MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Proposed updates to the Guidelines on the Regulation of Therapeutic Products in New Zealand: Pharmacovigilance

20 March 2024

Consultation outcome

Contents

Executive Summary

Background

The Guideline on the Regulation of Therapeutic Products in New Zealand (GRTPNZ): Pharmacovigilance provides information for sponsors* about their pharmacovigilance obligations and responsibilities in New Zealand.

Medsafe reviewed the current GRTPNZ: Pharmacovigilance (Edition 2.2, August 2020) and proposed updates throughout the Guideline. From 2 November 2023 to 14 December 2023, Medsafe consulted on the proposed updates. The consultation was aimed at sponsors* of medicines that are approved for use in New Zealand and organisations involved in pharmacovigilance activities (ie, on behalf of sponsors). This report is a summary of the submissions received.

Consultation results

We received 15 submissions to the consultation.

Most respondents agreed with the proposed updates. Several respondents suggested changes to wording, layout and/or formatting to improve clarity. There were also requests to add examples or additional detail to some sections to improve understanding and interpretation. Respondents also provided insightful feedback and suggestions on the Guideline. Where appropriate, we have incorporated the suggested changes into the revised Guideline.

However, some answers indicated that respondents may have read a sub-section of the Guideline in isolation rather than all the information in the relevant section. This may have led respondents to misinterpret parts of the Guideline. Medsafe stresses that sponsors need to read the information in each section of the Guideline in its entirety.

Revised Guideline

We have published the revised Guideline:

- Guideline on the Regulation of Therapeutic Products in New Zealand: Pharmacovigilance (Edition 3.0) (PDF, 521 KB, 36 pages).

The revised Guideline comes into effect from 1 July 2024, but sponsors may use it from the day of publication.

Medsafe would like to thank everyone for their contribution to this consultation.

*A sponsor is defined as an individual, company, institution or organisation that is responsible for the medicinal product in New Zealand.

Background information

Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and is responsible for the regulation of therapeutic products in New Zealand by administering the Medicines Act 1981 and Regulations 1984.

Therefore, Medsafe has specific New Zealand legislation to administer, and the requirements under the legislation are further outlined through the Guidelines on the Regulation of Therapeutic Products in New Zealand (GRTPNZ).

GRTPNZ: Pharmacovigilance provides information for sponsors about their pharmacovigilance obligations and responsibilities for the medicines that they supply and distribute in New Zealand.

GRTPNZ: Pharmacovigilance aligns as much as possible with guidelines from major recognised overseas regulators, within the limitations of the current local legislation and pharmacovigilance resource in New Zealand.

Consultation results

Thank you to everyone who responded to the consultation.

We have analysed and summarised the results.

The results are divided into 9 parts as follows:

1. Overview of respondents
2. Summary of responses – Section 3: Roles and responsibilities.
3. Summary of responses – Section 4: Individual Case Safety Reports (ICSRs)
4. Summary of responses – Section 5: Signal management
5. Summary of responses – Section 6: Safety issues
6. Summary of responses – Section 7: Safety monitoring documents
7. Summary of responses – Section 8: Safety communications
8. Summary of responses – Section 9: Best practice guidelines
9. Summary of responses – Other feedback and comments

Part 1 summarises the respondent type.

Parts 2 to 9 summarise responses to the questions asked about different sections of the revised Guideline. Where appropriate, we have grouped respondent comments into themes, and also included Medsafe's response and any subsequent changes to the revised Guideline.

Where subsequent changes have resulted in changes to section or table numbers in the revised Guideline, this outcome document includes both the original and the updated section or table number.

1. Overview of respondents

You can view the submissions that we have permission to publish.

We received 15 submissions via the consultation tool.

All responses were submitted by sponsors or organisations involved in pharmacovigilance activities.

2. Summary of responses – Section 3: Roles and responsibilities

Question 5

Do sections 3.1 'Medsafe' and 3.2 'Sponsors' adequately explain the roles and responsibilities of both parties? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 4 respondents who provided comments or suggestions for this question. These have been grouped into themes below.

Sponsor contact person

One respondent commented that there is ambiguity whether the person responsible for fulfilling the sponsor's obligations is the same person as the contact person for pharmacovigilance.

The respondent suggested that Medsafe clarify this requirement, noting information in the Australian Therapeutic Goods Administration (TGA) Pharmacovigilance Guideline.[1]

Medsafe's response:

New Zealand and Australia have different legislation.

Sponsors are responsible for notifying Medsafe of the contact person for pharmacovigilance.

The contact person is the person responsible for notifying Medsafe about safety issues. This person does not have to be the same person who conducts pharmacovigilance activities.

Unapproved medicines

There was a suggestion to incorporate unapproved medicines as well as approved medicines in section 3 of the Guideline.

Medsafe's response:

The guideline states that sponsors should continuously monitor the safety of any of their medicines supplied or distributed in New Zealand.

This statement automatically includes approved and unapproved medicines, and no further clarification is needed.

[1] Therapeutic Goods Administration Australia. 2023. *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements* Version 3.0, August 2023. URL: https://www.tga.gov.au/sites/default/files/2023-08/pharmacovigilance-responsibilities-medicine-sponsors-2023.pdf (accessed 9 January 2024).

Reporting timeframes for safety issues

Two respondents suggested including information in section 3 of the Guideline about the reporting timeframes for when New Zealand sponsors become aware of safety issues.

Medsafe's response:

Section 3.2.1 states that sponsors have a responsibility to notify Medsafe when they become aware of safety issues and refers to section 6 of the Guideline. Section 6 contains information about reporting timeframes for safety issues to Medsafe. Therefore, Medsafe considers that repetition of this information in section 3 is unnecessary.

