Comment: Proposed guidance for the use of Boxed Warnings for prescription medicines

Thank you for the opportunity to comment on the *Proposed guidance for the use of Boxed Warnings for prescription medicines*. While we generally support the contents of the guidance, we are concerned that it may, in its current form, underplay the serious adverse events associated with certain medicines and thereby hinder prescriber and public awareness about these risks. We offer several suggestions to address this issue.

Required evidence to support a Boxed Warning

Q1: Do you support the proposal for evidence?

c) with modification

Q2: Do you envisage any difficulties with the proposed evidence requirements?

The proposed level of evidence required to support a Boxed Warning is too stringent, requiring a higher level of certainty than is appropriate and thereby undermining the precautionary approach warranted in managing with major safety concerns.

Q3: What changes to the evidence requirements do you propose to address these difficulties, if any?

1. We strongly suggest modifying the statement, '*Generally, a causal relationship between the medicine and the safety signal that might merit a Boxed Warning should be assessed to be a reasonable possibility. A Boxed Warning may also be required where causality is not fully demonstrated, if the safety issue is of sufficient concern',* to more closely align with the precautionary approach that is appropriate for risk mitigation.

This approach involves taking **'action to prevent harm when there is scientific uncertainty and until a body of evidence establishes the requirement for alternative regulation' [1]**. In contrast, the proposed wording implies that the association between the medicine and safety signal should, in most cases, be *fully demonstrated,* which is both unrealistic and in violation of this principle. Instead, we argue that the addition of a Boxed Warning should generally be based on a reasonable likelihood of causation, with a lower level of evidence required in cases where the consequences of the harm are very serious and/or likely to affect many people.

2. *Minor changes to the suggested sources of clinical data.*

While we agree with the range of sources listed, it is unclear why there is a requirement of robustness for 'additional studies or independent sources' (bullet point 4) but not for other sources. We also suggest clarifying or expanding the reference to post-market sources (bullet point 2) – presumably, this includes Phase IV trials and routine post-market surveillance activities.

3. *Removal of the Boxed Warning*

We are concerned that the current guidelines may allow for removal of a Boxed Warning without sufficient evidence that the safety issue has ceased to be a reasonable possibility. As stated below under question 16:

The TGA should provide additional detail and clarification on the evidence requirements for removing a boxed warning. We suggest:

1. The evidence required for removal of the Boxed Warning should be of equal or greater strength, quality and robustness as that used for introducing the warning, and negate any reasonable possibility of a causal association between the medicine and the safety signal.
2. Clarifying the circumstances under which the boxed warning can be reviewed, specifically where 'other risk management tools are proposed'. Additional detail on the types of risk management tools that may remove the need for a Boxed Warning should be provided, as risk management tools would generally be expected to provide an *additional* mechanism for communicating or managing a risk rather than replacing a Boxed Warning.
3. Adding a requirement that there be a public notification/consultation prior to the removal of a Boxed Warning so that clinicians and consumers can have an input into the decision.

When a Boxed Warning is proposed

Q4: Do you support the proposed circumstances?

c) with modification

Q5: Do you envisage any difficulties with the circumstances under which a Boxed Warning is proposed?

We are concerned that the wording of bullet point 1 in particular may exclude certain cases where a Boxed Warning might be appropriate (see Q6 below for details).

Q6: What circumstances should be removed, or should additional circumstances be included?

1. Removal of the qualifier, '*relative to the potential benefit of the medicine'* from the first bullet point: *An adverse reaction is identified that is serious relative to the potential benefit of the medicine, and/or not reversible.*

We suggest that the potential benefit of the medicine is not relevant when determining the need for a Boxed Warning, which is by definition an indicator of risk. The proposed guidance describes a Boxed Warning as a '*risk mitigation strategy*', used to communicate the *'most serious of safety issues'* (p4), and with an important role in facilitating '*discussion of the benefit/risk balance and in informed consent'* (p6). Therefore, employing a benefit/risk analysis in the decision-making process violates the purpose of the Warning. A large potential benefit does not negate the need for a practitioner or individual to be informed about serious safety issues**.**

2. Qualification of the statement, '*The likely frequency of the reaction should also be a consideration'* in the first bullet point.

The likely frequency of the reaction may not be relevant in cases where the adverse event is very severe or irreversible, particularly if it can be prevented or reduced in severity or frequency by appropriate use of the drug. Where reliable information is available on frequency of an adverse event, information on frequency could be provided in the PI, CMI, safety alerts or other information materials that accompany a Boxed Warning.

