Response Monash University Department of Epidemiology and Preventive Medicine

Therapeutic Goods Association on *Strengthening Monitoring of Medicines in Australia:*

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<th>Questions</th>
<th>Response</th>
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<td>1. Do the proposed criteria for inclusion in the Black Triangle Scheme</td>
<td>Comments:</td>
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<td>appropriately target new medicines for which adverse event reports</td>
<td>• Black triangles provide an effective way of drawing public</td>
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<td>should be sought?</td>
<td>attention to potential safety issues</td>
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<td>• The criteria for applying a black triangle seem reasonable.</td>
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<td>• Text should specify why the black triangle is present, in</td>
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particular differentiating specific safety warnings from concerns relating to insufficient information about safety.

- Focus should be on persuading clinicians to be extra vigilant in reporting serious Adverse Drug Reactions (ADRs) associated with these medications.

- Must use the warnings judiciously to avoid overuse and risk them being ignored.

- Black triangles should exist on all marketing materials as well as packages and inserts.

Spontaneous reporting systems provide an important, but inadequate method of ADR surveillance.

- They have significant blind spots and are of limited value for delayed ADRs and ADRs which take the form of common illnesses (e.g., myocardial infarction).

- In many instances the value of ADR reporting may be enhanced by further epidemiological study. In particular, if the cases reported can be used as ‘cases’ in case control studies it may be possible to identify populations at particular risk of the ADR. This approach was used by Fairley et al to identify risk factors for flucloxacillin.¹

- To facilitate such analyses questionnaires should routinely be sent requesting further important clinical information.

- Collaboration with academic units capable of conducting and analysing ADR data in this manner should be encouraged. Current barriers to such collaboration should
| 2. What information, communication and education activities would assist health professionals and consumers to understand the Black Triangle Scheme and the importance of reporting adverse events for these medicines? | • Utilising the already well established methods of communication about drugs through the National Prescribing Service is advised.  
• A regular section in Australian Prescriber specifically about Black Triangle drugs would be beneficial. Consider utilising Therapeutic Guidelines Ltd which has broad reach with junior doctors and in general practice.  
• It is critical that sufficient education is provided to the profession about the Black Trial Scheme and the particular drugs the schemes reference. It is important to encourage fresh exploration of the Product Information which may have little impact if new information is not recognised. Without sufficient education, there is a risk that the Black Triangle's value may be underestimated.  
• Education should appear on the TGA website and in popular general practice publications. |
| 3. Are the proposed changes to the Product Information (PI) leaflet useful for health professionals? | • Doctors rarely have time to read a full PI so a brief summary on page 1 of the indications, contra-indications, precautions and adverse event information, would help.  
• As described above, the reason(s) for the caution needs to be spelled out.  
• Electronic PIs for medicines and devices should incorporate a link for practitioner and consumers to report suspected serious adverse events. |
<p>| 4. What support will sponsors need to comply with the new format and The proposed regulatory response seems appropriate. |</p>
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<th><strong>What are achievable timelines for implementation of the new format?</strong></th>
<th><strong>5. What activities could TGA undertake to assist sponsors in complying with their pharmacovigilance requirements?</strong></th>
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<td>Encourage and/or support drug registries.</td>
<td><strong>6. Is the information regarding RMP requirements included in the AusPAR sufficient to inform you of the risk minimisation and pharmacovigilance commitments that have been made by the sponsor?</strong></td>
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<td>This information seems sufficient.</td>
<td><strong>7. What activities could we undertake to assist sponsors in complying with their RMP requirements?</strong></td>
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<td>- The only scientifically valid way of establishing the balance between risks and benefits is through large scale clinical trials which include mortality and morbidity as end-points. Surrogate endpoints typically demonstrate only an indication of efficacy and are inadequate approach to monitoring safety or the balance of risks and benefits. Hence the TGA should insist on having results of morbidity-mortality studies before granting full registration to new chemically distinct drugs to be used for preventive purposes.</td>
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<td>- Furthermore, the adverse effects of many drugs may not adequately be evaluated in clinical trials, which typically focus on efficacy outcomes. This is especially relevant for preventive drugs, for which the balance between benefit and harm can be fine, and adverse effects may manifest only after a long time. Therefore <strong>clinical registries</strong> are the most scientifically appropriate approach for monitoring certain high significance drugs for which there are significant safety concerns. Clinical registries provide a measure of risk by capturing key information on both patient numbers exposed, and the numbers affected by a specific ADR.</td>
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Modern concepts of clinical registries typically involve a ‘spine and rib’ model where the spine is the minimum dataset of a clinical quality registry. It represents the ongoing data required to monitor quality of care (examples include myocardial infarction, prostate cancer and many others).

‘Ribs’ are additional specific data collections focusing on specific issues, such as the safety of a new drug or device. For example, data collections pertaining the safety of a new immuno-oncology agent could be added as a ‘rib’ to an existing ‘spine’ of a clinical quality registry of prostate cancer. This approach avoids multiple competing post-marketing registries.

Where no existing registry is available, there may be a case to require a drug specific registry such as those established at the Monash University Department of Epidemiology and Preventive Medicine for Bosentan\(^2\) and Novo-7\(^3\). Pharmacovigilance through registries is feasible and the Australian work leading this approach is distinguished\(^4\).

When monitoring the safety of high risk implantable devices, the TGA should mandate the use of unique device identifiers.


4. Monitoring drug safety with registries: useful components of postmarketing pharmacovigilance systems