A Bigger Picture of Medicines Shortages: an action update, and new perspectives

It started with members voicing their deep concerns, through SHPA channels, about the frequency, nature and information surrounding medicines shortages. This led to the publication of SHPA's influential report on the issue, *Medicine shortages in Australia: A snapshot of shortages in Australian hospitals* in 2017. Based on a member-driven prevalence survey of medicine shortages experienced across the country, the report highlighted the true extent and impact on patient care – an extent and impact previously unrecognised in the public discourse. The Federal Minister for Health and numerous regulatory bodies responded directly to the publication, and, gradually, change has been embraced, with SHPA lighting the path.

This is an example of SHPA members looking to the bigger picture when it comes to problems they're experiencing on the ground – which is what this issue of *Pharmacy GRIT* is all about. Here, we provide an update on SHPA's recent medicines shortages advocacy. However, because we know you, the SHPA members, already know so much about this complex matter, we also bring you a couple of unique viewpoints on its evolution and its consequences. *Pharmacy GRIT* Editorial Board chair, Kerry Watts, reflects on the creativity and resilience that can be sparked by such problems, encouraging us to be wary of automatically reverting to "business as usual" when supply returns. Meanwhile, SHPA member Sandip Manku – pharmacist and industry veteran – arms us with the industry perspective on medicines shortages, discussing some ways sustainability of access to medicines might be achieved, considering the pressures in this part of the supply chain.

After SHPA members shook things up: an update on our Medicines Shortages advocacy

By JOHANNA DE WEVER

General Manager – Advocacy and Leadership, SHPA

Since publication of our Medicine Shortages report in mid-2017, SHPA has been pleased to see greater attention given to the important issue of ensuring patients have access to appropriate medicines during their stay in hospital. Following strong media attention nationally, the report was well received by regulatory bodies who had been quietly concerned for some time. The data gathered by SHPA members, whilst anecdotal, was one of several incentives to consider changing the status quo.

As ongoing reports of shortages of vancomycin and fentanyl hit the newspapers, meetings began to be arranged by the Department of Health with a range of pharmacy and medical groups as well as medicine stakeholders to discuss revising the shortages protocol. Despite the repeated petitions of Chief Medical Officers, it appeared that the patient impact of shortages in hospitals had not previously been well understood, and several incorrect assumptions about priority supply for hospitals were corrected by SHPA. The working group met for a number of months on a proposed model which was considered by Minister for Health Greg Hunt before Christmas 2017.

SHPA is now keenly following the consultation recently opened by the Therapeutic Goods Administration regarding the proposed regulation of medicine shortage reporting. The proposed model addresses many of the concerns in our report, including the need for shortages to be considered with a 'patient-first' lens, and the necessity and priority of timely notification of shortages for clinicians. Fundamentally, it requires mandatory notification from suppliers of all shortages and then publication of some of these by the TGA depending upon the projected impact on patients. Sponsors who flout these laws would be liable for substantial penalties – the scope of which are up for consultation in the document.

Of particular interest to SHPA members will be the 'Medicines Watch List' – a proposed list of 127 medicines, shortages of which leave patients at 'extreme' or 'high' risk. The list includes a wide range of antibiotics, antivirals and emergency and critical care medicines essential to hospital operations, as well as vaccines and antivenoms. A quick review of the listed medicines indicates a majority are most likely to be used in a hospital setting, and 47% were listed by SHPA members as in shortage in April 2017, demonstrating again the severity of the problem and the key role Hospital Pharmacists play in its resolution.

For the proposed protocol to be enforced it would need to become legislation and pass parliament, and SHPA is hopeful this will be undertaken in the second half of 2018. The consultation documents have been shared with SHPA members and a collated response is due by April 27. Any interested members are encouraged to visit **<http://www.tga.gov.au/sites/default/files/consultation-management-and-communication-of-medicines-shortages.pdf>**, or to contact the Advocacy and Leadership team at SHPA to contribute to this work. ●

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Amid the dark clouds of medicines shortages, a rare silver lining

By KERRY WATTS

Chair, *Pharmacy GRIT* Editorial Board

In this issue dedicated to "zooming out" and getting a greater perspective on current pharmacy practice, the Chair of the *Pharmacy GRIT* Editorial Board, Kerry Watts, reflects on how medicines shortages have actually *forced* pharmacists to think about the big picture of medicines protocol and routine prescribing – and sometimes with surprising results...

The increased frequency and scale of medicines shortages in recent times demands, of course, correspondingly urgent and extensive action. During this ongoing challenge, though, it's worth pointing out when clinicians' responses form a silver lining to these dark clouds.

