market review. This may then have the advantage of not requiring other legislation to deal with unscheduled substances. It is envisaged that this would capture synthetic stimulants, cannabinoids, and doping agents even if they have not yet been synthesized.

Recommendations:

- Any product that has had changes to its scheduling must be evaluated using a post-marketing surveillance scheme.
- Rescheduling proposals are data-driven and literature evaluations are undertaken and provided to the Australian public prior to consultations for rescheduling proposals.
- Pro-active surveillance of state scheduling issues to allow rapid and pre-emptive adoption by the national scheduling authority.
- Consideration of another Schedule for chemical entities prohibiting manufacture, supply and use when they do not fall into Schedules2, 3 and 4 categories. This will require further consultation but would not encompass the development and investigation of those chemical entities for non-therapeutic intent (e.g. industrial).

3.Issues related to the Special Access Scheme (SAS)

Purpose and current processes for obtaining non-marketed medicines in Australia: It is understood that the purpose of the Special Access Scheme (SAS) is to provide clinicians and their patients with therapeutic options when the use of an Australian-registered medicine(s) will not provide further patient benefit. The scheme recognises various scenarios where availability of such medicines may be useful. For example, where registration for a number of medicines will likely never be sought because of the low volume of potential users in Australia or where a paucity of high level evidence may mean that a submission for marketing approval is likely to be or already has been rejected. SAS products may be requested for life-threatening situations (for which Category A applies) and in less urgent situations (for which Category B applies). Prescribers have 30 days to submit a Category A form to the TGA. Pharmaceutical companies will generally not supply Category B medicines without prior approval by the TGA. The current system for completing the paper forms is cumbersome, time-consuming and has poor clinician compliance.

By complying with such a scheme, prescribers and other clinicians should be cognisant that the SAS product may not have been manufactured to the high quality standards that would normally be required for marketing authorisation, and that use of an SAS product should require obtaining consent of informed patients (or carers) with a clear explanation of the likelihood of benefits, risks of harm and remaining uncertainties of treatments. It is unclear whether the scheme achieves these aims.

Other methods by which unregistered medicines may be obtained by hospitals include the nomination of an approved prescriber; manufacture within Australia via Schedule 5A or directly import via Schedule 19A. Schedule 5A can be used when an Australian manufacturer has a licence to manufacture from the TGA and agrees to do so. These options are more likely to be used when the use of a medicines is described within a hospital protocol e.g. fondaparinux or in response to a shortage of an essential medicine.

Hospital pharmacy departments find the SAS cumbersome and flawed; some of the flaws of the system are regulatory in nature, others are not but may be potentially assisted by the Australian regulator. It is currently unclear how the information obtained by the TGA regarding the SAS applications is used but given the time spent by hospitals identifying SAS products and complying with the Scheme, it is likely that there is multiplicity of effort on a broad scale leading to high burden of cost for Australian hospitals and ultimately the Australian taxpayer.

SAS issues faced by hospitals:

- The inability to pre-emptively stock SAS products. This is especially problematic for hospitals where medicines must be stocked as part of hospital's life-saving drug portfolio but are only obtainable as an SAS product.
- Timeliness of approval of SAS Category B by the TGA and lack of access by a patient to an SAS product that is not strictly life-saving but delay is likely to cause significant patient harm for the 3-4 days that will be required to obtain TGA approval (3-4 days if the product can be found in Australia; longer if not).
- Because of low volume numbers/infrequent use as stated previously, products may be withdrawn from the Australian market despite having high level evidence supporting their use in certain situations. However, if it can be relied upon that their manufacture has not changed; do they require downgrading to SAS status? Perhaps another category could be assigned and another organisation such as NHMRC be responsible for its sponsorship?
    - Health funds are becoming more reluctant to reimburse fund members for SAS medications despite there being valid reasons for their use because of perceived lack of evidence. For example, there is increasing reluctance to reimburse patients for urokinase, which costs approximately $10,000 per course. NSW TAG and SHPA believe that if this medicine had not been allocated to the SAS, this would not be an issue.
- The alternative method of obtaining unregistered products by using an authorised prescriber has become more unworkable as the requirements are increasingly analogous to requirements for the conduct of a clinical trial of the product.
- Hospitals can have concerns where the SAS product is manufactured and it can be difficult to identify this information.

