22 May 2015

Clinical Risk Management
Medsafe
PO Box 5013
Wellington 6145

Via email: medsafeadrquery@moh.govt.nz

Dear Medsafe

Re: Medsafe Proposed Pharmacovigilance Guidelines

Thank you for the opportunity to comment on Medsafe's *Guideline on the Regulation of Therapeutic Products in New Zealand. Part 8: Pharmacovigilance*. Medicines Australia is the peak association representing the research-based pharmaceutical industry in Australia. A number of Medicines Australia's member companies are responsible for the regulation of prescription medicines in both Australia and New Zealand.

Despite the cessation of the Australia New Zealand therapeutic Products Agency (ANZTPA) as a formal mechanism, it remains important to consider opportunities to achieve harmonisation of regulatory requirements in order to reduce duplication and increase efficiency in both regions.

1 MEDSAFE PROPOSED PHARMACOVIGILANCE GUIDELINES

1.1 BACKGROUND

The current Medsafe proposal aims to improve clarity and transparency around the pharmacovigilance regulatory requirements for New Zealand. The types of products that are considered within scope of this proposal are:

- All medicines
- Vaccines
- Biologicals
- Biosimilars

The types of products excluded from the proposed pharmacovigilance guidelines are as follows:

- Complementary medicines
- Medical devices

Medicines Australia supports Medsafe's initiative to incorporate greater detail into the Pharmacovigilance Guidelines for New Zealand and to provide alignment with the EU Good Pharmacovigilance Practice modules. However the current approach requires fine tuning in order to achieve clear guidelines that are consistently interpreted and avoid confusion for Sponsors.

Medicines Australia recommendations on the scope of the consultation are further outlined below together with specific comments on the *Guidelines on the Regulation of Therapeutic Products in New Zealand: Part 8 Pharmacovigilance Document*.

1.2 SCOPE OF CONSULTATION

Historically, the Medsafe Guidelines on Pharmacovigilance have included very little detail around the expectations and standards required for a local pharmacovigilance system. This has resulted in many Sponsors referring to the TGA Pharmacovigilance Guidelines for clarity on reporting timelines along with guidance on notification of safety issues. In 2012, the new EU framework of Good Pharmacovigilance Practice (GVP) modules was implemented and these modules have now become the basis for the pharmacovigilance system within many companies. The GVP modules reflect the increasing focus on all aspects of medicines safety and greater transparency demanded by all stakeholders involved. The TGA along with other regulatory bodies have adopted the GVP modules with minor edits to allow for local procedural changes.

The current Medsafe consultation is intended to capture elements of best practice in pharmacovigilance for Sponsors rather than to introduce additional requirements. To achieve this objective, Medicines Australia recommends that Medsafe consider formally adopting and referring to the GVP modules within the proposed guidelines. Furthermore there is an opportunity to harmonise standards internationally and benefit from the existing framework for the review and approval of Periodic Benefit-Risk Evaluation Reports (PBRERs) and Risk Management Plans (RMPs) within the European Union (EU). The proposed guideline references many elements of PBRERs and RMPs, and establishing a process for work sharing would result in efficiencies for both Sponsor companies and Medsafe.

1.3 OPPORTUNITY FOR WORK SHARING

In an effort to reduce regulatory and compliance burden on both Sponsor companies and Medsafe, consideration should be given to a work sharing initiative for PBRERS and RMPs. Sections 5 through to 7 of the proposed guidelines reference many individual elements that form the basis of the PBRER and RMP. The current framework of the PBRER and RMP templates encompasses a robust routine signal detection process that meets the requirements of timely communication to regulatory authorities around the evolving safety profile of a molecule.

Leveraging the review of PBRERs and RMPs performed by the TGA and /or the EU with a view to targeting any local review only on unique elements for the New Zealand healthcare system would increase efficiency and reduce duplication. There are existing successful initiatives that are ongoing between authorities with common standards of regulation e.g. EU, FDA, Health Canada and Switzerland including for generic medicines and Active Pharmaceutical Ingredients (APIs).

Given the integral role of the PBRER and RMP within the pharmacovigilance system it is important to consider whether some objectives of Sections 5-7 could be fulfilled through implementing routine submission of these documents in some capacity to Medsafe.

