



**MEDSAFE**

NEW ZEALAND MEDICINES  
AND MEDICAL DEVICES  
SAFETY AUTHORITY

A BUSINESS UNIT OF  
THE MINISTRY OF HEALTH

# Guideline on the Regulation of Therapeutic Products in New Zealand

**Part 8:**

**Pharmacovigilance**

**Edition 2.0**

**Month 201X**

# Contents

---

Section 1: Legislation .....	5
1.1 Legislation relating to pharmacovigilance .....	5
Section 2: Roles and Responsibilities.....	6
2.1 Introduction.....	6
2.2 Role of the Regulator.....	6
2.2.1 Statutory Benefit-Risk Review.....	7
2.3 Medicines Adverse Reactions Committee.....	7
2.4 Centre for Adverse Reactions Monitoring .....	8
2.5 Sponsors.....	8
2.5.1 Sponsors' obligations and responsibilities.....	8
2.5.2 Contact Person .....	9
2.5.3 Contractual agreements between sponsors, manufacturers, importers or distributors .....	9
2.5.3.1 Subcontracting pharmacovigilance functions .....	9
2.5.4 Emergency planning .....	9
2.6 Failure to comply with responsibilities and obligations.....	10
Section 3: Reporting .....	11
3.1 Introduction.....	11
3.2 What should be reported.....	12
3.2.1 Do NOT report: .....	12
3.2.2 Serious Adverse Event / Adverse Reaction .....	12
3.2.3 Non-serious adverse reactions .....	13
3.2.4 Spontaneous adverse reaction reports (Unsolicited reports) .....	13
3.2.5 Solicited reports.....	13
3.3 Reporting process .....	14
3.3.1 Collection of reports .....	14
3.3.2 Validation of reports .....	14
3.3.3 Follow-up of reports .....	15
3.4 Reporting timeframes for adverse reaction reports .....	15
3.5 Special situations .....	15
3.5.1 Consumer reports.....	15

3.5.2	Downgrading the severity of a case report.....	16
3.5.3	Adverse event following immunisation.....	16
3.5.4	Lack of efficacy.....	17
3.5.5	Misuse or abuse.....	17
3.5.6	Off-label use.....	17
3.5.7	Clinical trials.....	17
3.5.8	Post authorisation studies.....	18
3.5.9	Medication errors.....	18
3.5.10	Overdose or Occupational exposure.....	18
3.5.11	Medicines supplied under section 25 or section 29.....	18
3.5.12	Period after suspension or withdrawal of approval.....	18
3.5.13	Media reports.....	19
3.5.14	Reports from the scientific and medical literature.....	19
3.5.15	Suspected adverse reactions related to quality defect or falsified medicine.....	19
3.6	How to report to CARM.....	20
3.7	How to report to Medsafe.....	20
3.8	Suspected Medicine Adverse Reaction Search.....	20
Section 4:	Signal Management Process.....	22
4.1	Introduction.....	22
4.2	Signal management process.....	22
4.2.1	Signal detection.....	23
4.2.2	Signal validation.....	23
4.2.3	Signal analysis and prioritisation.....	23
4.2.4	Signal assessment.....	24
4.3	Outcomes of signal management process.....	24
4.4	Quality requirements.....	24
4.5	Early Warning System.....	25
4.6	Medicines Monitoring  .....	25
Section 5:	Significant Safety Issues.....	26
5.1	Introduction.....	26
5.2	What are significant safety issues.....	26
5.3	Timeframe for reporting significant safety issues.....	27
5.4	How to report.....	27
Section 6:	Submission of Safety Monitoring Documents.....	28

6.1	Introduction.....	28
6.2	Submission of PBRERs.....	28
6.2.1	Format of a PBRER .....	29
6.3	Risk Management Plans .....	29
Section 7:	Safety Communications .....	30
7.1	Introduction.....	30
7.2	Dear Healthcare Professional letter .....	30
7.3	Other safety communications.....	31
7.4	Other educational materials.....	31
Section 8:	Glossary.....	32

# Section 1: Legislation

---

## Section summary

*This section identifies the legislation and guidance documents to be read in conjunction with this part of the regulatory guidelines.*

## 1.1 Legislation relating to pharmacovigilance

The following legislation should be read in conjunction with this part of the guideline:

☞ [Medicines Act 1981 \(the Act\):](#)

