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Transparency Reforms and Evaluation Support Section
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

RE: Public Consultation: Boxed Warning guidance

Dear Sir/Madam,

Bristol-Myers Squibb (BMS), a diversified global BioPharma company, is pleased to have the opportunity to offer comments on the TGA consultation on Boxed Warning guidance.

BMS believes that the guidance as written, may give lead to their proliferation, possibly reducing their overall usefulness. Overall, the definition/criteria/triggers for elevation to a Boxed Warning are ill defined, and they are likely to be interpreted inconsistently by different Delegates/Sections. For example, may of the criteria in the guidance document equally apply to information relevant for the *Special Warnings and Precautions for Use* section of the PI and as such, the guidance is ambiguous as to the trigger to elevate a warning to a Boxed Warning to assist with the consistent application of Boxed Warnings to PIs across different clinical streams, BMS recommends the practice is overseen by the ACM.

Additionally, the level of evidence for the application of a Boxed Warning are wide and varied, yet the process and evidence for their removal is much less well defined and on the face of it, is likely to be much more rigorous.

Finally, education of HCPs/patients would be very helpful for them to understand if the presence of a Boxed Warning signals that they should be alert rather than alarmed/avoid use of the medicine. BMS recommends that the TGA undertake an education initiative so that healthcare

professionals (HCPs) understand the purpose of a Boxed Warning and the types of circumstances in which they are used. It is also important that HCPs have awareness that Boxed Warnings will be introduced into Consumer Medicine Information and that this may prompt conversations between the patient and HCPs involved in their healthcare. BMS recommends that the TGA should consider how education on Boxed Warnings could be incorporated into existing education efforts in relation to PI e.g. introduction of the black triangle and the PI SmPC-style reformatting.

We commend the TGA for developing a draft guidance to support the use of Boxed Warnings for prescription medicines. After thorough review, a response to TGA's specific questions, hereby follows below.

Required evidence to support a Boxed Warning

Q1: Do you support the proposal for evidence?

c) with modification. See Q2.

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

Yes.

BMS notes that 'additional studies or independent sources (if sufficiently robust) are included as evidence sources'. BMS asserts that the evidence for a Boxed Warning should be at least as rigorous as the evidence used to form the rest of the PI document. All PI wording is carefully formed based upon robust evidence and reviewed thoroughly by both the Sponsor and the TGA. The bar for evidence for a Boxed Warning should not be any lower than any other sections of the PI, and particularly so, as it is the most prominent section of the whole document.

Off-label use of the medicine as an evidence source should not be utilised as it will not provide evidence which is related to the indicated use of the product (see also further comments under Q4).

The draft guidance states "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." BMS requests that additional information or examples to be used to clarify the tipping point for causality not being "fully demonstrated" and a safety issue of "sufficient" concern. BMS asserts that causality should be established, i.e., the Boxed Warning should relate to a serious adverse drug reaction rather than an adverse event. Therefore, the sentence that there should be 'a reasonable possibility' should be amended in the guidance.

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

'Post-market sources' should be replaced with 'post-market studies'.

'Off-label use of the medicine (in certain circumstances)' should be removed.

'Additional studies or independent sources (if sufficiently robust)' should be replaced with 'Sponsor/TGA pharmacovigilance databases'.

When a Boxed Warning is proposed

Q4: Do you support the proposed circumstances?

c) With Modification.

BMS respectfully requests that the TGA include a more detailed description of what constitutes a "serious adverse reaction". For example, the Food and Drug Administration guidance states that a Boxed Warning, highlights to prescribers, an adverse reaction that could be, fatal, life threatening or permanently disabling. Thereby alerting the prescribers to the essential need to assess the risks and benefits of using the drug.

A Boxed Warning should be used as a risk mitigation measure for life-threatening, fatal or permanently disabling adverse reactions (i.e. where there is a likely causal relationship with the drug). It can also be used to describe safety findings which may otherwise be counter-intuitive (e.g. a symptom commonly associated with the disease but may also be a symptom of a life-threatening adverse reaction).

To provide details of the boxed warning in an off-label setting could be perceived as TGA/Sponsor endorsement to use the product for that indication. From a company perspective we are not recommending the use of the product for an off-label indication. Regardless of the presence of a Boxed Warning, if an HCP determines to use a product off-label then caution should be employed.

BMS would also like to note that on Page 4 of the guidance, under *Background* and *Overview of the proposed Boxed Warning*, there are several different descriptions on the purpose of a Boxed Warning e.g. 'most serious types of warnings', 'most serious of safety issues', 'highlight special warnings', 'concern prominent safety issues'. BMS recommends that consistent language is used so that the purpose of a Boxed Warning is more precise and unambiguous.

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

BMS believes the most significant challenge will be with TGA Delegates applying this guidance consistently. The guidance is currently written so that there is significant flexibility in what may be judged as appropriate circumstances to warrant a Boxed Warning. All of the circumstances described in the guidance for requiring a Boxed Warning equally apply to the *Warnings and Special Precautions for Use* section of the PI. BMS strongly recommends that the TGA guidance distinguishes the difference between information required for a Boxed Warning versus *Warnings and Special Precautions for Use*, and specifically when it is appropriate that a warning/special precaution be elevated into a Boxed Warning. To assist with the consistent application of Boxed Warnings to PIs across different clinical streams, BMS recommends the practice is overseen by the ACM.

