Technical Alert

Permitted Indications Update (2) including Biomarkers

Permitted Indications

The finalisation of the Permitted Indications is underway following the close of the consultation period on October 31. The TGA expect to have the list finalised for sign off by the delegate of the Minister in late November or in December, for the effective date of 1 January.

A summary of current state of regulatory reforms, including the Therapeutic Goods Amendment Bill No. 1 of 2017 and permitted indications as a Legislative Instrument is included in today's Member Alert here, and our most recent technical update on Permitted Indication is included here.

The TGA have advised that the final list will be published prior to publication.

Permitted Indication – Legislative Instrument

The Bill introduces a new Legislative Instrument: a list of permitted indications. All listed medicines must transition from free text indications to Permitted Indications within 3 years, after which time medicines that have not transitioned will be cancelled from the ARTG. In the first 18 months of the 3 year period, medicines may transition without paying a fee.

Proposed Changes Representing Increased Regulation by Permitted Indications

CMA is concerned that the proposed permitted indications list has removed some items or included other warning statements that represent an increase in regulation. Primarily, the items are the removal of indications refer to health maintenance of biomarker levels, the removal of healthy foetal development indications and the addition of two maternal health warning statements – including advice not to use pregnancy products in the first trimester without medical advice. The removal of all medicines for infants under 6 months is proposed.

In the very recent publication of an updated permitted indication list, many health enhancement claims were removed based upon the challengable assumption that they 'imply enhancement from a compromised state' (e.g. implied reference to serious condition). In addition, there is the likely removal of listed medicines with a tradition of use by failure to include traditional evidence qualifiers for those types of medicines.

Increased Regulation vs Deregulation

A medicines regulator needs to effectively and fairly regulate medicines. There is the need to achieve a balance between supply of medicines and information for consumers, whilst ensuring quality, safety, and efficacy / truthfulness in labelling and advertising. Where regulatory balance, transparency and clarity is achieved, there should be relative harmony between the regulator and the regulated industry.

The current level of regulation in Australia has generally worked favourably due to recognition of the quality of Australian goods. There is also a recognised need that appropriate and effective regulation enhances a fair playing field for all. However, there are also concerns that many changes currently proposed via legislative instruments represent new and increased regulation. The Department of Health's Policy Paper on Deregulation for the purposes of cutting red tape provided that 'The Australian Government's deregulation agenda is guided by the principle that **regulation should only be imposed where absolutely necessary**, and should not be the default position for dealing with public policy issues.' Increased regulation may occur both individually and as a combined effect, particularly where there may be other penalties or disincentives. Any proposed increase to regulation must be balanced with consideration as to whether industry can continue to operate effectively within the regulatory landscape.

The Office of Best Practice Regulation (OBPR), run by the Department of Prime Minister and Cabinet (PMC) define regulation as '*Any rule endorsed by government where there is an expectation of compliance'.* OBPR also provide that best practice regulation includes the timely use of evidence to inform decision making as required through the Australian Government's regulatory impact analysis system.

Concerns received from industry is that the proposed changes are not representative of problems that are occurring by the use of these medicines within the population. Usually, the magnitude and evidence of a problem are required by OBPR to be closely examined and captured within a Regulatory Impact Statement (RIS). This ensures that the proposed regulation is addressing a valid problem of public significance that warrants government investigation and action, rather than a perceived problem or one of private interest.

In this instance, the OBPR provided the TGA with an exemption because an equivalent process had been conducted (the MMDR review) and that all changes were deregulatory. In this instance, however, the MMDR only discussed general requirements of the listed pathway being lower risk, and did not examine the type of specifics described above. Therefore, CMA does not believe the assessment is equivalent and therefore that the RIS exemption is likely not applicable. CMA have written to the TGA in this respect and have also noted that the changes are not deregulatory, therefore the RIS exemption should not apply. We have asked that member submissions are closely considered when developing the final list with view to not increasing regulation, where the impact has not been fully assessed.

A RIS assessment is required by the OBPR where there will be significant financial impacts to businesses as well as effects upon the healthcare of individuals. CMA have continued to advocate to the TGA regarding the need for transparent, evidence based consultation on particular proposals, and for the provision of a regulatory impact statement where required by due government process.

The TGA have provided a response that they are continuing to review the 3,000 submissions received.

CMA is considering to evaluate options that may be available if necessary to protect the listed medicine category when the final draft by the TGA is released, which is expected in the next several weeks.

Biomarkers

A history of the discussion relating to biomarkers is included below. The CMA's submission on this matter is also included here.

CMA believes it is not appropriate to remove reference to the health maintenance of biomarkers for listed complementary medicines when viewed as part of the overall public health landscape as well as the comparative regulatory situation for foods. However, the TGA feel that the evidence is lacking and therefore that the claims may be misleading, unless they are pre-assessed by the TGA at the level of the new pathway.

The removal of biomarkers by the TGA is being achieved not only through the permitted indications list but also through additions to restricted representations in the Advertising Code, which would remove them from the listing pathway (but not the new assessed pathway).

There is suitable and relevant evidence for complementary medicines and biomarkers, but it depends upon how the study group populations are accepted by the TGA. If biomarkers can be retained, this evidence issue can be revisited for the proposed 2018 evidence guideline consultation.