<a href="#">Section 35</a>	Revocation and suspension of consents
<a href="#">Section 36</a>	Control of established medicines
<a href="#">Section 41</a>	Duty of importer or manufacturer to report untoward effects of medicines
<a href="#">Section 8</a>	Advisory and technical committees

The following New Zealand guidance documents may also be of interest:

☞ [Medicines New Zealand Inc. Code of Practice](#)

☞ [National Ethics Advisory Committee Ethical Guidelines for Health and Disability Research](#)

☞ [Pharmacy Council of New Zealand Code of Ethics](#)

☞ [Medical Council of New Zealand Good Medical Practice](#)

This guideline includes recommendations that are not currently underpinned by medicines legislation. These recommendations aim to provide guidance on best practice in terms of pharmacovigilance.

## Section 2: Roles and Responsibilities

---

### Section summary

*This section describes the role of the regulator and the responsibilities and obligations of the sponsor in establishing a risk based approach to the monitoring, reporting, and management of adverse reactions associated with the use of medicines.*

### 2.1 Introduction

New Zealand has an established pharmacovigilance system for collecting and evaluating information relevant to the benefits and risks of harm of approved medicines.

Before a new medicine is given consent to be distributed in New Zealand, the clinical benefits and risks of harm of the product are considered during the approval process. This information is usually obtained from clinical trials on limited numbers of patients and/or for a limited period of time. This means that at the time of approval, the evidence of safety is relatively limited. It is not until the medicine begins to be used widely that additional information may be gathered. Any new information that changes the balance of benefit and risk may affect the acceptability of the medicine. In addition, the evaluation of this balance may change over time as new information becomes available.

### 2.2 Role of the Regulator

It is one of Medsafe's responsibilities, as a part of the Ministry of Health, to continually monitor the benefits and risks of harm of approved medicines. Medsafe detects, investigates and takes action on safety issues arising from safety reports and other sources of information. One of the sources of new information is the reporting of adverse reactions.

Post-market reports of suspected adverse reactions to medicines are collected in New Zealand. This is contracted by the Ministry of Health to the Centre for Adverse Reactions Monitoring (CARM). Medsafe and CARM work together to identify safety concerns from these reports. After evaluation of the information on a safety issue, Medsafe will make a decision on the most appropriate regulatory action to take. Actions include:

- no action to be taken at the present time
- continued monitoring of the situation
- a request for additional information or studies from the sponsor to gain further evidence on the issue
- an instruction to sponsors to communicate to healthcare professionals (for example a Dear Healthcare Professional letter)
- a change to the product information

- ⌚ suspension of the distribution of the medicine while investigations are ongoing
- ⌚ advice to the Minister of Health to revoke consent for the medicine to be distributed.

### 2.2.1 Statutory Benefit-Risk Review

Section 36 of the Medicines Act 1981 makes provision for a review of the safety or efficacy of a medicine. This section of the Act allows the Director-General of Health to require the sponsor to provide evidence to support the safety or efficacy of the product. Outcomes of such a review may include imposing conditions on the supply of the medicine or prohibiting the supply of the medicine.

Sponsors will be informed in writing if such a review is to be conducted and will be requested to provide evidence to support the efficacy or safety of their product(s). Sponsors have 60 days to respond before any action is taken. An extension of this time period may be allowed if sponsors can provide adequate justification.

Sponsors requiring more information in the event of such a review should contact Medsafe.

### 2.3 Medicines Adverse Reactions Committee

The Medicines Adverse Reactions Committee (MARC) is a technical advisory committee established under section 8 of the Medicines Act 1981 to advise the Minister of Health on the safety of approved medicines. The MARC provides expert advice on medicines' safety issues referred by Medsafe. Based on review of these safety issues, the MARC may make recommendations to manage any risk of harm associated with the medicine and improve the risk-benefit profiles of medicines.

The Chair and other members of the Committee are drawn from experts in various fields of clinical medicine, clinical pharmacology, pharmacy, pharmacovigilance, epidemiology and other medical specialities such as cardiology, biostatistics, and medicines regulation. The Committee also holds a position for a lay person (non-healthcare professional) to represent consumer interests.

Members are appointed for a three year term, which may be renewed once for a further three years.

The MARC meets four times a year. Secretarial support is provided by Medsafe. Minutes of the meetings are published on the Medsafe website ([www.medsafe.govt.nz/profs/MARC/Minutes.asp](http://www.medsafe.govt.nz/profs/MARC/Minutes.asp)).