Of recent shortages, one of the most memorable was the year-long shortage of piperacillin-tazobactam (piptaz). Piptaz is a broad-spectrum antibiotic providing cover for both gram positive *streptococci, methicillin sensitive staph aureus* (MSSA) and gram negative *E.coli, klebsiella, proteus, pseudomonas* and *anaerobes*.

A vital antibiotic, piptaz is used to treat complicated infections such as diabetic foot ulcers and hospital-acquired pneumonias involving a risk of multi-resistant organisms.

The piptaz shortage was fortunately paralleled with the timely availability of intravenous amoxicillin/clavulanic acid (Augmentin IV). Augmentin IV demonstrates a similar antibiotic profile to piptaz, making it an appealing substitute option for piptaz. However, Augmentin IV is not a surrogate for piptaz, as it has a reduced gram-negative spectrum and no pseudomonas cover.

Urgent multidisciplinary team meetings were organised around the country to make decisions on replacement intravenous antibiotics. Clinicians needed alternative guidelines (such as

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those described in Table 1) to treat serious and life-threatening infections previously treated with piptaz – febrile neutropenia, for example. The introduction of Augmentin IV was clearly valuable during the piptaz shortage; however, the lack of pseudomonas cover and cost concerns provided limitations for a first line alternative to piptaz.

Statistics showed that the usage of substitute antibiotics had not increased as significantly as Antimicrobial Stewardship Committees had expected. The National Antimicrobial Utilisation Surveillance Program (NAUSP) reported a reduction in total usage and rates for the substitute antibiotics fell below the national average. This reduction in intravenous antibiotic use may directly correlate with increased reliance on infectious diseases advice. The shortage of piptaz, that is, may have caused clinicians to review clinical parameters and patient factors more closely, affecting overall antibiotic therapy. On the ground, too, within at least one large hospital, the infectious diseases team reported no obvious increase in mortality and morbidity when the alternative guidelines were in use.

The question is: do we revert to the original use of piptaz?

In 1945, Sir Alexander Fleming raised the alarm regarding overuse of antibiotics and warned that the "public will demand penicillin…then will begin an era of abuses".1 The modern-day misuse of antibiotics in agriculture and hospitals negatively impacts on drug-resistance and in 2013 the Centre for Disease Control and Prevention (CDC) announced the human race to be in the "post-antibiotic era".[1] Given the global magnitude of antibiotic resistance, the decision to revert straight back to the previous use of piptaz should not be automatic.

Recently, the London Underground strike saw two-thirds of the system closed for 48 hours. The disruption to normal service forced commuters to stop and rethink their travel route. Economists saw an opportunity to monitor the alternate routes commuters took. Interestingly, as services were restored, tens of thousands of commuters didn't go back to their previous travel route, preferring to continue using the route adopted during the closure. After an obstacle was placed in the way, commuters were forced to solve the problem, and in the process, some devised a route that was even better than their original way to work.

The piptaz shortage, first seen as an inconvenience, effectively led to the creation of a 'new route' and a new perspective in routine prescribing. It forced stakeholders to rethink and formulate a positive change in practice.

Currently, discussion centres on the implementation of narrower-spectrum antibiotic guidelines (Table 2). The availability of Augmentin IV can be utilised in place of piptaz to treat infections where pseudomonas is not expected. This is a positive step in the fight against antibiotic resistance.

The drug shortage caused clinicians to stop and think about current practice. The development of temporary guidelines has established an alternative treatment pathway. There is no evidence to suggest that the new antibiotic guidelines have negatively impacted patient outcomes; and they are potentially providing a positive impact on reducing antibiotic resistance.

In such cases, could the dark cloud of a medicines shortage have a silver lining? ●

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Table 1: Examples of alternative antibiotics guidelines.

	Suggested antibiotics
Aspiration pneumonia	Ceftriaxone & metronidazole
Gastrointestinal infections	Ampicillin, gentamicin & metronidazole
Febrile neutropenia	Cefepime
AMS/ID approval for amoxicillin/clavulanic acid IV (Augmentin IV)	

Table 2: Potential future antibiotic guidelines.

	Suggested antibiotics
Intra-abdominal infections	Amoxicillin/clavulanic acid IV (Augmentin IV) as monotherapy
Cellulitis	Cefazolin or flucloxacillin
Non-diabetic leg ulcers (where pseudomonas is not expected)	Amoxicillin/clavulanic acid IV (Augmentin IV)

Medicines Shortages – Reflections from Industry

By SANDIP MANKU
SHPA member, pharmacist, and owner of a specialty pharmaceutical company

Pharmacy is a big ecosystem, and SHPA members are spread throughout it, leading the way in improving all its facets to evolve and optimise medicine use for the benefit of patients.

