Medsafe consultation submission

Guideline on the Regulation of Therapeutic Products in New Zealand - Part 8: Pharmacovigilance (Edition 2.0)	
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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
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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*):

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☐ Importer	☒ Manufacturer	☐ Supplier	☒ Sponsor
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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?

Suggest inclusion of references below:

- The EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products* can be viewed online at: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c>
- The ICH guideline E2D *Post-approval safety data management* (CPMP/ICH/3945/03) can be viewed online at: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590>
- The ICH guideline E2B (R2) *Data elements for transmission of individual case safety reports* can be viewed online at: <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2B/Step4/E2B_R2__Guideline.pdf>
- The ICH guideline E2A *Clinical safety data management: Definitions and standards for expedited reporting* (CPMP/ICH/377/95) can be viewed online at: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590>

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?

No comment

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.

Re section 3.2.1 Do NOT report

Suggest remove last bullet point

- reports that supply of a medicine to a patient has been terminated, or is no longer required by the patient

This may cause confusion. For example in case the reason for termination of supply is patient death this might lead sponsors not to report cases of death

Re Section 3.2.4 Spontaneous adverse reaction reports (unsolicited reports)

Suggest amend wording as per below as it gives the impression that the guideline is directed to those listed when this guideline should be only for sponsors

A spontaneous report is an unsolicited communication that describes one or more suspected adverse reactions. Spontaneous reports may ~~be submitted by~~ come from such sources as :

- a healthcare professional
- a consumer
- a medicines regulator
- an international body
- a sponsor
- an organisation (eg, the New Zealand Poisons Centre or a district health board)
- the Judicial system (eg, Coroner, Police, legal processes).

Re Section 3.3.2 Validation of reports

Amend wording for the sentence as per below to avoid ambiguity as to where the contact details are being recorded e.g. in sponsor database or on report to regulator

'Whenever possible, contact details should be ~~recorded~~ collected so that follow-up activities can be performed by the sponsor'

Re Section 3.3.3 Follow-up reports

Regarding provision of CARM reference number when providing follow-up information

'Where sponsors receive significant additional information for a case already reported to CARM, sponsors should quote the CARM reference number and the date of the original report when sending further information'

This is not always possible. There is considerable delay between submission of initial reports to CARM and acknowledgement of receipt. Sometime no acknowledgement is received. Systems at CARM need improvement in this respect.

Re Section 3.4 Reporting timeframes for adverse reaction reports

Regarding wording

'In cases where the sponsor has a good reason to expect that significant additional information on a valid ICSR will be available shortly after 15 calendar days, it is acceptable to delay initial reporting of the case in order to incorporate the additional information.'

This provision is unnecessary. Clarity is required on reporting timelines.

Re Section 3.5.1. Consumer Reports

Regarding highlighted wording

'Where the sponsor disagrees with the reasonable possibility of a causal relationship between the suspected medicine and the adverse reaction reported by a consumer, the ICSR must still be reported. The opinions of both the consumer and the sponsor should be recorded in the adverse reaction report, including the criteria on which the sponsor has made their assessment. '

The concept is not different from what is required in EU PV Module VI. (section B.2 Validation of reports), where the basic principle is that when the sponsor and the primary source of information are not in agreement around causal relationship, both opinions have to be clearly reported in the ICSR. The same is applicable for seriousness.

Not clear why there is specific reference to consumer reports in light of the fact that 1) it is questionable that a consumer reports an explicit causal relationship, and 2) consumer reports are always followed-up (where possible) with the primary health care professional to seek additional information, so it would be more probable that the latter may not agree with what stated by the consumer initially and in this case both opinions (i.e. the consumer and the HCP) should be provided in the ICSR.

Re Section 3.5.2. Downgrading the severity of a case report

'A valid case reported by a primary source should not be downgraded to a non-serious adverse event if a secondary source involved in the care of the primary source disagrees with the primary source's suspicion. The opinions of both the primary source, and the secondary source (or source of follow-up information) should be recorded in the adverse reaction report, including the criteria on which the secondary source has made their assessment. '

Suggest replacing the word 'severity' in section heading with the word 'seriousness' as these are separate concepts.

This paragraph is referring only to seriousness. It sounds odd especially considering that this paragraph immediately follows 3.5.1 where causal relationship is discussed only in the context of consumer reports.

We suggest it would be more logical to discuss how ICRSs have to be managed when different opinions on seriousness and/or causality are reported by the primary source of information (either consumer or HCPs) vs. sponsors.

Re Section 3.5.4 Lack of Efficacy

Suggest editing as per below making third bullet point more specific

'All cases of a lack of therapeutic efficacy for any medicine should be reported to CARM, as the consequences may be potentially very serious for:

- vaccines
- contraceptives
- ~~medicines used in critical conditions or life-threatening situations.~~ antibiotics

For example, a lack of efficacy for antibiotics or vaccines may indicate newly developing resistance or waning immunity, both making further study necessary.'

The wording of the following sections is confusing regarding what to report:

Sections 3.5.5 Misuse or abuse

Section 3.5.6 Off-label use

Section 3.5.9 Medication errors

Section 3.5.10 Overdose or Occupational Exposure

Some wording in the guideline is as follows:

Section 3.5.5 'Misuse or abuse may occur with any medicine. Reports of intentional misuse or abuse where no adverse reactions are associated do not need to be forwarded to either CARM or Medsafe. Sponsors should routinely follow up on these reports and include them in their ongoing review and analysis (PBRER).'

Section 3.5.6 'Valid ICSRs associated with off-label use should be forwarded to CARM. If the off-label use of an approved medicine occurs as part of a blinded clinical study, sponsors should not report adverse reactions until the identity of the medicine has been confirmed (see also Section 3.5.7).'