Further information about the MARC is available on the Medsafe website ([medsafe.govt.nz/committees/marc.asp](http://medsafe.govt.nz/committees/marc.asp)).

## 2.4 Centre for Adverse Reactions Monitoring

The Centre for Adverse Reactions Monitoring (CARM) is contracted by the Ministry of Health to collect, collate and analyse adverse medicine reaction reports for Medsafe. Each report submitted to CARM is evaluated by a medical assessor who determines the extent of the association between the adverse reaction(s) described and the medicine(s) involved.

CARM uses the World Health Organization (WHO) causality assessment criteria for this evaluation. Routine summary reports of adverse reactions and any individual report or clusters of reports that highlight an issue of concern are provided to Medsafe and the MARC. CARM provides the MARC with a quarterly review of adverse reactions reported in New Zealand.

CARM also collaborates with the WHO International Drug Monitoring Programme based in Uppsala, Sweden.

CARM can be contacted at:

Post           Freepost 112002  
                  The Medical Assessor  
                  CARM  
                  PO Box 913  
                  Dunedin

Fax             + 64 (03) 479 7150

Telephone    + 64 (03) 479 7247

Email         [carmnz@otago.ac.nz](mailto:carmnz@otago.ac.nz)

Further information about CARM is available on CARM's website ([www.otago.ac.nz/carm](http://www.otago.ac.nz/carm)).

## 2.5 Sponsors

Medicine importers and manufacturers (referred to as “sponsors”) are expected to collect and review new information on their medicines. Sponsors must inform Medsafe as soon as possible when this new information impacts on the balance of benefits and risks of harm of their medicines.

### 2.5.1 Sponsors' obligations and responsibilities

Under section 41 of the Medicines Act 1981, sponsors have a statutory obligation to report any substantial untoward effects of their medicines, including safety concerns, to the Director-General of Health.

In order to meet this obligation, sponsors should continuously monitor the safety of their medicines and inform Medsafe of any changes to the safety profile that might have an impact on the balance of benefits and risks of harm. Sponsors should notify Medsafe of any emerging safety issue within 72 hours.

Any request from Medsafe for the provision of additional information regarding safety concerns must be answered fully by the sponsor within the requested timeframe.

When establishing their pharmacovigilance monitoring and reporting systems, sponsors should follow the guidance in ICH guideline *E2E – Pharmacovigilance Planning* ([www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E2E/Step4/E2E\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf)).

## **2.5.2 Contact Person**

Medsafe strongly recommends that sponsors nominate a contact person for dealing with pharmacovigilance matters and reporting to Medsafe.

This contact person should preferably be located in New Zealand or at least be contactable during normal New Zealand business hours. The pharmacovigilance contact person should have access to the expertise of a medically qualified person when necessary.

## **2.5.3 Contractual agreements between sponsors, manufacturers, importers or distributors**

Where two or more companies have an arrangement to market the same medicine (eg, under their separate company's brand names), each company is responsible for ensuring that they meet their regulatory pharmacovigilance obligations. Sponsors may, however, make contractual arrangements with each other and/or the manufacturer or importer regarding who will be responsible for the regulatory reporting of safety matters and the monitoring of the literature and reports.

Sponsors should take steps to ensure that duplication of reporting of the same case report does not occur.

### **2.5.3.1 Subcontracting pharmacovigilance functions**

Sponsors may elect to subcontract out their pharmacovigilance responsibilities to specialised pharmacovigilance organisations. When subcontracting tasks to another provider, the sponsor should draw up sub-contracts that are sufficiently detailed, up-to-date, and which clearly specify the contractual arrangements between the sponsor and the provider. These should describe the arrangements for delegation, delegated tasks, related interactions and data exchange, timelines and the responsibilities of each party.

The sponsor retains responsibility for ensuring that an effective pharmacovigilance system is in place.

## **2.5.4 Emergency planning**

Sponsors are expected to have in place plans for dealing with critical incidents. These may include situations such as recalls, or new urgent safety information that may alter the benefit-risk balance of their medicines.

## **2.6 Failure to comply with responsibilities and obligations**

Sponsors should be aware that refusal or failure to meet their responsibilities may result in suspension or withdrawal of consent to distribute the medicine under section 35 of the Act. Alternatively conditions may be imposed on the sale or supply of the medicine under section 36 of the Act.