3. Addition of an extra condition under bullet point 2, *A serious adverse reaction is identified that can be prevented or reduced in frequency or severity by appropriate use of the drug, encompassing:* Patient Behaviour or Awareness.

In certain cases, the actions of the patient are key in preventing or reducing the severity or frequency of a serious adverse reaction. Examples of this type of situation might include severe drug interactions with food or alcohol. While these cases may fall under the category, '*Managing patients in a certain manner*', a separate category on Patient Behaviour or Awareness shifts the focus of the behaviour to the patient rather than the healthcare practitioner. This also has implications for the importance and phrasing of the Boxed Warning within the CMI.

4. *'Non-actionable' reactions*

In determining whether 'non-actionable' reactions warrant a Boxed Warning, consideration should also be given to their importance in facilitating recognition of the adverse effect by the clinician.

Content of the Boxed Warning in the PI

Q7: Do you support the proposal?

c) with modification

Q8: What changes would you propose?

We support the requirements for the content of the Boxed Warning. While we agree that details of the data sources for the safety issue should not generally be included within the warning itself, we suggest that this information be made available either within the text of the PI or through a hyperlink/url to a separate document. The TGA might also consider adding a requirement for a reference to the relevant part of the PI text within the Boxed Warning, as per FDA guidance e.g. *[See Warnings and Precautions (Section number)]* [2]. Use of non-bolded italics within square brackets would minimise any distraction caused by this additional text.

Further, any actions to be performed by the prescriber should be clearly worded in active language at the beginning of the Boxed Warning. For example 'Do not prescribe to people with impaired renal function' or 'Conduct liver function tests before starting treatment and monitor 3 monthly' or 'Inform patients of the need to avoid [food or drug] while being treated with [drug x]'.

Content and Format of the Boxed Warning in the CMI

Q9: Do you support the proposal?

c) with modification

Q10: Are there other modifications or additions to the proposal you would like to make?

We support the proposed content and format of the boxed warning in the CMI, as consistent with the Warning in the PI but adapted for the needs of the lay consumer.

However, we suggest expanding the guidelines to include more specific formatting requirements. These requirements should, at least, be consistent with those outlined for the PI in the following section, but would preferentially be adjusted in accordance with best practice guidelines for medicines information for consumers (e.g. use of bullet points, active voice, short sentences, avoiding unnecessarily complex medical language etc.). The TGA should also provide guidance on minimum font size, with consideration to the high proportion of elderly medicine users in the

population. Given that most consumers do not read the CMI in full, we strongly suggest use of bold type throughout the Warning as employed by the FDA.

Further, given the importance of ensuring that consumers receive accurate, complete and understandable information in CMI black box warnings, in order to prevent serious harm, the TGA should institute review and pre-approval of Boxed Warning text and formatting in CMIs to be sure that these messages are understandable to consumers with low English literacy levels.
The TGA should work with consumers to determine the best way of presenting the Boxed Warning, particularly if data on best practice are lacking for the Australian context. In addition, an evaluation of the efficacy of the warning in alerting consumers to the safety issue should be conducted before implementation.

Format of the Boxed Warning in the PI

Q11: Do you support the proposal?

c) with modification

Q12: What changes would you propose?

We suggest the following changes:

1. Use of bold throughout to increase contrast and prominence
2. Use of bullet points or subheadings to increase readability
3. If multiple warnings exist, subheadings should be employed with the warning of greatest clinical significance listed first. Assessment of clinical significance should be based on a consideration of relative severity, likelihood, and ability to prevent or reduce the adverse effect.
4. Included a non-bolded, italicised reference to the main text for more information e.g. *[See Warnings and Precautions (Section number)]* [2]
5. Consider a maximum length recommendation, due to evidence that long warning statements are less likely to be read.

Q13: Are there other modifications to the proposal you would like to make?

The final format should be pilot tested by a variety of clinicians to ensure usability and to be certain that messages are not misinterpreted.

Changing or Removing a Boxed Warning

Q14: Do you support the proposal?

c) with modification

Q15: Do you envisage any difficulties with the proposed process?

We are concerned that the current guidelines may allow for removal of a Boxed Warning without sufficient evidence that the safety issue has ceased to be a reasonable possibility.

Q16: Are there other modifications to the proposal you would like to make?

The TGA should provide additional detail and clarification on the evidence requirements for removing a boxed warning. We suggest:

1. The evidence required for removal of the Boxed Warning should be of equal or greater strength, quality and robustness as that used for introducing the warning, and negate any reasonable possibility of a causal association between the medicine and the safety signal.
2. Clarifying the circumstances under which the Boxed Warning can be reviewed, specifically where 'other risk management tools are proposed'. Additional detail on the types of risk management tools that may remove the need for a Boxed Warning should be provided, as risk management tools would generally be expected to provide an *additional* mechanism for communicating or managing a risk rather than replacing a Boxed Warning.