- The appraisal conducted by the TGA in its approval of SAS products is unclear to hospitals and clinicians. For example, the literature used in the appraisal, such as comparative information about the quality of manufacture may be useful for hospital clinicians when they are sourcing products.
- Locating SAS products is challenging because the products cannot be marketed. Furthermore they are often costly unless there is competition between suppliers. However the time to identify various products and their costs takes significant time and this work is duplicated across Australia. Hospitals may also be required to spend significant time changing hospital-based treatment protocols for the new product. Although these are not strictly regulatory issues, the TGA could assist by sharing information with hospitals or with an organisation that could collate this information. This request regarding increased transparency regarding the information and literature used in the appraisal would be useful for Australian clinicians, particularly pharmacists seeking to supply an SAS product as well as other clinicians to ensure safe prescribing, dispensing and administration.
- Strengths of a product approved in Australia for use may not be the most used/relevant strengths e.g. a different strength of fondaparinux is imported by some hospitals.
- As manufacture of many medicines becomes centralised across the world, drug shortages are becoming more frequent and are having increasing and significant impact. The SAS and other procurement methods for unregistered drugs are increasingly used to fill medicine supply gaps related to drug shortages. The use of unregistered drugs by clinicians exposes hospitals to greater liability for which they cannot obtain insurance and requires governance and risk mitigation.
- A recent case regarding the discontinuation of a product highlights a number of hospital concerns that are likely to increase in the future due to increasing drug shortages. A brand of phentolamine injection 'Regitin' was discontinued by Novartis. It was global decision and would not be reversed. Phentolamine is the first line emergency treatment for acute intra-operative hypertension particularly when due to alpha sympathetic agonists. It is a vital emergency drug for use during surgery for phaeochromocytoma. A new product was sourced and was available from a supplier via the SAS. The ampoules of the new product are labelled in Asian characters (it is not entirely clear as to the country of origin and there is no English on the ampoules). The strength of the product is not in English on the ampoule, however each ampoule is individually stamped with an expiry, which is legible. When the new product is ordered, an English version of the product information can be requested but is not automatically provided. NSW TAG undertook an group email discussion with its members to identify how members were dealing with the discontinuation. There was also discussion with NSW Health.

Recommendations:

- Extend applicable Category A medicines to include medicines where the delay of treatment using the SAS medicine for up to a 4-7 days would result in patient harm.
- Operate the SAS via an online approval system. All forms are readily accessible no matter where the prescriber is and may be completed online. Notification of application and approval (once approved) to the nominated pharmaceutical supplier and dispensing pharmacy/pharmacy department should be automated. A patient consent form should be

automatically produced for the prescriber to use. A link to patient information should be provided wherever possible and relevant.

- Have the TGA (in consultation with frontline clinicians) develop risk mitigation strategies when SAS products are approved. For example, in the phentolamine scenario described above, the TGA should ensure that the Product Information and consumer information is in English and that advice regarding other risk mitigation strategies is provided, when relevant.
- Model the online SAS approval system on the streamlined PBS authority scheme where prescribers must acknowledge their compliance with SAS requirements. In order to mitigate inappropriate use of the scheme, particularly for Category B products, a delegate of the responsible hospital/local health district Drug and Therapeutics Committee (DTC) should conduct an independent review and when satisfied endorse the SAS request. For example, in a manner analogous to NSW car registration requirements (where prior insurance and independent mechanics/safety compliance check is required).
- Consider a different system of categorisation that aligns with the level of potential harm posed by the SAS product in order to streamline the SAS approval system such that some SAS products (both Category A or non-Category A) may obtain immediate approval while others may require different levels of review by the TGA.
- Hospitals should be able to procure and hold a supply of SAS stock where use is within a hospital DTC-approved protocol or part of a hospital's life-saving drug portfolio (as prescribers may vary). DTC sign-off should be required prior to approval. A method should be developed that enables pharmacies to procure additional SAS stock in the event of product expiration. Once this stock is used or discarded due to expiry, hospital pharmacies will need to complete an online form stating the reasons for use/discard and so on, similar to the current form requirements. As above, notification of application and approval to the nominated pharmaceutical supplier and dispensing pharmacy/pharmacy department should be automated. We recommend that a patient consent form should be automatically produced for the prescriber to use and link to patient and product information should be provided wherever possible and relevant.
- The Panel consider how the TGA has been using the information gained from the SAS. At the very least, there should be some system that includes monitoring of applications and approvals, their circumstances such that the TGA can prospectively identify issues and where appropriate, enable approval for marketing of such products (with or without pharma-sponsorship). An online system would facilitate the TGA's ability to monitor for possible rorting, it's forward planning and may assist a third party to deal with other highlighted SAS issues that are not part of the regulator's purview.
- Consider TGA (or TGA support for another organisation) to develop a portal that provides information about SAS products- evaluation, availability, level of use, adverse effects, cost.
- The TGA to re-evaluate the 'authorised prescriber' method with regard to its utility, workings and outcomes.