## Section 3: Reporting

---

### Section summary

*This section outlines sponsor responsibilities for reporting suspected adverse reactions to medicines.*

### 3.1 Introduction

The reporting of suspected adverse events or adverse reactions to medicines is fundamental to pharmacovigilance. Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any medicine-related problem.

An adverse drug reaction is a noxious and unintended response to a medicine. In accordance with the ICH E2A guideline, the definition of an adverse reaction implies at least a reasonable plausibility of a causal relationship between a medicine and an adverse event.

This includes adverse reactions which arise from:

- ☞ the approved use of a medicine
- ☞ the unapproved use of a medicine, (eg, in overdose or off-label use)
- ☞ medication error
- ☞ occupational exposure.

For the purposes of reporting adverse reactions in New Zealand, if an event is spontaneously reported, it meets the definition of an adverse event, even if the relationship is unknown or unstated.

Therefore, all spontaneous reports notified by healthcare professionals or consumers are considered to be suspected adverse reactions, unless the reporter specifically states that the events are unrelated or that a causal relationship can be excluded. This interpretation is in accordance with the ICH E2D guideline – *Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*.  
([http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E2E/Step4/E2E\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf))

Sponsors must report all serious spontaneous reports of suspected adverse reactions even if they disagree with the reporter(s) assessment of causality.

## 3.2 What should be reported

Sponsors are expected to report valid case reports to CARM.

- ☞ All reports of serious expected and/or serious unexpected adverse reactions associated with:
  - approved medicines
  - approved medicines in a blinded study, after the identity of the suspected medicine has been determined.
- ☞ All serious expected and/or serious unexpected reports of adverse reactions associated with reports from solicited sources, where an assessment of causality conducted by the sponsor, the investigator or the reporter indicates a positive correlation.

Sponsors are not required to report non-serious adverse reactions. However, sponsors should be able to provide these reports on request from Medsafe, and include these in Periodic Benefit Review Evaluation Reports (PBRERs).

### 3.2.1 Do NOT report:

- ☞ cases occurring outside New Zealand
- ☞ clinical trial cases for unapproved medicines – the reporting requirements for these cases are specified in [Part 11 of the Guideline for Therapeutic Products in New Zealand: Clinical trials – regulatory approval and good clinical practice requirements](#)
- ☞ blinded clinical trial cases for approved medicines when the identity of the suspected medicine or the patient has not been identified
- ☞ non-serious reports
- ☞ solicited reports not considered to have a causal relationship
- ☞ reports that supply of a medicine to a patient has been terminated, or is no longer required by the patient.

### 3.2.2 Serious Adverse Event / Adverse Reaction

A serious adverse event or adverse reaction is defined in ICH guideline E2D as any untoward medical occurrence that at any dose:

- ☞ results in death
- ☞ is life-threatening
- ☞ requires in-patient hospitalisation or results in prolongation of existing hospitalisation
- ☞ results in persistent or significant disability or incapacity
- ☞ is a congenital anomaly or birth defect
- ☞ is a medically important event or reaction.

An important medical event (or IME) is considered to be one where intervention of some form is required to prevent a life-threatening situation or death, or where non-intervention is

likely to lead to disability, incapacitation, hospitalisation, serious morbidity or birth defect or congenital anomaly.

Medsafe recommends that sponsors follow the European guidance on important medical events ([www.eudravigilance.ema.europa.eu/human/textforIME.asp](http://www.eudravigilance.ema.europa.eu/human/textforIME.asp)).

### 3.2.3 Non-serious adverse reactions

All adverse reactions that do not meet the above definition of a serious adverse reaction are considered to be non-serious adverse reactions. These should not be routinely reported, whether the reactions were expected or not, and whether the report was an unsolicited or a solicited report. The sponsor should record these reports in their database and use them for signal detection and evaluation activities. These should be included in the PBRER, if one is required.

### 3.2.4 Spontaneous adverse reaction reports (Unsolicited reports)

A spontaneous report is an unsolicited communication that describes one or more suspected adverse reactions. Spontaneous reports may be submitted by:

- ☞ 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).

Spontaneous reporting of adverse events or reactions is usually initiated by a suspicion that observed signs and symptoms could have been caused by a medicine.

Unsolicited consumer reports should be treated as spontaneous reports irrespective of any subsequent medical confirmation.

Stimulated reporting, such as following media coverage of an incident or the issuing of a Dear Healthcare Professional communication, are considered to be spontaneous reports.