There are a variety of timeframes for reporting different pharmacovigilance activities. These timeframes are outlined in the appropriate sections of the Guideline.

Question 6

Is Medsafe's process for collecting spontaneous reports (section 3.1.1) clearly explained? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 3 respondents who provided comments or suggestions, all of which were similar.

Reference to section 4 of the Guideline

Respondents suggested that section 3.1.1 of the Guideline should cross-reference to section 4 of the Guideline, which provides details about reporting relevant for sponsors.

Medsafe's response:

Section 3.1 relates to the roles and responsibilities of Medsafe, with sub-section 3.1.1 explaining the collection and storage of spontaneous adverse reaction reports. Information about how sponsors should report suspected adverse reactions is not applicable to this section.

Question 7

Do you have any other comments or suggested changes for section 3 of the Guideline?

Y/N

- Yes, n = 2
- No, n = 13

There were 2 respondents who provided additional comments. Both comments related to the same topic.

Timeframe for notification of pharmacovigilance contact person to Medsafe

Respondents proposed adding a timeframe for notifying Medsafe of the pharmacovigilance contact person.

A notification timeframe of within 15 days of appointment by the sponsor was suggested.

Medsafe's response:

Medsafe agrees to add a timeframe for notification of the contact person for pharmacovigilance.

Sponsors should notify Medsafe of the contact person for pharmacovigilance within 15 days of their product approval under Section 20 or 23 of the Medicines Act, if the contact person for pharmacovigilance for their products has not been previously notified to Medsafe.

Any changes to the contact person for pharmacovigilance must be notified to Medsafe within 15 days of appointment by the sponsor.

We have incorporated this requirement into section 3.2.1.1 of the revised Guideline.

3. Summary of responses – Section 4: Individual Case Safety Reports (ISCRs)

Question 8

Does section 4.1 'Collection of reports' adequately explain the sponsor's role in collecting and collating adverse reaction reports? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 4 respondents who provided comments or suggestions. These have been grouped into themes.

Case with no identifiers

One respondent suggested adding 'if you believe that there is a real patient involved (without any identifiers), it is considered sufficient for reporting' to section 4.1.

Medsafe's response:

Medsafe considers a case without an identifiable patient would be an invalid report and should not be reported to the New Zealand Pharmacovigilance Database.

In these circumstances, the invalid report should still be recorded in the sponsor's pharmacovigilance system for use in product safety evaluation activities, such as Periodic Benefit Risk Evaluation Reports (PBRERs).

Privacy considerations

Two respondents suggested adding information relating to privacy considerations for collection of reporter and patient information for ISCRs.

Medsafe's response:

Sponsors should be familiar with their obligations in relation to the collection, use and disclosure of personal information.

Sponsors cannot disclose personal information in ISCRs to Medsafe/ the Centre for Adverse Reactions Monitoring (CARM) without reporter and/or patient consent.

We have added a statement to section 4.1 about considerations for privacy legislation.

Of note, Medsafe does not require contact details of the reporter to be included in ISCRs that are reported to us.

Additional information to Table 2: Mandatory items for a valid ICSR report

There was a suggestion to add a description for 'suspect medicine' and 'suspect reaction' to Table 2, in section 4.1.1 (revised Guideline section 4.2.2).

One respondent suggested adding 'reporter type' into the description for identifiable reporter.

Medsafe's response:

We have updated Table 2 in section 4.1.1 (revised Guideline section 4.2.2) as per the suggestions from respondents.

Question 9

Is section 4.2 (revised Guideline section 4.4) 'How to report' easy to understand? Please make any comments or suggestions.

Y/N

- Yes, n = 15
- No, n = 0

There were 5 respondents who provided comments or suggestions. These have been grouped into themes.

Reporting adverse reactions for medicines used in clinical trials

Some respondents queried about different requirements for reporting of adverse reactions in section 4.2 of this Guideline and the requirements in GRTPNZ: Clinical Trials.

Medsafe's response:

The two Guidelines have different requirements for adverse reaction reporting to reflect the different situations.

GRTPNZ: Clinical Trials (Edition 2.0, November 2018) is currently being revised and will include updated information about reporting of adverse reactions.

New Zealand Adverse Reactions reporting form

In section 4.2, one respondent sought clarification about 'reporting using the New Zealand Adverse Reactions reporting form' and the process for this.

One respondent queried if a log-in option will be available for companies in the New Zealand Pharmacovigilance Database.

Medsafe's response:

The New Zealand Adverse Reactions Reporting Form is an online webform that can be used to submit valid ICSRs to the New Zealand Pharmacovigilance Database. Sponsors may use the webform to submit reports.

We have added a new table to the revised Guideline that describes the types of reporting and provides directions – Table 3: How to report valid serious ICSRs to Medsafe.

The New Zealand Pharmacovigilance Database does not have a log-in option for sponsors.

Other

One respondent asked for clarification to the reference 'PDF 108 KB, 1 page' mentioned after CIOMS reporting form.

Medsafe's response:

PDF 108 KB, 1 page relates to the PDF size and number of pages of the CIOMS reporting form.

Question 10

Are sections 4.4 (revised Guideline 4.2) and 4.5 clear about what to report and what not to report?

Please make any comments or suggestions.

Y/N

- Yes, n = 4
- No, n = 11

There were 13 respondents who provided comments or suggestions. These have been grouped into themes.

Solicited reports

In Table 4 'What not to report to the NZ Pharmacovigilance Database' (Table 5 in the revised Guideline), a respondent asked if the statement 'Solicited reports not considered to have a causal relationship' should also apply to unsolicited reports.

Medsafe's response:

Unsolicited reports represent spontaneous reports as stated in the Guideline.