We also strongly recommend adding a requirement that there be a public notification/consultation prior to the removal of a Boxed Warning so that clinicians and consumers can have an input into the decision.

Promotional material

Q17: Which of the above options do you support?

a) Option 1

Q18: Do you have any suggestions for how Boxed Warnings should appear or be referenced in promotional material (taking into account the different formats and media types which might be used to display this material)?

We strongly support Option 1 over Option 2 for several reasons: (a) the complete Boxed Warning is easily recognisable as an indicator of a serious safety concern, (b) it contains sufficient information to succinctly convey the nature of the warning without requiring reference to other sources, which may not be consulted by the healthcare practitioner, (c) it prevents erosion of important information or potential minimisation of effects that may arise through Option 2. For these reasons, we also recommend that the original format of the Boxed Warning be maintained in any advertisements or other promotional material.

We recognise that, in certain cases, displaying the entire boxed warning may be difficult or impractical, such as where advertising space is limited or where the warning is particularly long. Indeed, a long warning may go unread, reducing its effectiveness. In these cases, it may be appropriate for a shortened version of the Boxed Warning to be displayed, which includes at a minimum what the adverse effect is and its severity in plain language and refers the reader to a source of the full Boxed Warning. The modified Warning should be approved by the TGA and its use restricted to pre-defined situations. This shortened warning should be displayed using the same formatting as the original to ensure it is easily identifiable as a Boxed Warning.

We also suggest that the TGA include specific guidance on minimum standards for displaying the Boxed Warning, including prominence, formatting, relative size and location. In all media formats, the Warning should be placed in a position most likely to attract attention on the first page of the format.

In line with the Medicines Australia Code of Conduct guidelines [3], the prominence of the Boxed Warning in electronic and audiovisual media, including electronic detail aids, should be similar (in text size and location) as print media and not displayed as a pop up. The Warning should be

displayed on *all* advertisements related to the product, regardless of whether the warning applies to the indication being promoted.

We also suggest the requirement to display the Boxed Warning on advertisements be retroactively applied, such that new advertisements released by companies with pre-existing Boxed Warning must also comply with the new guidelines.

The US Food and Drug Administration prohibits advertising of prescription-only products to health professionals via reminder (or short) advertisements, which state only the brand name of a medicine and do not make any health claims, if those products have Boxed Warnings [4]. We recommend a similar restriction on these advertisements in Australia, in order to avoid emotive branding unaccompanied by health information for products associated with serious risks.

Timelines and implementation

Q19: Do you support the proposal?

b) no

Q20: Do you envisage any difficulties with the proposed prospective implementation?

We strongly disagree with the prospective implementation of these guidelines and argue that the proposed guidelines should also apply to currently marketed products with Boxed Warnings. Consistency in the application and format of Boxed Warnings across medicines is vital in order to ensure that Boxed Warnings are easily recognisable, and that practitioners and the public are properly informed. We suggest that a grace period of 6 – 12 months could be applied for currently marketed products with Boxed Warnings.

Q21: Are there other modifications or additions to the proposal you would like to make?

1. We recommend that the TGA conduct an assessment of the effectiveness of the guidelines a year after implementation.

2. We also strongly suggest that the TGA undertake a communications strategy to ensure that prescribers are aware of the meaning and significance of Boxed Warnings. Research has shown that prescriber awareness of Boxed Warnings can be low, even in jurisdictions they are commonly used [5,6]. To this end, the TGA should also consider adding a symbol to indicate that a Boxed Warning is present as another means of drawing attention to the warning.

3. Given that many prescribers may not read the product information in full, or view it infrequently, we recommend that the TGA request that medicines information compendiums (e.g. MIMs, AMH), particularly those that are integrated with prescribing software, investigate ways to ensure this information appears when prescribers select the drug or it is dispensed by pharmacists. Any mitigating action required by patients as part of the warning (e.g. for administration or interactions) could be considered as an addition to the pharmacy label and/or the medicine box.

4. Finally, the TGA may like to consider publishing a publicly available, up-to-date list of products with Boxed Warnings on its websites.

Thank you for this opportunity to comment and we look forward to the outcome of this consultation.

Yours sincerely,

On behalf of the Pharmaceutical Policy Network, including:

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6. Cook DM, Gurugubelli RK and Bero LA. Risk management policy and black-box warnings: a qualitative analysis of US FDA proceedings. *Drug Safety* 2009; 32: 1057-1066.