Biomarker excerpt – CMA correspondence to TGA Delegate of the Minister, 6-11-2017

> 'We ask you to consider the impact of the changes upon the sector and the community in respect of the food and medicine landscape. We draw your attention to the fact that the proposed changes to the 'Biomarker claims' such as restricting the use of a claim relating to the maintenance of healthy cholesterol levels, is at stark odds with the position of FSANZ and the claims that are available to foods currently. It seems unusual to us that a medicine that complies with the quality and GMP standards enforced by the TGA, is unable to make an equivalent claim to a food using the same active ingredients, even though the consumer protection of quality manufacturing in the food environment is demonstrably weaker than for a medicine. In fact, foods are able to make much stronger claims than those that are proposed for the permitted indication determination. Complementary medicines cannot be considered in isolation from pharmaceutical medicines and foods, and must be regulated fairly within the reality of this consumer landscape. For example, we ask whether it is regulatorily appropriate that persons try to reduce cholesterol levels using several litres daily of phytosterol-enriched dairy milk, when complementary medicines will not be able to refer to the maintenance of healthy cholesterol levels. The anomaly of the situation is further highlighted by the RACGP guidelines which recommends, during the recommended lipid profiling schedule, that lifestyle (i.e. non-pharmacological, self-managing) measures are recommended in individuals over 45 of low to moderate cardiovascular risk[1].'

Biomarker excerpt – correspondence from TGA Delegate of the Minister to CMA, 11-11-2017

> 'As you are aware, TGA post-market compliance monitoring of listed complementary medicines has consistently found very high levels of non-compliant products listed in the Register. A significant majority of this non-compliance is in relation to the evidence held by sponsors to support indications and/or inappropriate indications being included in the Register or on product labels.
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> The introduction of the permitted indications reform also needs to be considered in the context of the new pathway for assessed listed medicines. This new pathway will expand the listed medicines pathway to allow higher-level indications than are currently appropriate for listed medicines. However, to be able to make these claims, the efficacy of the medicine has to be demonstrated to the TGA. Currently, listed medicines making

[1] Royal Australian College of General Practitioners, Guidelines for preventive activities in general practice 9th edition: 8.3 Cholesterol and other lipids, retrieved electronically: https://www.racgp.org.au/your-practice/guidelines/redbook/8-prevention-of-vascular-and-metabolic-disease/83-cholesterol-and-other-lipids/

such claims represent the majority of non-compliance and the highest safety risk for consumers'. As the regulator, in the interest of safety for the consumer, we need to know that these medicines work.

Indications which we are confident fit the risk profile of the middle pathway are indications referencing biomarkers (for example: glucose, cholesterol and blood pressure levels). Biomarkers are known risk factors for serious diseases (such as: diabetes and cardiovascular disease), the measurement of which cannot be self-assessed and requires ongoing medical supervision. Consistent with the eligibility criteria for low risk indications, indications implying serious diseases and those that cannot be self-diagnosed or self-managed will not be included in the list of permitted indications.'

Biomarker excerpt – CMA correspondence to TGA Delegate of the Minister, dated 14-11-2017

'Members are significantly concerned of the view that health maintenance claims are perceived to imply serious disease. While there is a recommended testing protocol for biomarkers, they are normal biological substrates whose levels can aimed to be maintained for the purposes of maintaining overall health, both before required testing schedules and also when doctors advise self-management of biomarker levels (lifestyle measures) – in all of these cases there is no requirement for regular, ongoing medical supervision.

Using the cholesterol example, by Australian clinical guidelines, this self-management period applies to older individuals who are low to moderate risk and applies until they reach their next recommended testing period (two to five years depending on cardiovascular risk). It is not unusual or harmful for Australian consumers to proactively self-manage their health by a number of means.

Biomarker claims are consistent with low risk indications and have been considered compliant (when correctly worded) for over 25 years since the inception of the Act. There isn't - that we are aware - evidence to suggest that during this time Australian consumers have been harmed through the use of supplements as part of health maintenance measures for biomarkers, until such time as it is determined that they are higher risk and require more serious and higher risk pharmacological measures from their healthcare practitioner. Despite the lack of evidence of misuse or harm over a quarter of a century, industry have agreed to mitigate any theoretical risk of off-label use or misuse, by way of a specific warning statement(s) as outlined in our submission.

The view that it is suitable for a consumer, who has been advised to self-manage by their practitioner until symptoms worsen was provided by the AAT case regarding cystitis, and in this case the same principle applies as there is medically advised self-management in the interim period of 1 to 5 years between required checks.

Complementary medicines for biomarkers are not intended for use in serious conditions or for high risk individuals. The continued use of the low-level maintenance claims in combination with a warning statement is a far more conservative regulatory approach than allowing for the silent but potentially mis-educated off-label use. Your consideration of this larger regulatory picture is greatly appreciated.'

Member Actions

CMA encourages its members to continue to engage in the regulatory process and to provide feedback to us, which can be provided to technical@cmaustralia.org.au Feedback on the level of impact any permitted indication changes may have upon your business is particularly welcome, including estimates of financial impacts.

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