Unsolicited reports should be reported if they meet the requirements set out in section 4.

Product quality issue reports

One respondent commented on differences between product quality complaints and true quality defect issues. Reports of product quality complaints are investigated to confirm if a quality defect exists. The respondent suggested including a definition of quality defect in section 4.4.2.6 (revised Guideline section 4.4.3.6), and that these should only be reported when confirmed by the sponsor to avoid receipt of product quality complaints which are not yet confirmed or been investigated.

In section 4.4.2.6 (revised Guideline section 4.4.3.6), several respondents asked about which product quality defects without an adverse reaction should be reported to Medsafe.

One respondent asked whether any individual report of an adverse reaction associated with a suspected or confirmed quality defect requires reporting as a safety issue, or if the sponsor needs to conduct an internal safety investigation first to determine if there is a reportable safety issue.

One respondent asked for clarity about quality defect reports with lack of therapeutic effect.

Another respondent asked if non-serious reactions related to suspected or confirmed quality defects are in scope.

Medsafe's response:

As the Guideline already states, product quality *complaints* should not be reported to Medsafe until it is determined there is a quality *defect*.

The definition of a quality defect is outlined in the definition section of the Guideline.

Reports of confirmed quality defects, including adulteration or contamination or falsified medicine (such as counterfeit or tampering) should be reported to Medsafe's Product Safety Team.

A report of a serious adverse reaction that is associated with a confirmed quality defect should be reported to Medsafe's Product Safety team. Such reports are not required to be reported to the New Zealand Pharmacovigilance Database.

A non-serious adverse reaction report associated with a confirmed quality defect should be reported to the Medsafe Product Safety team as part of the company review of the issue.

A report of lack of efficacy associated with a confirmed quality defect should be included in the report to the Medsafe Product Safety Team.

If, after investigation of a serious adverse reaction report associated with a product quality complaint, a quality defect is not confirmed, such a report should be reported to the New Zealand Pharmacovigilance Database only. Day 0 is the day that the quality defect was refuted. The report is now a routine reportable ICSR.

We have added information to section 4.4.2.6 (revised Guideline section 4.4.3.6) to aid in sponsors' understanding of the above.

Vaccine lack of efficacy reports

One respondent asked if a non-serious lack of therapeutic effect vaccine report is required to be reported.

Similarly, one respondent asked if all lack of efficacy cases for vaccines should be reported as serious. Another asked for clarification if no serious criterion is specified in the report.

One respondent asked for confirmation if the seriousness criteria for an adverse event following immunisation (AEFI) is the same as for other medicine adverse events.

Medsafe's response:

We consider all reports of lack of therapeutic effect with vaccines to be serious, because we consider them to be medically significant Therefore, they should therefore be reported.

The seriousness criteria for an AEFI are the same as for other medicine adverse events.

Medicines used in clinical trial reports

In Table 4 'What not to report to the NZ Pharmacovigilance Database' (Table 5 in the revised Guideline), there was a request to further clarify 'Blinded clinical trial cases for approved medicines when the identity of the suspected medicine or the patient has not been identified', as this statement may not be relevant to the guideline.

One respondent suggested adding instructions for reporting of serious adverse reactions occurring during the use of approved medicines in a clinical trial.

Medsafe's response:

We have removed the blinded clinical trial statement from the table as guidance on reporting of serious adverse reactions occurring during the use of approved medicines in clinical trials is outlined GRTPNZ – Clinical trials. Please note this Guideline is currently under review.

Lack of therapeutic effect reports

In Table 3 'Guidance on what to report in certain situations' (revised Guideline Table 4), some respondents asked whether all cases of lack of therapeutic effect need to be reported.

Respondents asked if all cases of lack of therapeutic effect associated with the listed therapy types are to be reported, regardless of the sponsor's medical assessment, and particularly around ICSR seriousness criteria (ie, should all cases be serious or always considered serious for the purposes of reporting to Medsafe). In addition, respondents asked if the reporting requirement for events associated with a lack of therapeutic effect relates to an approved indication and/or an unapproved use of a medicine.

One respondent suggested that lack of therapeutic effect reports associated with a quality defect should be reported to both the Product Safety team and the New Zealand Pharmacovigilance Database.

Medsafe's response:

We have updated Table 3 'Guidance on what to report in certain situations' (revised Guideline Table 4) to state 'Cases where lack of therapeutic effect is considered to be serious for the individual using the medicine for the approved indication'. Therefore, such a report is considered to be serious and should be reported. This overrides the reporter's assessment of the report as non-serious.

Examples of lack of therapeutic effect reports that are considered to be serious are vaccines, contraceptives and antibiotics.

We have added an explanatory footnote to the table (revised Guideline Table 4) about cases of lack of therapeutic effect.

Reports of lack of therapeutic effect associated with a confirmed quality defect should be reported to the Product Safety Team, as outlined in the Guideline.

Media reports

In section 4.4.2.5 (revised Guideline 4.4.3.5), a respondent suggested changing the wording to 'sponsors should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions'.

A respondent asked whether a case should be reported if it was identified in the New Zealand media, but the country of the patient is not known.

Medsafe's response:

We have updated this statement in the Guideline as suggested.

If it is unclear if the report relates to a patient in New Zealand, then this does not need be reported.

Valid reports that meet the Guideline's criteria for reporting should be reported.

Unapproved medicine reports

In Table 3 'Guidance on what to report in certain situations' (revised Guideline Table 4), a respondent queried whether reports relating to supply of unapproved medicines should only include 'reports with an unexpected serious adverse reaction' or should align with that of other safety concerns (ie, reports with an associated serious adverse reaction).