2 GENERAL COMMENTS

In reviewing the proposed guidelines, Medicines Australia noted that there were many sections where the text could be interpreted in multiple ways. Thus throughout the detailed comments sections included below there is reference to suggestions to improve the wording of the proposed guideline. The general wording of each section currently does not clearly differentiate between responsibilities that are mandatory and those that are optional. The lack of clarity from this perspective can lead to confusion for Sponsors who are attempting to ascertain their role in the New Zealand pharmacovigilance system.

An additional area requiring clarification is the target audience of the proposed guideline. There are some sections which refer to Sponsors, others that refer to consumers or healthcare professionals. Introducing a statement in the initial sections of the document stating clearly that the guideline is intended for Sponsors would greatly improve the level of clarity and minimise the risk of misinterpretation. It is unlikely that any consumers or healthcare professionals would refer to this guideline and expect to find reporting requirements applying to them contained within the document.

There is also an opportunity to cross reference sections through the proposed guideline, as there are numerous areas of overlap that without cross referencing could lead to confusion.

3 DETAILED COMMENTS BY SECTION

3.1 SECTION 1 LEGISLATION

Medicines Australia recommends the addition of a separate subsection listing all the relevant ICH Guidelines and EU Good Pharmacovigilance Practice modules. This would support clarity on the background and context of many elements of the pharmacovigilance system described in the proposed guideline.

3.2 SECTION 2 ROLES & RESPONSIBILITIES

- The process for notification of a PV contact person to Medsafe is not clear from the current statement. Medicines Australia recommends the inclusion of contact details for whom to notify of the relevant PV contact person.
- Section 2.5.1 describes the process of how the notification of Director-General of Health occurs in appropriate situations. From the current paragraph it is unclear what, if any, responsibility the Sponsor has in a situation where notification is required.
- The inclusion of a cross reference to Section 5 would support the link between the management of a significant safety issue and notification of the Director-General of Health.
- A suggestion to improve clarity for Section 2.5 is included below:
    - 2.5: Sponsors should inform Medsafe "as soon as possible" when information impacts on the benefit/risk balance.
    - 2.5.1: Sponsors should notify Medsafe of an emerging safety issue "within 72 hours".
- Information that impacts the benefit/risk balance can include an emerging safety issue therefore it is requested that these two instances be more clearly distinguished from one another if they are to have different timelines.
- To be consistent with section 41 of the Medicines Act, one suggestion is to amend the wording of Section 2.5.1 so that only "substantial" emerging safety issues should be notified to Medsafe within 72 hours and only "substantial" new information that impacts on the balance of benefits and risks of harm of their medicines.
- One recommendation for how to clearly lay out all aspects of a Sponsor's responsibilities in establishing a pharmacovigilance system is to capture in Section 2.5.1 a bullet point list covering all of the Sponsor's responsibilities including routine expedited reporting to Medsafe. The current TGA guidelines include a similar section and this allows a Sponsor to use the list as a guide for each of the elements of a local pharmacovigilance system.
- The Sponsor roles and Responsibilities for pharmacovigilance in post authorisation studies (for Investigator Initiated vs company sponsored) is not currently captured in this section. The addition of a statement along with a cross reference to relevant regulations maximises clarity around the role of the Sponsor in this type of situation

3.3 SECTION 3 REPORTING

The table below captures the detailed comments from Medicines Australia relating to this section of the proposed Medsafe guideline.

Section #	Page #	Comments
3.2.2	13	The Eudravigilance hyperlink included does not currently link to the relevant website. Suggest adding "(when possible)" to the end of this sentence as follows: 'An identifiable reporter characterised by qualification (when possible)'.
3.2.4	13	Unclear as to the target audience of this section. Does it apply to Sponsors or healthcare professionals? No reference to different types of products (e.g. devices).
3.3.1	14	Reference relevant Privacy Laws
3.3.2	14	Clarify where contact details should be recorded for the purpose of follow up, for example on the CIOMS form or in the Sponsor's database. Suggest including a statement from TGA Guidelines on digital media and cases originating from this channel.
3.3.3	15	Sponsors experience significant delays in the receipt of CARM, thus the inclusion of this in reporting follow up may not be possible. The addition of an example of how Sponsors should identify follow up information would ensure that there is no confusion regarding how this should be done (e.g. use of pdf highlighting tool).
3.3.4	15	Open to interpretation as to what 'shortly after 15 calendar days' may mean. Should either remove or define a specific duration of time. Consider the use of an example to ensure that interpretation is clear. Safety databases would also not permit a scheduling of CIOMs for an ambiguous amount of time – need definite number of days.
3.5.1	16	Potential to interpret that guideline applies to consumers and HCPs as well as Sponsors. It is not standard practice to include information around consent to follow up being declined in the CIOMs form. Is this mandatory or optional?
3.5.3	16	AEFI routinely included in PBRERs, therefore unclear of threshold for notification to Medsafe. How would a sponsor fulfill this requirement? Is it a potential of duplication for Sponsors?