When it comes to the issue of medicines shortages, the pharmaceutical industry is obviously a key player, and understanding the perspectives of industry can only help efforts to address the issue. For *Pharmacy GRIT* readers, then, we have asked Sandip Manku – an SHPA member who has breathed "the industry side of things" for many years – to give us an insight into the industry perspective.

Sandip received his pharmacy degree from Monash University in 1995 and an MBA from Nottingham University, UK in 2002. He has worked as a hospital pharmacist in the UK, and he has also owned and operated a community pharmacy in rural Victoria. Sandip commenced his pharmaceutical industry work in 1998 and has had several industry roles focusing on hospital generic sales and business development. In 2015, he started his own speciality pharmaceutical company focused on the development, registration and supply of hospital medicines in Australia.

Medicines shortages have been a large focus of my current position, which has involved providing alternative overseas products via both the Special Access Scheme and S19a pathways. This includes intravenous (IV) antibiotics and IV oncology products. We also distribute and supply TGA-registered products which are on various national and state hospital tenders.

In the last year or two, there have been an unprecedented number of market shortages for which no alternative product has been available, or the alternative product has been unable to cover the shortage. Here, I provide some reflections on the communication of shortages by manufacturers, causes of shortages and some of the challenges faced by the manufacturers in the Australian market, all from an industry perspective.

Communication of a Shortage (or lack thereof)

One of the biggest challenges felt all along the supply chain is communicating with suppliers to confirm whether there is an actual shortage in the market. Some of the Australian suppliers publish shortages on the TGA website, however, **it is not currently compulsory for sponsors to make these reports.**

If there is a definite shortage, then there might already be an alternative product that can be used in its place – however, this can also cause a cascade of events, especially if these alternative products themselves fall into shortage, triggering extra communication requirements and other workarounds. Consider, for example, the recent gentamycin recall and its effect on tobramycin demand; these situations show the importance of widely available up-to-date information.

Currently, the hospital pharmacy team is expected to confirm whether there is an actual shortage in the market, and then identify an alternative product. The early stages of this process are vital: any alternative product poses a challenge to hospital protocols and increases the

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likelihood of errors – products may have foreign labels, for example, and the variation in their manufacturing quality (GMP standard) can come into question as usually, alternative SAS or S19a products are all unlicensed. Therefore, anything that can support the hospital pharmacy team earlier in this process – such as improved access to information about the reality of shortages – should be a priority.

Causes of Shortages in Australia

There has been a lot written in the media about the causes of shortages, with blame being directed at everything from manufacturers, governments, PBS reform, Active Pharmaceutical Ingredient (API) shortages and quality problems, to earthquakes and fires.

Mergers and Acquisition activity

Some large manufacturing companies have merged and hence the number of available products in the market has decreased. Additionally, API suppliers of these products may have also ceased production for varied reasons.

Prices in Australia

The medicines in shortage over the last two years have often been older, well-established, and low-priced products – interestingly, I have observed the same products priced higher in Europe and North America. Lowering of prices either through government processes or through companies tendering is certainly a factor in the increasing frequency of medicines shortages; I explain this in more detail below.

Regulatory Processes

The complexities of a product in market are not always easily understood. While a product may be available in the USA or Europe, it may not necessarily be available in Australia due to differences in either the API, formulation, or the manufacturing site of the product. One product often goes through multiple processes in its assembly to get to the finished form available in a pharmacy, and the steps in-between are all of interest to regulators. The more tailored the product to a specific market, the more risk of a shortage occurring, with regard to both the consistency of supply and the possibility of one-off production problems.

When considering API shortages, it is logical to ask whether an API can be obtained from two or more sources. In theory, yes it can, however, this adds substantial costs to product development as each API needs to be validated and tested and API manufacturers won't manufacture and hold stock unless it has been forecast. The lead time for producing an API can also range widely – some APIs come from plants, for example, and therefore seasonal variations or storms/floods can disrupt supply. Further, time must be dedicated to working through any regulatory changes with the TGA – such changes won't provide a "quick fix" when a problem befalls a product, and in any case, these TGA processes are the reason that Australia has one of the highest standards of medicines quality in the world.