Medsafe's response:

As per the Guideline, only serious unexpected adverse reactions to unapproved medicines are required to be reported.

In Table 3 'Guidance on what to report in certain situations' (revised Guideline Table 4), we have added an explanatory footnote about cases with an unexpected serious adverse reaction (ie, an adverse reaction not currently listed in the Company Core Data Sheet).

Question 11

Do you have any other comments or suggested changes for section 4 of the guideline? Please make any comments or suggestions.

Y/N

- Yes, n = 6
- No, n = 9

There were 6 respondents who provided comments or suggestions. These have been grouped into themes.

Timeframe for reporting ICSRs

There was a suggestion to clarify 'Day 0' as receipt of information by the New Zealand sponsor.

One respondent suggested to add the definition of 'Day 0'.

Medsafe's response:

We have added information to section 4.3 to state that sponsors should submit valid ICSRs within 15 days of receipt. Day 0 is the day that the NZ sponsor receives the information.

Format and layout

One respondent suggested that section 4.4 and 4.5 should be at the beginning of section 4.

Medsafe's response:

We have reviewed the layout of section 4 and have reorganised appropriate sections for clarity.

Section 4.4.2.8, Table 3: Guidance on what to report in certain situations

A respondent commented that although the table in section 4.4.2.8 (revised Guideline Table 4, section 4.4.3.8) simplifies the presentation of this information, the table has less information and is not as clear as the current Guideline (edition 2.2).

Medsafe's response:

With the revised Guideline, we have attempted to simplify the information presented in the sections relating to reporting ISCRs for special situations. This includes moving definitions into the Definitions section at the beginning of the Guideline and adding the table on what to report in certain situations.

We have ensured that the important information has been maintained in the updated section.

As outlined above, additional information about lack of therapeutic effect reports has been added as a footnote to Table 3 'Guidance on what to report in certain situations' (revised Guideline, Table 4).

Consumer reports

In section 4.4.2.2 'Consumer reports' (revised Guideline section 4.4.3.2), one respondent suggested providing examples to the bullet point that says 'Additional follow-up may not be necessary for non-serious reactions'.

Medsafe's response:

We have reviewed this bullet point and removed it from the Guideline. The requirement for reporting ISCRs in New Zealand relates to serious reports only.

4. Summary of responses – Section 5: Signal management

Question 12

Is section 5 'Signal management' clearly explained? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 2 respondents who provided comments or suggestions.

Reporting of safety signals

One respondent noted that information about reporting of safety issues in section 5 and section 6 was not aligned and suggested alternative wording.

Medsafe's response:

We agree that there were slight differences and have amended the statement in the Introduction (section 5.1) to state 'Section 6 outlines information for sponsors about notification of safety issues to Medsafe'.

Formatting changes

One respondent suggested formatting changes in section 5, which was further explained by the respondent in question 13.

Medsafe's response:

These suggestions are reviewed as part of question 13 (see below).

Question 13

Do you have any other comments of suggested changes for section 5 of the Guideline?

Y/N

- Yes, n = 3
- No, n = 12

There were 2 respondents who provided comments or suggestions.

Reporting of safety signals

One respondent proposed that section 5.1 should be updated to state that Medsafe must be notified of safety signals that have been confirmed (ie, the sponsor has completed the safety investigation and action will be taken).

Medsafe's response:

The type of safety issue (significant safety issue or other safety issues) determines if the sponsor should notify Medsafe when investigating the safety issue or when the investigation is completed. This information is further discussed in section 6.

As stated above, we have amended the statement in the Introduction (section 5.1) about notification of safety signals to Medsafe.

Formatting changes

One respondent suggested moving the part of section 5.2 that describes signal management to the beginning of section 5.1.

Medsafe's response:

We agree with the suggestion and have made the change.

5. Summary of responses – Section 6: Safety issues

Question 14

Do you agree that safety issues can be classified as either 'Significant' (section 6.1.1) (revised Guideline section 6.2.1) or 'Other' (section 6.1.2) (revised Guideline section 6.2.2.)? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 5 respondents who provided comments or suggestions. These have been grouped into themes.

Criteria for significant safety issues (SSIs) and other safety issues (OSIs)

Two respondents suggested that it would be helpful if the SSIs and OSIs criteria were more closely aligned with the TGA's Pharmacovigilance Guideline.[2]

In doing so, this would streamline internal reporting processes across both Australia and New Zealand and ease the implementation of the changes in reporting requirements for sponsors.

Medsafe's response:

We acknowledge feedback from respondents in relation to aligning the SSIs and OSIs criteria in the Guideline with the TGA's Pharmacovigilance Guideline.

However, we believe that the criteria are very similar.

The Australian guideline provides additional examples of SSIs. However, we consider these additional examples to be covered by our definition of SSIs in this Guideline.

Sponsors should use their professional judgement to determine whether a safety issue is a significant safety issue.

We also acknowledge the European Medicines Agency's (EMA) Signal Management Guideline[3], and what is considered an 'emerging safety issue'.

We have added information to section 6 about SSIs and OSIs.

[2] Therapeutic Goods Administration Australia. 2023. *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements* Version 3.0, August 2023. URL: https://www.tga.gov.au/sites/default/files/2023-08/pharmacovigilance-responsibilities-medicine-sponsors-2023.pdf (accessed 9 January 2024).

[3] European Medicines Agency. 2017. *Guideline on Good Pharmacovigilance Practices: Module IX – Signal Management* (Rev 1). URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf

Innovator products that are not marketed

One respondent suggested clarifying the reporting of safety issues for innovator products that are not marketed and there is no generic product marketed.

Medsafe's response:

Sponsors of approved innovator medicines must notify Medsafe of safety issues for their medicines.