### 3.2.5 Solicited reports

Adverse events reports that are actively sought from studies or organised data collection systems are not spontaneous reports. These are solicited reports. Examples of solicited sources include patient support and disease management programmes, and surveys of patients or healthcare providers. Valid reports of serious adverse reactions, where a positive causal association to a suspected medicine has been assessed, should be reported to CARM.

## 3.3 Reporting process

### 3.3.1 Collection of reports

Sponsors should take appropriate measures to collect and collate all reports of suspected adverse reactions associated with their medicines originating from unsolicited and solicited sources. For this purpose, sponsors should establish a pharmacovigilance system that will allow the acquisition of sufficient information for the evaluation of these reports.

Where the sponsor is aware that the suspected adverse reaction may also have been reported to another body (eg, a district health board or the National Poisons Centre), the report should still be considered to be a valid Individual Case Safety Report (ICSR) and should be forwarded to CARM. Where possible the name of the agency should be mentioned to facilitate the identification of potential duplicate reporting.

### 3.3.2 Validation of reports

An ICSR refers to the format and content of one or more suspected adverse reactions in relation to a medicine that occur in a single patient/consumer at a specific point in time. Only valid ICSRs should be reported.

Sponsors should attempt to follow up cases where necessary to obtain information that meets the minimum criteria for reporting. A valid report contains:

- ☞ an identifiable reporter (or reporters) characterised by qualification, for example:
  - physician, consumer etc
  - name
  - initials
  - address.

Whenever possible, contact details should be recorded so that follow-up activities can be performed.

- ☞ one single identifiable patient characterised by one or more of the following:
  - initials
  - patient identification number
  - date of birth
  - age or age group or gender.
- ☞ one or more suspected medicine(s)
- ☞ one or more suspected reaction(s).

The lack of any of these four items invalidates the case and it should not be reported. However, invalid cases should be recorded in the sponsor's pharmacovigilance system for use in product safety evaluation activities.

### 3.3.3 Follow-up of reports

The information in suspected adverse reaction reports may be incomplete on first receipt. Incomplete reports should be followed up as necessary. Follow-up of incomplete reports is particularly important for prospective reports of exposure during pregnancy, reports of death and reports of new safety concerns. For example, if “death/sudden death” is the only detail contained in the report and no causal association to a suspected medicine(s) has been attributed by the reporter, the report should not be reported to CARM until further detail is available which informs suspicion that the death might be due to the suspected medicine(s).

If incomplete information is received directly from a consumer, sponsors should make attempts to contact the consumer directly or obtain consent to contact a nominated healthcare professional for further 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. Sponsors must clearly identify the additional information being forwarded.

## 3.4 Reporting timeframes for adverse reaction reports

Serious expected and serious unexpected adverse valid ICSRs should be submitted to CARM within 15 calendar days from receipt of the information. 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.

Where a report was originally classified as ‘non-serious’ and later information, such as review by a healthcare professional indicates that the case should be reclassified as ‘serious’, the information must be reported within the reporting timeframe for serious adverse reactions. Day zero is then considered to be the date the additional information was received.

## 3.5 Special situations

The following provides guidance on how sponsors should respond in specific situations.

### 3.5.1 Consumer reports

Where sponsors of medicines receive adverse reaction reports or complaints directly from consumers, they should be guided by the following:

- ☞ Unsolicited reports received directly from consumers should be regarded as spontaneous reports and those meeting the “serious” criteria should be forwarded to CARM.

- ☞ Consumers should be encouraged to report adverse reactions directly to CARM.
- ☞ Consumers should also be encouraged to discuss adverse reaction(s) with their healthcare professional.
- ☞ Sponsors should make every attempt to obtain sufficient information to ascertain the nature and seriousness of the reaction.
- ☞ Sponsors should seek and document permission from consumers to allow contact with their primary healthcare professional to obtain additional relevant medical information.
- ☞ If permission to seek further information is denied or explicitly withheld, the sponsor must indicate on the reporting form that it is a consumer report and that the name and contact details have been withheld at the request of the reporter.
- ☞ Sponsors must document all consumer adverse reaction reports and take these into account when overall safety assessments are made.
- ☞ Additional follow-up may not be necessary for an apparently non-serious adverse reaction.

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.

### 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.

### 3.5.3 Adverse event following immunisation

The WHO defines an adverse event following immunisation (AEFI) as any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine.