Section #	Page #	Comments
3.5.4	17	It is currently unclear if only serious cases of lack of efficacy are required to be reported or if all cases require reporting. It is suggested that a statement on the lack of efficacy cases in the absence of a reportable AR should only be reported when the following medicines are used i.e. vaccines, contraceptives medicines used in life threatening situations be included in the guidance. Medicines Australia seeks clarity on whether the interpretation of vaccine lack of efficacy is consistent with the EU interpretation.
3.5.4	17	If Medsafe would like to receive lack of efficacy cases for all other medicine types can it be clarified that they only want to receive cases when a serious ADR is associated with it? Medicines Australia recommends aligning with TGA wording around lack of effect with antibiotics (TGA guidelines Section 2.5.5): "Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, sponsors are not required to report lack of efficacy of antibiotics used in life-threatening situations where the medicine was not appropriate for the infective agent. However, sponsors must report any cases of life threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, in accordance with timeframes for serious adverse reactions".
3.5.5	17	Unclear if only serious cases of misuse or abuse are required to be reported or if all cases require reporting.
3.5.6	17	Unclear if only serious cases of off label use are required to be reported or if all cases require reporting. "Valid ICSR's associated with off-label use should be forwarded to CARM". It is not entirely clear from this wording if all "Off-label Use" cases should be reported to Medsafe or only those associated with a valid adverse event. Suggest to clarify the wording and make it more consistent with the wording used for Misuse/Medication error/ Overdose and therefore be changed to "Reports of Off-label use associated with a suspected reportable Adverse Reaction should be forwarded to CARM.
3.5.8	18	Unclear if only serious cases are required to be reported or if all cases require reporting. Responsibilities of Sponsor in ISS. Definition of a Sponsor – in clinical trials vs routine vs for registered.

Section #	Page #	Comments
3.5.9	18	It is unclear if medication error reports are required for all product types or just specific ones. Valid unsolicited report - definition? Spontaneous reports? What is the process for reporting solicited medication error/overdose cases? Further information is required regarding how MERP would work. If intended for HCPs then delete this section as it is captured in PBRER. Currently medication errors not associated with a serious ADR are collected and classified as non-serious cases. Requiring Sponsors to report this information is inconsistent with the general principles outlined in Section 3.2.
3.5.10	18	Unclear if only serious cases of overdose or occupational exposure are required to be reported or if all cases require reporting. Cross reference with 3.4
3.5.12	18	Unclear as to which specific situations this would apply. It would be good to cross reference relevant regulatory sections to provide clearer picture. "All valid serious ICSR's identified by the sponsor after suspension or withdrawal of a product should be reported". Can Medsafe please put some extra clarifications around this statement i.e. until when is the sponsor responsible for these products? Suggest to include a timeframe for when a sponsor is no longer required to report events after their product is discontinued etc.
3.5.13	19	Medicines Australia has significant concerns regarding the proposal to routinely monitor digital media sources which are not company sponsored. Medicines Australia does not support monitoring of non-company sponsored sites using conventional adverse event collection The current proposals would create a significant burden for industry that is not commensurate with risk and is unlikely to result in improved public health protection.
3.5.14	19	It may be difficult to verify if a product was funded or in use at the time of the ADR receipt. There is a risk that this requirement could result in a delay in submission of the report to Medsafe whilst waiting for clarification.