An exception is for innovator products that are not marketed and there is no generic product available in New Zealand. Sponsors are not required to notify Medsafe of safety issues for these products.

Sponsors of generic medicines where the New Zealand innovator product is not approved (including approval lapsed) must notify Medsafe of safety issues for their medicines.

We have added new section 6.2.3 'Responsibility for reporting safety issues' to the revised Guideline to clarify the requirements.

New 'other safety issues (OSIs)' category

One respondent commented that introduction of 'other safety issues' category is very broad and may result in over reporting of issues that would also be reported by data sheet updates.

A respondent suggested removing the 'other safety issues' category to align with EMA's Signal Management Guideline.[4] Alternatively, notification of OSIs would be via data sheet update submission only.

Medsafe's response:

As part of the proposed updates to the Guideline, section 6.1.2 (revised Guideline section 6.2.2) provided an option for sponsors to notify us of OSIs by submitting a changed medicine notification (CMN).

However, where notification through CMN submission is not possible within the required timeframe, sponsors must notify Medsafe of other safety issues by email. Notifying us by email about proposed changes to the data sheet means we are aware of new side effects in an acceptable time frame.

Overall, we received positive feedback about the introduction of the OSIs category, and have retained it in the revised Guideline (section 6.2.1).

Editorial changes

In section 6.1.1 'Significant safety issues', one respondent suggested in an editorial change from 'which may lead to a contraindication' to 'which may lead to an addition of a contraindication'.

Medsafe's response:

We have updated this wording in section 6.1.1 (revised Guideline section 6.2.1) as suggested.

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[4] European Medicines Agency. 2017. *Guideline on Good Pharmacovigilance Practices: Module IX – Signal Management* (Rev 1). URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf

Question 15

Do sections 6.1.1 (revised Guideline 6.2.1) and 6.1.2 (revised Guideline 6.2.2) clearly explain the difference between significant and other safety issue?

Please make any comments or suggestions.

Y/N

- Yes, n = 8
- No, n = 7

There were 9 respondents who provided comments or suggestions. These have been grouped into themes.

Definitions

Respondents recommended adding the definitions of 'significant safety issue' and 'other safety issue' to the Definitions section at the beginning of the Guideline.

Some respondents commented that it should be made very clear that other safety issues are other safety-related changes that do not meet the definition of a significant safety issue.

Medsafe's response:

We have added information to section 6 that outlines the SSIs criteria and added SSIs to the Definitions section.

'Other safety issues' are those that do not meet the criteria of a significant safety issue. We have incorporated this into the Guideline.

Significant safety issues (SSIs)

Some respondents said that the proposed changes to SSIs are too vague and may result in a SSI not being reported. They suggested including further information and/or providing examples of what is considered to be a SSI.

In section 6.1.1 'Significant safety issues' (revised Guideline section 6.2.1), a respondent recommended changing the first bullet point from 'change of an approved indication' to 'modification or removal of an approved indication (for safety reasons)'. Another respondent asked us to review the use of 'may' in this same bullet point.

Medsafe's response:

We have reviewed and updated the SSIs section (revised Guideline section 6.2.1).

Sponsors should use their professional judgement to determine whether a safety issue is significant. This includes assessing the impact on the medicine's safety, benefit-risk balance and/or implications for public health.

If sponsors are unsure whether a safety issue is a significant safety issue or not, we recommend notification.

Other safety issues (OSIs)

There was feedback that the types of OSIs in the Guideline were lacking in specificity or lacking clarity. The proposed updates are broad and may result in over-reporting of signals.

One respondent suggested that it should be made clear that OSIs are safety-related changes that do not meet the definition of a significant safety issue (SSI).

A respondent asked if sponsors should report OSIs when they apply to both serious and non-serious adverse events.

There was a comment that there may be circumstances where the data sheet is not updated following Company Core Datasheet (CCDS) changes.

A respondent suggested providing additional information and examples about what constitutes OSIs relative to CCDS updates and safety-related changes requested by recognised regulatory authorities, such as specifying the relevant sections of prescribing information. They proposed creating a Frequently Asked Questions (FAQ) document to address this.

Medsafe's response:

OSIs are those that do not meet the SSIs criteria.

OSIs include both serious and non-serious adverse reactions.

As mentioned in responses to the above questions, we have added information to section 6 of the revised Guideline to aid in sponsors' interpretation of SSIs and OSIs. We have also added SSIs and OSIs to the Definitions section.

Quality-related other safety issues

In section 6.1.2, there were questions about the definition of quality-related safety issues that are not considered to be significant safety issues.

Medsafe's response:

We have removed all references to quality-related safety issues from section 6.

We have added more information to section 4.4.2.6 'Suspected adverse reactions relating to quality defects or falsified medicines' (revised Guideline section 4.4.3.6).

If sponsors have queries about quality defects, they should contact the Medsafe Product Safety Team.

Reporting of safety issues

One respondent proposed that notification of SSIs to Medsafe should only take place once safety investigations are complete and the issue is confirmed by the sponsor, similar to other safety issues.

Medsafe's response:

We have updated section 6.3.2 (revised Guideline section 6.4.2) to state that sponsors must notify Medsafe about OSIs if the safety investigation completed and action is to be taken.

Given the potential urgency of new safety information and impact to public health for SSIs, sponsors should notify Medsafe as soon as the safety issue is validated (ie, it will be investigated). Sponsors can provide further information to Medsafe once the investigation and outcome are completed.

Medsafe is unable to support companies in the management of benefit-risk for their medicines if there are delays in notifying us about SSIs.