4.Direct to consumer advertising of Schedule 3 products

NSW TAG and SHPA understand from the Panel interviews that direct to consumer advertising (DTCA) of Schedule 4 products is not contemplated by the Panel. However the potential harms and possible benefits of DTCA of Schedule 3 products will be considered. It is unclear to NSW TAG and

SHPA why it is considered that DTCA for Schedule 3 products has a lower risk than Schedule 4 products. Only two countries in the world have DTCA of medicinal products, New Zealand and the United States of America. A review of the literature[1-10] notes the following:

- Most of the studies/publications refer to DTCA of prescription (as opposed to pharmacist only) medications.
- There doesn't appear to be studies that directly measure the harm caused by DTCA. However, there are indirect references to harm, as DTCA may cause an increased and possible inappropriate use of medications, where they were widely used before adverse effects were fully known. (The two main examples stated in the literature are rofecoxib and tegaserod). There was also a paper that reported DTCA leadingto the over-diagnosis of high cholesterol and over-treatment of populations where risks outweighed the benefits.[3]
- DTCA may indirectly cause harm by diverting resources from more cost-effective interventions.[4] Another argument against DTCA is that many new drugs are no better and more expensive than older therapies.[5] However they may gain increased use out of proportion to their actual clinical benefit through DTCA.
- There are two articles which presents arguments for and against the use of DTCA.[4,6] While proponents of DTCA argue that there is a lack of evidence to show that DTCA is harmful to consumers the converse can be said regarding the benefits, that is, that there are no proven benefits of this advertising. During the panel interview an example was discussed postulating that DTCA of the emergency contraceptive pill may reduce unwanted teen pregnancies. Robust evidence is required to convince NSW TAG that advertising of the emergency contraceptive pill would be of public benefit in contrast to education included in school sex education programs as well as other external educational programs that not only discuss contraception but also discuss sexually transmitted diseases.
- There are concerns that the advertising to the consumers is poor and does not meet regulatory requirements, can be vague and emotive and does not adequately communicate information that promotes shared informed treatment choice.[1,5]
- A letter to the editor by Greene and colleagues discusses the changes in DTCA when medications were changed from prescription only to OTC status. These authors reported that the provision of information on the potential harms/adverse effects was diminished in the advertising of OTC medications.[7]
- Liang and Mackey address the inappropriate use of medications following DTCA via internet and social media avenues.[8] It is likely that this form of media would be difficult to regulate.

Recommendations:

- **Direct to consumer advertising (DTCA) of Schedule 3 (and 4) products in Australia is not recommended**. We believe DTCA would be a revenue/sales-generating strategy for drug companies, rather than actually benefitting the consumer. This money is far better spent on QUM awareness programs or other programs for consumers. It could increase the costs of medicines because once one pharma competitor advertises, the others must follow (a vicious cycle) and then recouping of advertising costs would not be achieved through

increased sales. It would be much better if pharma considered that their market share would be increased with the benefits that they can provide to patients through support of QUM programs. It is clear that, despite grave concerns by New Zealand clinicians of the harm that DTCA has had in New Zealand[1], recalling DTCA once the 'cat is out of the bag' is very difficult, if not impossible. NSW TAG and SHPA believe when the above are considered, the DTCA has a negative benefit: harm ratio for the Australian public.