Section 3.5.9 'Reports associated with a suspected adverse reaction should be reported to CARM provided they are valid unsolicited reports.'

While discussing when to report as opposed when not to report by using: 'valid ICSRs' vs. 'Reports associated with a suspected adverse reaction' vs. 'no adverse reactions are associated'.

It would be better, to avoid any confusion, to use the same approach and apply the same language across all groups and clearly state when to report vs. not. Suggest referring back to section 3.2 which is clear on only reporting serious ADRs.

As well **Section 3.5.9** refers to MERP and reporting medication errors whether or not associated with a suspected adverse reaction. Please clarify if sponsors are required to submit reports here or is this intended for HCPs in hospitals? If the former this is at variance with other jurisdictions where sponsors are certainly required to collect reports of medication error but are only required to report those associated with a serious adverse reaction. If the latter such guidance should be captured in a separate document.

Re Section 3.5.12 Period after suspension or withdrawal of approval

'All valid serious ICSRs identified by the sponsor after suspension or withdrawal of a medicine should be reported to CARM'

Clarification required of terms 'suspension or withdrawal'. Does this mean market authorisation has been withdrawn? Is not regulatory reporting of adverse events predicated on having a market authorisation? If there is no longer a market authorisation what is the regulatory basis for requiring ongoing regulatory reporting?

Re Section 3.5.13 Media Reports

'Reports of suspected adverse reactions originating from a non-medical source, such as the lay media, should be considered to be a spontaneous report.

Sponsors should regularly monitor and review lay internet sites (such as chat rooms and discussion forums) for potential reports of suspected adverse reactions. Sponsors should also regularly monitor and review digital media sites for which they are responsible. When sponsors become aware of unsolicited cases of suspected adverse reactions from the internet or digital media, these should be considered to be spontaneous reports and reported to CARM, subject to the criteria for a valid report (see Section 3.3.2).'

This wording obliges sponsors to review non-sponsored lay internet sites, essentially the entire worldwide web. This will produce a significant unnecessary workload considering that most of reports will be considered invalid. In addition it will be very difficult to have a privately contactable reporter. Is this is the intention?

According to EU PV Module VI: Marketing authorisation holders should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorisation holder. Suggest making wording consistent with EU guidance.

Re 3.5.14 Reports from the scientific and medical literature

'Sponsors should frequently review and assess reports of suspected adverse reactions from the scientific and medical literature to identify and record ICSRs. It is recommended that reviews should be conducted not less than every three months. Reviews should only commence from the time that the medicine is placed on the market and not from the time of submission of the new medicine application, or from the grant of consent to distribute a new medicine.'

This is different from the guidance adopted as per EU PV Module VI (see Appendix 2 – VI.App2.1 When to start and stop searching in scientific literature) that states:

'In addition to the reporting of serious and non-serious ICSRs or their presentation in periodic

safety update reports, the marketing authorisation holder has an obligation to review the worldwide experience with medicinal product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation.'

Also the wording from this section

'Sponsors should report only cases occurring in New Zealand for a medicine they distribute. If the brand of medicine is not reported, sponsors should only report if their medicine was funded or was in use in New Zealand at the time of the suspected adverse reaction reported in the publication. This helps to reduce duplicate reporting. A reference and/or copy of the publication should accompany the report.'

Reference to a funded medicine is inappropriate in a pharmacovigilance guidance document where the focus is on capture and reporting of clinical information to update the safety profile of a sponsored medicines. Whether a product is funded in New Zealand cannot be captured in safety database reporting rules and evaluating this would potentially introduce unnecessary delays in regulatory reporting possibly leading to non-compliance.

Re Section 3.5.15

The suggestion that sponsors should not report to CARM adverse reaction associated with suspected or confirmed quality defects is surprising. Whether or not the ADR is associated with a suspected product defect may not be immediately apparent given the time it may take to investigate the defect and the 15 day reporting timeline. It may take more than 15 days to determine if the suspected defect is genuine, due to individual circumstances or constitutes a significant safety issue. We suggest that all serious adverse drug reactions be reported whether or not they are associated with a product defect

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?

No comment

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?

Re Section 5.2 What are significant safety issues?

The first bullet point: "addition, modification or removal of an approved indication, a change to the contraindications, warnings, precautions or adverse reactions statements in the product information for safety reasons in any country where the medicine is marketed".

This definition is very broad since addition of "warnings, precautions or adverse reactions statements in the product information for safety reasons in other countries" can range from being routine and not impacting clinical practice to being a clinically significant event. The definition of "significant" requires greater clarity to distinguish between routine label updates and those requiring notification within 72 hours of the event taking place in a foreign country.

Section 6: Submission of Safety Monitoring Documents eg,

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

More guidance should be provided on the format and content of Risk Management Plans (RMPs). Suggest reference to EMA Guideline on good pharmacovigilance practices: Module V Risk management Systems (EMA/838713/2011 Rev1*). Ideally there should be a separate guidance document for RMPs.

Safety communications and educational materials are elements of risk management plans. We suggest incorporating Section 7.3 and 7.4 into section 6.3 Risk Management Plans when these are required. For example

'When RMPs include safety communications or other educational material these should be made available to Medsafe prior to distribution'

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?

As per section 6 comments above; Safety communications and educational materials are elements of risk management plans. We suggest incorporating Section 7.3 and 7.4 into section 6.3 Risk Management Plans when these are required. For example

'When RMPs include safety communications or other educational material these should be made available to Medsafe prior to distribution'

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?

The draft PV Guideline would be simplified if Medsafe formally adopted EU PV, RMP and PBRER guidelines. The draft PV Guideline is ambiguous in many places as written and appears to speak to different audiences. This document should be specific to sponsor responsibilities

Please include additional pages if necessary.