We have improved the Appendix flow diagram to help sponsors' interpretation of reporting safety issues. There are now two appendices, with significant safety issues (SSIs) separated from other safety issues (OSIs).

Reporting of safety issues for medicines under application

Respondents asked for clarification about whether or not submission of safety issues is applicable for medicines under application in New Zealand.

Medsafe's response:

Yes. Submission of SSIs is applicable for medicines under application in New Zealand.

We have revised the Guideline (new section 6.2.3) to incorporate this.

Question 16

Do you agree with the 72-hour timeframe for reporting significant safety issues to Medsafe (section 6.3.1)? Please make any comments or suggestions.

Y/N

- Yes, n = 11
- No, n = 4

There were 11 respondents who provided comments and/or suggestions. These have been grouped into themes.

Awareness of the New Zealand sponsor – SSIs

The majority of respondents asked for clarification as to whether this 72-hour timeframe is related to notification of the SSI to the local sponsor by the global affiliate.

One respondent asked Medsafe to consider allowing reporting of SSIs within no later than 5 working days instead of the proposed 72 hours. This would address differences in time zones, particularly if the sponsor becomes aware of the issue immediately before a weekend or public holiday.

Some respondents suggested changing 'identification' to 'awareness'.

Medsafe's response:

We confirm that the timeframe is 72 hours from when the local (NZ) sponsor is notified or made aware of the emerging SSI. We consider that the proposed timeframe of 72 hours is acceptable.

We have updated section 6.3.1 (revised Guideline section 6.4.1) to address this.

Addition of a timeframe for notification of SSIs to the New Zealand sponsor

Some respondents recommended adding a timeframe for notification to the New Zealand sponsor of any SSI by their global headquarters.

There was a suggestion to include information similar to the TGA's Pharmacovigilance Guideline,[5] which recognises that issues may be identified globally before being disseminated to the Australian sponsor. The TGA Guideline includes a separate 3 calendar day timeline for global counterparts to notify local sponsors of SSIs, and then the 72-hour timeframe for reporting to the TGA. The respondent said that having similar information in the proposed NZ Guideline would make the reporting timeline clearer and allow sponsors to maintain a consistent process for both Australia and New Zealand.

Medsafe's response:

Medsafe acknowledges that safety information may be received and processed by global counterparts before being disseminated to the local New Zealand sponsor.

We expect sponsors to have appropriate processes in place to ensure timely communication of safety information between global and local counterparts.

We have updated the introductory paragraph in section 6.3 (revised Guideline section 6.4) to note the above.

Question 17

Do you agree with the 30-day timeframe for reporting other safety issues to Medsafe (section 6.3.2) (revised Guideline section 6.4.2)?

Please make any comments or suggestions.

All respondents (15) provided an answer to this question. Most respondents agreed with the 30-day timeframe for reporting OSIs to Medsafe.

Comments and suggestions for this question have been grouped into themes.

Awareness of the New Zealand sponsor – OSIs

In section 6.3.2 (revised Guideline section 6.4.2), several respondents asked if '30 days' meant within 30 days of the New Zealand sponsor's awareness of the OSI.

Medsafe's response:

Yes. The timeframe is within 30 calendar days of the New Zealand sponsor's awareness of the OSI.

We have updated the revised Guideline to address this.

Data sheet updates

Respondents commented that the 30-day timeframe is unlikely to be met for data sheet updates and associated Changed Medicine Notification (CMN) submissions.

One respondent suggested to only have the 30-day timeframe for notification of OSIs, and a separate CMN submission can be made at a later date.

Medsafe's response:

[5] Therapeutic Goods Administration Australia. 2023. *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements* Version 3.0, August 2023. URL: https://www.tga.gov.au/sites/default/files/2023-08/pharmacovigilance-responsibilities-medicine-sponsors-2023.pdf (accessed 9 January 2024).

OSIs can be notified to Medsafe via email or via CMN submission.

CMN submission is an option for sponsors to use to notify Medsafe – where CMN submission meets the 30-day timeframe.

We understand that it may not be possible for sponsors to submit a CMN within the 30-day timeframe. It is likely that sponsors will use email to notify Medsafe of OSIs. At a later date, sponsors would submit the appropriate CMN .

We have maintained the option for sponsors to notify Medsafe of OSIs through CMN submission, which can be used if applicable.

OSIs from recognised regulatory authorities

Several respondents provided feedback about the requirement to submit OSIs by recognised regulatory authorities and stated that additional clarification is needed.

One respondent noted circumstances where a request from a regulatory authority may not necessarily mean that the regulatory authority has confirmed the signal. The sponsor may refute the signal and the regulatory authority may accept this outcome. Further clarifications are needed.

Medsafe's response:

Sponsors must notify Medsafe of any product information safety-related changes required by a recognised regulatory authority, even if the sponsor does not agree with the changes.

Sponsors do not need to notify us of signal reviews requested by recognised regulatory authorities.

Question 18

For other safety issues that require data sheet updates, is the option to notify Medsafe via CMN submission (section 6.3.2) (revised Guideline 6.4.2) helpful to sponsors? If yes, is the 30-day framework acceptable?

All respondents (15) provided an answer to this question.

CMN submission timeframe for notification of OSIs

Several respondents commented that the timeframe of 30 days would not be feasible for CMN submission. To meet the timeframe of 30 days, an email notification would still be required in the first place, and then a CMN submitted at a later date.

One respondent queried if notification via CMN was mandatory for reporting of OSIs.

Respondents suggested that CMN submission should not be the sole method for safety issue reporting.

Some respondents suggested a timeframe of 3 or 6 months.

There was some positive feedback, in that this option would allow for reduced workload and limit duplication of sharing of information by both pharmacovigilance and regulatory personnel from sponsor companies.