Any AEFI has the potential to undermine confidence in a vaccine and ultimately has dramatic consequences for immunisation coverage and disease incidence, if it is not dealt with rapidly and effectively.

AEFIs judged to be serious should be reported to CARM within the standard timeframe for reporting serious adverse reactions to medicines.

Clusters of non-serious AEFIs may indicate a significant safety issue and should be reported to Medsafe as specified in Section 5.

### 3.5.4 Lack of efficacy

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.

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

### 3.5.5 Misuse or abuse

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).

If adverse reactions are associated with valid ICSRs of misuse or abuse, they should be forwarded to CARM.

### 3.5.6 Off-label use

Off-label use is defined as the use of an approved medicine under the direction or supervision of a healthcare professional for any of the following:

- ☞ An unapproved indication.
- ☞ An unapproved age group.
- ☞ Unapproved dosage.
- ☞ Unapproved route or form of administration.

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).

### 3.5.7 Clinical trials

Suspected adverse reactions occurring in clinical trials investigating new medicines should be reported as detailed in the Guidelines on the Regulation of Therapeutic Products in New Zealand Part 11: *Clinical trials – regulatory approval and good clinical practice requirements*.

### **3.5.8 Post authorisation studies**

Sponsors should report valid ICSRs of adverse reactions which are suspected by the principal investigator to be related to an approved medicine used in the study.

### **3.5.9 Medication errors**

A medication error is defined as “any unintentional error in the use of a medicine or vaccine”. This includes under-dosing as well as overdose, and the erroneous administration of any medicine other than the intended medicine at the intended dose and frequency.

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

Reports of medication error, whether associated with a suspected adverse reaction or not, are also encouraged to be reported to the Medication Error Reporting Programme (MERP).

MERP collects and analyses voluntary reports of potential and actual medication errors with the aim of enhancing the safety of medication use. This is achieved by analysing for patterns, trends and issues, and sharing the information about medication errors to reduce and prevent harmful errors and inform quality and safety initiatives nationwide.

MERP can be accessed at: [www.nzphvc.otago.ac.nz/merp/report/](http://www.nzphvc.otago.ac.nz/merp/report/)

### **3.5.10 Overdose or Occupational exposure**

Reports of overdose or occupational exposure with associated adverse outcomes should be reported to CARM provided they are valid unsolicited reports. These should be routinely followed up to ensure that the information is as complete as possible with respect to symptoms, treatment and outcome.

Reports of overdose with no associated adverse outcome should not be reported as adverse reactions. Reports of overdose associated with a medication error should be reported to MERP.

Reports of occupational exposure with no adverse reaction should not be reported but should be considered in PBRERs.

### **3.5.11 Medicines supplied under section 25 or section 29**

Supply of medicines under the exemption provisions in sections 25 or 29 of the Act is considered to be similar to named patient use in other countries. Valid ICSRs detailing serious unexpected suspected adverse reactions to these medicines should be reported.

### **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.

### **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).

### **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.

If multiple medicines are mentioned in the publication, only those that are identified by the author(s) as having at least a causal relationship with the suspected adverse reaction should be considered by the sponsor.

One case should be created for each single identifiable patient, subject to the criteria for a valid report (see Section 3.3.2). Relevant medical information should be provided and the publication author(s) should be considered to be the primary source(s).

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.

### **3.5.15 Suspected adverse reactions related to quality defect or falsified medicine**

A report of adverse reactions associated with suspected or confirmed quality defects including adulteration or contamination, or falsified medicine (such as counterfeit or tampering) constitutes a significant safety issue.

When such a report is received by the sponsor, it must be reported to Medsafe as soon as possible. This is generally within 72 hours of receipt of the information by the sponsor.

Suspected adverse reactions related to quality defects or falsified medicine should not be reported to CARM.

### 3.6 How to report to CARM

Valid ICSRs should be reported using the Council for International Organizations of Medical Sciences (CIOMS) reporting form. The CIOMS reporting form can be downloaded from [www.cioms.ch/index.php/cioms-form-i](http://www.cioms.ch/index.php/cioms-form-i)

Reports should be sent to:

Post	Freepost 112002 The Medical Assessor CARM PO Box 913 Dunedin
Fax	+ 64 (03) 479 7150
Telephone	+ 64 (03) 479 7247
Email	<a href="mailto:carmnz@otago.ac.nz">carmnz@otago.ac.nz</a>
Online	<a href="http://www.otago.ac.nz/carm">www.otago.ac.nz/carm</a>

CARM's preference is for reporting online or by email.