Section #	Page #	Comments
3.5.15	19	A single report? Clarify threshold as well as receipt of information vs confirmed safety issue. Routinely submit to CARM only major safety issues usually reported to Medsafe? It is not clear if Medsafe want all AR's associated with a quality issue to be reported within 72 hours or only those which are serious and which result in a significant safety issue (following an internal investigation into the quality defect). Should sponsors report serious adverse reactions associated with a quality issue (which is not considered a significant safety issue) to CARM within 15 days? Based on the answers to the questions on section 3.5.15, the opening statement in section 3.7 will need to be altered. Suggest "Significant safety issues due to product defects or falsified medicines should be sent to:"
3.8	21	Should Sponsors access information from SMARs? Is there a requirement to do so? It would be helpful for Sponsors if the trade name could be provided. This would help eliminate duplicate reporting in company databases.

3.4 SECTION 4 SIGNAL MANAGEMENT PROCESS

For Sponsors that are unfamiliar with the different levels of signal management processes, the addition of a section or paragraph that explains the Sponsor's responsibility to establish a signal management process depending on the type of products, company size etc. would aid a clear understanding.

3.5 SECTION 5 SIGNIFICANT SAFETY ISSUES

The inclusion of a comprehensive list of examples relating to different types of safety issues that may arise is useful however the first bullet point in Section 5.2 suggests that routine changes to a Data Sheet may fit within the definition of a significant safety issue. Thus Medicines Australia recommends that the word 'addition' along with 'or adverse reactions statements' is deleted from the first bullet point. Notification of routine changes to product information documents is not current standard practice, would add administrative burden and would not contribute significantly to the management of safety issues.

It is suggested that the last bullet point in Section 5.2 regarding safety issues for which the sponsor is sending a DHCP letter include a cross reference to Section 7.2.

Medicines Australia considers the use of the term, 'untoward effects' as subjective and wording could be understood quite differently by sponsors. Medicines Australia recommends amending the wording to "It is a statutory requirement that sponsors must report any *significant safety issues* for any medicine...."

3.6 SECTION 6 SUBMISSION OF SAFETY MONITORING DOCUMENTS

Section 6.2 is vague and contradictory for biologics, biosimilars and vaccines. Clarity is needed as using the expression 'should routinely submit' makes interpretation uncertain. Following on from the above, when would Medsafe want Sponsors to stop submitting PBRERs if they have been routinely submitting them? The TGA conditions of registration have a fixed time period when PBRER submission is required. Further details are required in this section to ensure that Sponsor responsibilities relating to PBRER submission are clear.

Medicines Australia requests further guidance around the process for how sponsors should submit PBRER's. If Medsafe request the submission of a PBRER for a specific medicine, will this be a once-off request or will the sponsor be required to continue to submit PBRERs until Medsafe advises otherwise? Will Medsafe state that a PBRER is required in the condition of approval, including for those medicine types (biologicals, biosimiliars and vaccines included in immunisation programme) that a PBRER is routinely required for?

Section 6.3 should include a link to Section 7 as it appears that Medsafe are requesting the review of risk minimisation tools without the RMP. The review of risk minimisation tools in isolation, without the RMP, is likely to result in confusion around the context of each of the tools and the risks to which they correspond.

The guidance is currently unclear on the method for submitting an RMP and who should they be sent to. Medicines Australia further requests clarity on whether the RMP submission could occur as part of post marketing surveillance rather than as part of the actual submission for evaluation. This would allow Medsafe to benefit from the TGA review of the RMP.

3.7 SECTION 7 SAFETY COMMUNICATIONS

Section 7.1 requires clarification as to whether these safety communications would be linked to an RMP or whether any communication tools that are part of an RMP would be out of scope of this section. The current wording is unclear and is likely to result in many different interpretations of a Sponsor's responsibility.

Section 7.2 DHCP letters are not currently used to notify routine changes to precautions, warnings and adverse reactions statements etc. in product information. This section should state explicitly that review or approval of the DHCP letter would be required only within the context of significant safety issues.

Section 7.3 is unclear as to which situations this would apply in, and it is suggested that the inclusion of some examples may assist. The current section appears to suggest that all communications implemented in New Zealand by a Sponsor to communicate safety messages would require inclusion in this process. This type of activity usually occurs within the bounds of an RMP rather than as a standalone process.

The review process for medicines safety communications is not described in detail. Medicines Australia requires clarification on how this process would work in practice. Particularly the timelines for review of materials as this could result in delay of the materials being implemented. Does Medsafe intend to review all safety communications prior to their implementation; how would any changes be managed?