- **TGA-approved and ip-to-date 'product information' should be mandatory for all registered and listed medicines (and must include the basis for the therapeutic claim(s)) no matter what their scheduling.** It would be accessible to the general public on the TGA website (and other websites such as NPS MedicineWise). Currently there is no guarantee that a Schedule 2 product will have a PI or CMI. NSW TAG members have indicated that they often find it very difficult to identify excipients of Schedule 2 products, particularly when the product is not to hand. There is also a need to consider harm mitigation from the perspective of minimal health literacy of Australian population.
- **The TGA should undertake the role of handling complaints regarding advertising of all registered and listed medicines.** In the past, NSW TAG has brought a complaint against a pharmaceutical company through Medicines Australia for failure to provide balanced information and lack of disclosure of financial and other interests on a company-petitioning website. The company was fined and NSW TAG was impressed by the Medicines Australia Code of Conduct Review process. However not all companies are members of Medicines Australia (MA) and complaints against these non-MA companies have led to legal action against individual complainants. Such situations should not be allowed to arise in Australia. If advertising of S3 products was allowed, the TGA or another independent government body would have to take a key role in the handling of complaints. This benefit to reducing red tape and increasing productivity is doubtful.

DTCA References:

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5. Transparency and accountability of the Australian regulator

NSW TAG and SHPA welcome the recent efforts that have been undertaken at the TGA to improve its accessibility, usefulness and website. However we would like to make comment regarding difficulties in identifying the relevant section/person within the TGA to discuss an issue or follow-up with, once an issue has been lodged. For example, recently a NSW TAG member found that the CMI of Septrin Forte and Septrin Sugar-Free Suspension was incorrect with Serenace being documented in the CMI rather than Septrin. The member reported the error to info@tga.gov.au and specifically requested advice that the email had been received. To date (almost 2 months later), the member has not received acknowledgment or any response of his email. It remained the responsibility of NSW TAG to alert its members to this error, however it is unknown how or if other users have been alerted.

NSW TAG and SHPA understand that a generic portal to the TGA may be useful but recommend that:
1) an automated email is received by the submitter so that they know that the email has been received;
2) the TGA responds to such submissions within 1 working day of the submission by allocating a case worker and providing the case worker's name and contact details to the submitter as well as a proposed pathway for resolution and a timeframe for resolution; and
3) that such processes are identified on the TGA website. NSW TAG has also encountered similar difficulties when wishing to alert the TGA to labelling and packaging issues that our members believe increase risk of patient harm.

As these issues have become more frequent, NSW TAG has a webpage identifying products where look-alike and sound-alike issues have been reported. We also contact the responsible pharmaceutical companies with varying amounts of success. Again, NSW TAG has assumed a safety and monitoring/ dissemination role that is more suited to a national regulator, with rapid and consistent response mechanisms.

We believe that changes in packaging and labelling should not be approved by the TGA without prior consultation with consumers and frontline health practitioners, that is, pharmacists, nurses and doctors, in both the hospital and community settings and that changes in packaging and labelling should not just appear on shelves without adequate forewarning and explanation. We believe that the TGA as the regulator should apply rigorous evaluation of proposed packaging and labelling changes noting that selection error is a common reason for patient harm.

6. Other 'red tape' issues

A NSW TAG member recently had an issue with regard to obtaining a sterile product interstate. The product was made by two manufacturers in Brisbane, Queensland and Western Australia that were not TGA-authorised manufacturing laboratories. The TGA would not approve the use of the product by a NSW hospital located in Coffs Harbour. However it would have been possible for any hospital in Queensland to use the Queensland-based product. The resolution of this issue was time-consuming and costly. It is unclear what the exact problem was: are standards for manufacturing sterile products not national or is it that some laboratories have not applied to the TGA for authorisation (because of cost or other issues) or is there a waiting list for assessment for authorisation or another

reason? It is acknowledged that the TGA has safety responsibilities but it is unclear whether this issue arose because of 'rules' or from valid safety concerns.

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