### 3.7 How to report to Medsafe

Reports of adverse reactions associated with quality defects or falsified medicines should be sent to:

Post	Product Safety Team Medsafe PO Box 5013 Wellington 6415
Fax	+ 64 (04) 819 6807
Telephone	+ 64 (04) 819 6800
Email	<a href="mailto:recalls@moh.govt.nz">recalls@moh.govt.nz</a>

Medsafe's preference is for reporting by email, with as much information provided as possible.

### 3.8 Suspected Medicine Adverse Reaction Search

Sponsors can access information on suspected adverse reaction reports in New Zealand through the Suspected Medicine Adverse Reaction Search (SMARS) database on

Medsafe's website. SMARS contains anonymised information from reports of suspected adverse reactions to medicines that were reported to CARM.

SMARS includes reports considered by CARM to be causally related to the medicine. SMARS includes reports received from sponsors. Some non-causally related suspected adverse reactions may be included in SMARS if the report also contained a causally related suspected adverse reaction.

SMARS does not include:

- any report where it is considered that the patient may be identifiable (eg, due to the rareness of the reaction)
- reports from the last three months.

The SMARS database is updated once a month.

Where case reports on SMARS are identified by sponsors, these should not be re-reported to CARM as individual adverse reactions. However, if upon further analysis of these reports the sponsor believes that the benefit-risk of harm balance of the medicine may possibly be affected, this possibility should be communicated to Medsafe as a potential significant safety issue (see Section 5).

SMARS can be accessed at: [www.medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp](http://www.medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp)

If more information on using SMARS is required, please contact:

Post            Clinical Risk Management Branch  
                  Medsafe  
                  PO Box 5013  
                  Wellington 6415

Telephone    + 64 (04) 819 6800

Email           [Medsafeadrquery@moh.govt.nz](mailto:Medsafeadrquery@moh.govt.nz)

## Section 4: Signal Management Process

### Section summary

*This section provides guidance on how sponsors should monitor the safety of their medicines in order to comply with the requirements of section 41 of the Act.*

### 4.1 Introduction

A “signal” is defined as new information on a possible risk of harm due to treatment with a medicine. This information may suggest a new risk or a new aspect of an already identified risk.

The sources for identifying new signals are diverse and include all scientific information concerning the use of the medicine, including quality (eg, manufacturing data), non-clinical and clinical data, pharmacovigilance and pharmacoepidemiological data.

Once a signal has been identified, investigations are necessary to refute or confirm the signal and quantify the risk. These investigations consider the likelihood that the medicine caused or contributed to the effect and try to identify risk factors and estimate the frequency of occurrence.

In order to identify new safety issues, Medsafe encourages sponsors to put in place a signal management process for each medicine they distribute. Medsafe recommends that sponsors follow the guidance in the EMA document EMA/827661/2011, *Module IX – Signal Management*

([www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129138.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf)).

### 4.2 Signal management process

The signal management process is a set of activities performed to identify whether the risks known about a medicine have changed. These activities include but are not limited to:

- ☞ examination of individual case safety reports (ICSRs)
- ☞ review of aggregated data from active surveillance systems or studies
- ☞ review of literature information
- ☞ clinical studies
- ☞ pre-clinical studies.

The process includes all steps from initial signal detection through validation and confirmation, analysis and prioritisation, signal assessment, recommending action, communication, and reviewing the result of any action taken.

Some flexibility in the sequence of these steps may be required. For example, when a signal is detected from the results of a study, it may not be possible or practical to assess each individual case study report and validation may require collection of additional data.

#### **4.2.1 Signal detection**

Sponsors should note that the detection of signals is a multidisciplinary approach. As a general principle, signal detection should follow a recognised methodology. This may vary depending on the type of medicine. The detection method should be appropriate for the data set. Data from all appropriate sources should be considered. Systems should be present to ensure the quality of the detection activity and the data should be reviewed in a timely manner. The whole process should be adequately documented including the rationale for the method and periodicity of the signal detection activity.

#### **4.2.2 Signal validation**

Signal validation is the process of evaluating the detected signal to determine potential causality and justification for further analysis.