Medsafe's response:

As mentioned above and outlined in the Guideline, sponsors must notify Medsafe OSIs by email or alternatively by CMN submission.

Sponsors are not required to submit CMNs within 30 days from completed safety investigations. CMN submission for notification of OSIs is not mandatory and only serves as an alternative means of notification where a CMN submission application is prepared and can be submitted within the 30-day timeframe.

We agree that using CMN submission for notifying us of OSIs that are related to data sheet updates would be helpful in reducing workload and duplication. Therefore, we have provided this as **an option** for sponsors.

In most cases, sponsors will likely notify us of OSIs by email within 30 days. If data sheet updates are planned, sponsors would submit a CMN at a later date.

Question 19

Does Appendix 1 'Summary flowchart for reporting of safety issues' align with section 6 of the Guideline? If yes, is it a useful summary for sponsors?

Y/N

- Yes, n = 12
- No, n = 3

Overall, the respondents found Appendix 1 to be helpful and a useful addition to the Guideline.

One respondent suggested splitting OSIs into internally assessed signals and requests by recognised regulatory authorities.

Medsafe's response:

We have updated the Appendix based on respondents' suggestions and other updates to the Guideline.

There are now two appendices, with significant safety issues (SSIs) separated from other safety issues (OSIs).

Question 20

Do you have any other comments or suggested changes for section 6 of the Guideline?

Y/N

- Yes, n = 6
- No, n = 9

There were 6 respondents who provided comments or suggested changes. These have been grouped into themes.

Some comments were repeated from previous questions, and these have not been discussed again.

Safety issue reporting

One respondent commented that section 6 gives the impression that CMN submission is replacing the standard safety issue reporting by email. They suggested that CMN submission should not completely replace standard safety reporting but can be submitted in addition to the safety notification if a data sheet update is needed.

Medsafe's response:

Medsafe's pharmacovigilance team is notified of safety issues by sponsors and also reviews CMNs for safety-related data sheet updates.

As discussed previously, using CMN submission to notify us of OSIs is **an option** for sponsors. In most cases, sponsors will likely notify us of OSIs by email within 30 days.

We believe that using CMN submission to notify us of OSIs, where possible, will help reduce workload and duplication for both sponsors and the regulator and help streamline and prioritise workflow.

CMN submission

A respondent suggested that Medsafe review the alternative supporting documents for CMN submission for safety-related data sheet changes.

Medsafe's response:

We consider the company core data sheet and a signal review assessment to be appropriate supporting documents for CMN submissions.

We acknowledge that, in some circumstances, sponsors may use alternative supporting documents. In such circumstances, we will review these alternative documents as part of the CMN evaluation.

Recognised regulatory authorities

One respondent asked for clarification of what is meant by 'recognised regulatory authorities'.

Medsafe's response:

We recognise the following regulatory authorities, as currently outlined in Medsafe's GRTPNZ – New Medicine Applications (January 2023)[6]:

- Australian Therapeutic Goods Administration (TGA)
- European Medicines Agency (EMA)
- Health Products and Food Branch of Health Canada
- Singapore Health Sciences Authority (HSA)
- UK Medicines and Healthcare products Regulatory Agency (MHRA)
- Swissmedic
- United States Food and Drug Administration (FDA).

This list may change depending on any updates to GRTPNZ – New Medicine Applications.

[6] Medsafe. 2023. *Guideline on the Regulation of Therapeutic Products in New Zealand – New Medicine Applications* January 2023. URL: https://www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/new-medicine-applications.pdf

6. Summary of responses – Section 7: Safety monitoring documents

Question 21

In section 7.1.1, is Table 5: 'Products requiring routine submission of PBRERs' (revised Guideline Table 6) easy to understand?

Please make any comments or suggestions.

Y/N

- Yes, n = 12
- No, n = 2
- Not answered, n =1

There were 5 respondents who provided comments or suggestions. One comment included 'yes' and is not further discussed.

Definitions

One respondent suggested referring to the Definitions section for marketed advanced therapy medicinal products.

One respondent suggested adding a definition for 'chemotherapy agents' to avoid confusion and/or misinterpretation.

Medsafe's response:

We have added a footnote to Table 5 (revised Guideline Table 6) to refer to the Definitions section of the Guideline for further information on the types of medicines listed in the table.

We have added a definition for chemotherapy agents to the Definitions section. For this Guideline, chemotherapy products are products with approved indications for use in cancer.

Periodic Benefit Risk Evaluation Reports (PBRER) submission timeframes

A respondent suggested having a consistent timeframe for products requiring PBRER submission for all product categories, noting differences between vaccine PBRER submission and some other products.

Another respondent proposed linking the timeframe for products requiring PBRER submission to the date of consent rather than based on market usage.

One respondent sought further clarification about the term 'in use'.

Medsafe's response:

Medsafe considers that it is important to review PBRERs of vaccines on the New Zealand National Immunisation Schedule. Therefore, a timeframe is not required as a vaccine may be on the schedule for an extended period of time.

We agree that the timeframe for products requiring routine PBRER submission should be based on the date of consent rather than market usage. We have amended the Guideline.

We have also clarified that PBRER submission is for innovator products only.

Question 22

Do you have any other comments or suggested changes for section 7 of the Guideline?

Y/N

- Yes, n = 3
- No, n = 11
- Not answered, n = 1

There were 3 respondents who provided comments or suggestions.

Duration of submission of PBRERs

Some respondents suggested that it would be helpful to specify a timeframe after which routine submission of a PBRER would no longer be required.

There was also a suggestion to align with PBRER submission with that of other regulators, such as the TGA.