Safety data on off-label use is likely to be limited. Therefore, any Boxed Warning related to off-label use will need to consider the appropriateness of the evidence standards.

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

Concerns related to off-label populations should be removed for reasons described above.

Information on markedly reduced effectiveness or evidence of net harm in certain patient populations should be removed since this is the purpose of the *Contraindications* section of the PI.

TGA guidance says that the likely frequency should also be a consideration. This point is unclear and should be removed or clarified (i.e. does this imply that a Boxed Warning is only for frequent events or for rare events?).

<u>Content of the Boxed Warning in the PI</u>

Q7: Do you support the proposal?

c) with modification.

BMS would like to recommend that when the frequency of events in a Boxed Warning is described that the terminology used is aligned with CIOMS standards. For example, terms such as common or rare, should be only used with reference to their CIOMS definition. Additionally, when summarising text for the Boxed Warning, the language should be as consistent as possible to content in the body of the PI to avoid ambiguity and to clearly link with the body of the PI. Also, medical terminology to describe AEs in a Boxed Warning should be consistent with text in other sections in the PI.

BMS agrees that the Boxed Warning should be succinct and refer the reader to the body of the PI. If the Boxed Warning appears fully comprehensive it introduces the risk that time-poor HCPs may not feel it necessary to review the rest of the PI where critical information on the safe and effective use of the medicine is described. The recently implemented reformatting of the PI in Australia, now enables easier location of critical information.

Q8: What changes would you propose?

None.

Content and Format of the Boxed Warning in the CMI

Q9: Do you support the proposal?

c) with modification.

BMS recommends that a standard sentence be used to introduce all Boxed Warnings in the CMI. This sentence would convey the overarching message to talk to your doctor about the following special risks with the product.

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

Patient language will need careful consideration due to highly heterogeneous levels of health literacy in the general public. Language should also not alarm patients with the potential for medication non-compliance. Language which directs the patient to discuss an appropriate issue rather than state the issue alone may be more appropriate.

Format of the Boxed Warning in the PI

Q11: Do you support the proposal?

a) Yes.

Q12: What changes would you propose?

n/a

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

None.

Process Requirements

Q14: Do you support the proposal?

c) with modification.

Timing of a TGA requested Boxed Warning should occur no later than the Delegates request for pre-ACM advice for major Category 1 applications. This then avoids delays to approval of the product/variation due to a more protracted post-ACM PI negotiation phase. Furthermore, the ACM also has the opportunity to consider the appropriateness of the Boxed Warning with an accompanying opportunity from the Sponsor to comment on the proposal. Please also see Q5 above.

It should also be clarified that the TGA will not implement amendments to a Boxed Warning unilaterally. The sponsor should always have an opportunity to evaluate proposed amendments to existing Boxed Warnings before implementation.

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

Yes.

The guidance has very specific descriptions on the evidence which may lead to a Boxed Warning. There is much less guidance on the evidence required to remove a Boxed Warning. The sense is that it will be much easier for the TGA to require and implement a Boxed Warning but it is vague for the Sponsor on how that Boxed Warning can be removed.

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

Yes.

The recent draft updates to the TGA guidance on risk management plans do not describe any requirements to update an RMP when introducing a Boxed Warning, or how to do so. An update to RMP/ASA alone with respect to a Boxed Warning, would not require a submission to the TGA in its own right unless the risk profile of the drug is changed.

The text that the Boxed Warning may be amended by the TGA based on evidence from reputable sources, should be amended as it is too broad and undefined. The evidence should be robust and should reflect the amended content proposed by BMS for page 5 of the guidance document (see Q2 and Q3 above).

TGA should consider and confirm whether a Comparable Overseas Regulator (COR) pathway to assess the implementation/modification/removal of a Boxed Warning is permissible.

Promotional material

Q17: Which of the above options do you support?

b) Option 2. This is aligned with the current Medicines Australia Code of Conduct requirements. An allowance for the Boxed Warning to sit as the first part of the minimum PI is also more practical considering the range of communication channels now available.

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)?

The Boxed Warning should be part of the minimum PI section as that where the PI is referenced with the key call outs. It would be incongruous to start a promotional material with a warning.

For completeness, BMS recommends that the guidance confirms that "Boxed Warnings are not required on non-promotional materials including those defined as Additional Risk Management Materials.

Timelines and implementation

Q19: Do you support the proposal?

a) Yes.

BMS agrees with the proposal on the principle that Boxed Warnings provide the most value in the early use of medicines following registration of the product or upon their introduction following a change in use of the product or new significant safety information. There is diminished value of retrofitting materials for existing products and indications.

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

Upon receipt of a condition of registration to include a Boxed Warning on promotional materials, there will need to be a permissible amount of time for a company to update and implement changes to materials, particularly for hard copy materials.

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

None.

BMS appreciates the opportunity to provide comments and respectfully requests that TGA give consideration to our recommendations. We would be pleased to provide additional pertinent information or clarifications as may be requested.

In Confidence

[redacted]