Manufacturers are facing increased, substantial price reductions in the Australian market due to PBS price disclosure, as well as competition from other manufacturers in the perpetual fight for market share. Community pharmacy banner groups are merging and aligning to particular wholesalers and their preferred generic companies. The remaining generic companies in the market then fight for the shrinking number of "independent" community pharmacies, and also tender to the hospital market. The hospital market is seen as fairly easy to enter in terms of barriers, however real challenges are involved in successfully supplying throughout the entire contract period, including penalties for non-supply.

Another factor is that 'price erosion' is occurring more quickly in Australia due to shorter PBS cycles and the removal of the originator molecules from PBS calculations. See Figure 1 for the effect of PBS price disclosure on a hospital PBS product such as Pemetrexed 500mg, for example.

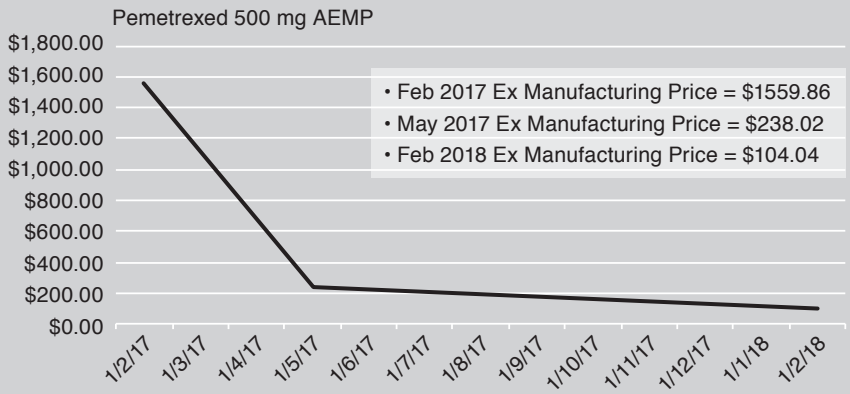

Figure 1. PBS price disclosure 'price erosion' effect on Pemetrexed 500 mg.[1]

As listed on the TGA website there are nine manufacturers for Pemetrexed 500 mg; each would have invested around AUD$150,000 for filing regulatory documents with the TGA in 2015. Did each of these nine manufacturers see this as a sustainable business and will each of those nine make a return on their investment? Will some leave the market? Will the manufacturing cost remain the same? Is this price now an incentive for those manufacturers to continue making Pemetrexed 500 mg? How important is the Australian market now for these manufacturers when the price in other regions may be as high as AUD$2000 per vial? As this competition among generic manufacturers plays out, the risk of potential innovation away from the molecule to newer patented molecules may also occur – therefore, the market itself might become a lot smaller; this is another factor in manufacturer's decision-making.

There are also the "within tender" changes that occur when subsequent batches are purchased. For example, there can be unforeseen currency exchange rate changes, rises in API costs, changes in API availability, and manufacturing issues within factories. These factors can especially influence product supply in long tenders that can last up to four years.

Manufacturing factories run 24/7 in many countries, and they have rigid production schedules. The scheduling of more profitable and larger volume medicines will likely take precedence over the lower-profit and smaller volume medicines. The fact that Australia is a smaller market compared to Germany (85 million people) or the USA (300 million people), for instance, is also a factor in medicines meant for Australia getting onto production lines.

Some suggestions to help achieve sustainability

The requirements around supply of products for hospital contracts that have a MINIMUM expiry time of 12 months leads to a lot of product wastage. Saving stock that would otherwise be written-off translates into lower prices for hospitals – to this end, PHARMAC in New Zealand has allowed for the supply of medicines with 6 months left before their expiry or 75% of a products total shelf life.[2]

Another idea that could improve the sustainability of our supply arrangements would be for the PBS pricing disclosure process to also capture extra data from manufacturers, such as variations in the exchange rate from the last report, Global Price comparisons, API price changes and other manufacturing cost changes. Such factors directly impact future supply of a product, and therefore this data could help to illuminate market dynamics in Australia and signal whether there are companies exiting or planning to exit the market, potentially leading to medicines shortages. These factors could also be scrutinised for the purpose of actively ensuring the market remains viable for manufacturers. A closed tender process or PBS price disclosure isn't necessarily the best pricing mechanism for all products, for example. Product viability and importance from a public health perspective should also be a consideration (for example, when considering a last line antibiotic product such as vancomycin).

Ultimately, prices will rise as risks faced by suppliers increase through contract penalties or due to other suppliers leaving the market. We are fortunate in Australia to have alternative suppliers – hopefully their viability is considered as work is carried out to address the increasing phenomenon of medicines shortages, so they can continue to explore and navigate global supply chains and provide innovative solutions to this complex issue. ●

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