Medsafe's response:

As currently outlined in the Guideline, we will advise sponsors when routine submission is no longer necessary. For clarity, we have added a new section to the revised Guideline (section 7.1.3) to reflect this.

Medsafe request for a PBRER

A respondent asked why Medsafe would request a PBRER for a product where routine submission is not required.

Medsafe's response:

We may request a PBRER for a product if closer monitoring of its safety is required, for example, in response to a signal review or health sector concern relating to a safety issue.

PBRER requirement on consent of medicines

There was a suggestion that Medsafe consider stating the PBRER requirement on the consent letter for the product.

Medsafe's response:

Medsafe has taken this comment into consideration.

Risk Management Plans (RMP)

For section 7.2, one respondent suggested that more guidance about RMPs would be helpful. Medsafe's expectations for distribution of RMP materials in New Zealand are unclear, especially if these exist in Australia.

Another respondent similarly asked if Medsafe had plans to update the RMP section to align with European Medicines Authority (EMA) or TGA requirements, and if Medsafe may issue separate guidance in the future.

Medsafe's response:

Currently, we do not require routine submission of RMPs unless specifically requested.

We do not require a New Zealand-specific annex for an RMP.

If sponsors are planning to distribute RMP materials in New Zealand, such as safety communications or educational resources, these should be made available to Medsafe for review before distribution.

7. Summary of responses – Section 8: Safety communications

Question 23

Does this section adequately explain the requirements for sponsors when publishing or distributing safety communications? Please make any comments or suggestions.

Y/N

- Yes, n = 14
- No, n = 1

There were 2 respondents who provided comments or suggestions.

Submission of education materials

One respondent asked how education materials should be sent to Medsafe (section 8.4).

Medsafe's response:

Sponsor education materials should be sent by email to medsafeadrquery@health.govt.nz.

We have updated section 8 to state that sponsors should send safety communications to Medsafe by email (medsafeadrquery@health.govt.nz).

Dear Healthcare Professional Letters

In section 8.2 'Dear Healthcare Professional letters', one respondent suggested aligning the common examples of changes that should be communicated in a DHCP letter with the EMA Guideline.

Medsafe's response:

We have updated section 8.2 for clarity to state that new information that significantly affects the risk-benefit balance of a medicine may require a letter to healthcare professionals.

Medsafe recommends that sponsors follow the guidance in the EMA's Safety Communications Guideline.[7]

Question 24

Do you have any other comments or suggested changes to section 8 of the Guideline? Please make any comments or suggestions.

Y/N

- Yes, n = 6
- No, n = 9

[7] European Medicines Agency. 2017. *Guideline on Good Pharmacovigilance Practices: Module XV – Safety Communications* (Rev 1) 9 October 2017. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

There were 4 respondents who provided comments or suggestions. One comment has been addressed in question 23 above.

Dear Healthcare Professional Letters

One respondent asked for further clarification about which safety issues require a DHCP letter to be prepared.

Medsafe's response:

We recommend that sponsors follow the guidance in the EMA's Safety Communications Guideline.[8]

We have updated section 8.2 to improve clarity about DHCP letters and our expectations of sponsors.

Editorial change

One respondent suggested adding 'Health New Zealand' next to Te Whatu Ora in section 8.2.

Medsafe's response:

We have added 'Health New Zealand' as suggested.

[8] European Medicines Agency. 2017. *Guideline on Good Pharmacovigilance Practices: Module XV – Safety Communications* (Rev 1) 9 October 2017. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

8. Summary of responses – Section 9: Best practice guidelines

Question 25

Are there any additional guidelines that should be added to this section? Please make any comments or suggestions.

Y/N

- Yes, n = 0
- No, n = 15

No respondents provided any comments or suggestions.

Question 26

Do you have any other comments or suggested changes to section 9 of the Guideline?

Y/N

- Yes, n = 0
- No, n = 15

No respondents provided any comments or suggestions.

9. Summary of responses – Other feedback and comments

Question 27

Do you have any other feedback or suggested changes for the Guideline?

There were 10 respondents who provided an answer to this question, of which, 4 included no other comments or suggestions. Other answers have been grouped into themes.

Comments that have previously been mentioned in responses to other questions are not discussed here.

Therapeutics Product Act 2023

Some respondents requested clarity relating to the repeal of the Therapeutic Products Act 2023 and whether the Medicines Act 1981 will be reviewed/amended.

Medsafe's response:

Sponsors can look for any updates about the Therapeutic Products Act 2023 on the Ministry of Health website.

Definition for Post-Authorisation Safety Study

One respondent suggested adding the definition for post-authorisation safety study.

Medsafe's response:

We have added post-authorisation safety study to the Definition section of the revised Guideline.

Understanding updates to the Guideline

A respondent suggested that it would be beneficial for Medsafe to provide a FAQs document with examples of reporting of safety issues and/or run a webinar about the updates to assist sponsors with implementation of the revised Guideline.

Medsafe's response:

We are happy to respond to queries and can discuss this suggestion with sponsors at the next industry meeting.

In addition, the proposed changes reviewed in the consultation are highlighted within the consultation documents, which are available on the consultation website.

Date of publication and transition period

Some respondents wanted further information about when the updated Guideline would become effective and if there will be a transition period to support sponsors in adjusting their internal processes.

Medsafe's response:

We have published the revised Guideline on the Regulation of Therapeutic Products in New Zealand: Pharmacovigilance (Edition 3.0). It will be effective from 1 July 2024, and must be used from this date.

However, sponsors may also use the revised Guideline from time of publication. The time between the publication date and implementation date acts as a transition period to support sponsors in adjusting to changes in the revised Guideline.

Other

We also received some additional comments on the proposed updates after the consultation closed. We have taken these comments into consideration.