Medicines Australia suggests that a reference is included in this section for information on direct-to-consumer advertising in New Zealand. The distinction between risk minimisation and safety communications, and direct-to-consumer advertising needs to be clarified.

It is likely that the majority of medicines safety communications would be part of an RMP to some degree, thus it may be difficult to perform a review of these materials without the context provided in the RMP.

4 SUMMARY

Overall Medicines Australia is supportive of Medsafe's initiative to harmonise the Pharmacovigilance guidelines with international best practice and introduce greater clarity into the guidelines for New Zealand. Medicines Australia would welcome the opportunity to further contribute to the implementation of a robust pharmacovigilance framework that maintains the current standard for managing risks and protecting public health in New Zealand.

Please do not hesitate to contact Alice George, Regulatory Manager, Medicines Australia at: alice.george@medicinesaustralia.com.au for any further assistance.

Yours sincerely

Tim James

CEO

Medsafe consultation submission

Guideline on the Regulation of Therapeutic Products in New Zealand - Part 8: Pharmacovigilance (Edition 2.0)	
Name and designation	Tim James, CEO
Company/organisation name and address	Medicines Australia
Contact phone number and email address	+612 6122 8500 Tim.james@medicinesaustralia.com.au

I would like the comments I have provided to be kept confidential: *(Please give reasons and identify specific sections of response if applicable)* (Reasons for requesting confidentiality must meet Official Information Act criteria)	☐ Yes ☒ No
I would like my name to be removed from all documents prior to publication on the Medsafe website.	☐ Yes ☒ No
I would like for my name not to be included within the list of submissions published on the Medsafe website.	☐ Yes ☒ No

It would help in the analysis of stakeholder comments if you provide the information requested below.

I am, or I represent, an organisation that is based in:

☐ New Zealand ☒ Australia ☐ Other (*please specify*):

I am, or I represent, a: *(tick all that apply)*

☐ Importer	☐ Manufacturer	☐ Supplier	☐ Sponsor
☐ Government	☐ Researcher	☐ Professional body	☒ Industry organisation
☐ Consumer organisation	☐ Member of the public	☐ Institution (e.g. university, hospital)	
☐ Regulatory affairs consultant	☐ Laboratory professional		

☐ Health professional – *please indicate type of practice*:

☐ Other - *please specify*:

Please return this form to:

Email: medsafeadrquery@moh.govt.nz including 'Pharmacovigilance guideline' in the subject line

Or Post: Clinical Risk Management
Medsafe
PO Box 5013
Wellington 6145

Medsafe is seeking comments on:

Section 1: Legislation eg,

- Are the guidance documents appropriate?
- Are there other guidance documents that would be relevant to the conduct of pharmacovigilance in New Zealand?

Section 2: Roles and Responsibilities eg,

- Does the information adequately describe the roles and responsibilities of the various parties?
- Was the information appropriately presented?
- Was the information easy to find?
- Are there any changes you would like to suggest?

Please include additional pages if necessary.

Section 3: Reporting eg,

- Do you have any suggestions regarding the definitions and interpretations used in this section?
- Do the subsection headings appropriately and adequately describe each reporting circumstance?
- Is each reporting circumstance and the process involved adequately described and explained?
- Would it be easy to find the information you need in each particular reporting circumstance?
- Are there circumstances that are not in this guideline but should be? If yes, please provide more details.

Section 4: Signal Management Process eg,

- Does the content of each subsection adequately explain what the steps in the process involve?
- Do the subsections on the Early Warning System and Medicines Monitoring adequately explain how these tools can be used?
- Do you understand what the role of the sponsor is in these situations?

Please include additional pages if necessary.

Section 5: Significant Safety Issues eg,

- Does the text in this section adequately explain what is required?
- Are there other pharmacovigilance-related safety issues or safety concerns about medicines that you consider should be included in this section?

Section 6: Submission of Safety Monitoring Documents eg,

- Are there other suggestions or recommendations that could be included in this section?

Please include additional pages if necessary.

Section 7: Safety Communications eg,

- Are there other suggestions or recommendations that could be included in this section?
- Is it appropriate to use the European template for safety communications?

Additional Comments

- Is the order of the information presented in each section appropriate?
- Do you agree with the proposed structure of the guideline?
- Is the information easily understood?
- Is there any other information or subject that should be included in this guideline?

Please include additional pages if necessary.