This process takes into account the clinical relevance of the signal (such as its plausible mechanism), the seriousness and severity of the reaction and its outcome, as well as the novelty of the reaction. Other factors such as medicine interactions, occurrence in various populations and previous awareness of a signal should also be considered.

Sponsors should be mindful that where the signal is not able to be validated, further monitoring may gather additional data to enable a subsequent analysis to be made. Therefore, tracking systems should be employed to capture the outcome of the validation of signals. These systems should include the reasons why signals were not validated, information that would facilitate further retrieval of ICSRs and validation of signals.

#### **4.2.3 Signal analysis and prioritisation**

A key principle of any signal management process is to ensure valid signals with important public health implications are prioritised for management, together with a timeframe for action.

A prioritisation process should assess the strength and consistency of the evidence (ie, plausibility), potential impact on patients, consequences of treatment discontinuation, clinical context of the suspected adverse reaction (eg, whether the association suggest a clinical syndrome that may include other reactions), public health impact, increased frequency or severity of a known adverse reaction and stage of the product life cycle.

Priority may also be considered for medicines that may have high media or stakeholder interest.

#### 4.2.4 Signal assessment

Signal assessment is performed to further evaluate a validated signal and to determine if there is a need for additional data collection or for any regulatory action.

An assessment should be as complete as possible and should include all available information from pharmacological, non-clinical and clinical data, and other sources. Information could include sources such as the application dossier, literature articles, spontaneous reports, expert consultation and information held by sponsors or the regulator. The search for information to assess the significance of a signal may also need to be extended to other products of the class and to other adverse reactions (ie, a broader level assessment).

Sponsors are reminded that if their assessment at any stage supports the conclusion that a potential risk is present, they should take the appropriate action to prevent or minimise the risk in a timely manner.

#### 4.3 Outcomes of signal management process

Following the signal management process, a recommendation may be made for an appropriate course of action such as:

- no further action considered to be necessary
- a periodic review of the signal
- requesting additional information to confirm plausible links
- post-market safety studies
- update of product safety information
- immediate measures (temporary or otherwise) including voluntary suspension of distribution by the sponsor, or the possibility of imposed suspension or withdrawal of consent.

An appropriate timeframe should be proposed for the initiation or completion of the action, including requirements for the provision of progress reports and interim results.

#### 4.4 Quality requirements

Sponsors are encouraged to build quality system requirements into their signal management processes. This allows clear descriptions of the tasks required, the roles, responsibilities and expertise of personnel, enables system improvement, and facilitates the recording, tracking, and documentation of all validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting and all other key steps.

## 4.5 Early Warning System

Medsafe and the Therapeutic Goods Administration of Australia (TGA) have developed a system to ensure that concerns with particular medicines are able to be communicated to users and prescribers shortly after they have been identified. These potential concerns have been identified through Medsafe's and the TGA's signal management processes. Some of the safety concerns may not have been fully investigated and therefore may not result in any further action. These are communicated through monitoring communications. In other instances, Medsafe may issue an alert communication once a completed review of the safety concern has been completed and a causal link is indicated.

Medsafe will contact the sponsor prior to publication on the Early Warning System. This may initially be for additional information to help investigate the signal. Sponsors will be provided with a copy of the text intended for publication to review for factual accuracy prior to actual publication.

## 4.6 Medicines Monitoring

The medicines monitoring  scheme highlights safety concerns generally identified from reports of suspected medicine adverse reactions sent to the Centre for Adverse Reactions Monitoring (CARM). The aim is to seek more information on these safety concerns.

Sponsors should note these safety concerns, and that no action is currently required on their part.

## Section 5: Significant Safety Issues

---

### Section summary

*This section provides guidance on what constitutes significant safety issues which may need to be reported to Medsafe under section 41 of the Act.*

### 5.1 Introduction

It is a statutory requirement that sponsors must report any untoward effects for any medicine for which they are the sponsor and indicate what action they are proposing to take on these issues. Medsafe interprets “untoward effects” as including any significant safety issues or concerns that sponsors are aware of that may affect the balance of benefits and risks of harm of the medicine.

### 5.2 What are significant safety issues

From a pharmacovigilance perspective, significant safety issues generally include but are not limited to:

- 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
- investigations of safety issues or concerns of the medicine in another country by that country’s medicines regulator (eg, European Union (EU) referral procedures for safety reasons)
- withdrawal or suspension of availability of the medicine in another country
- issues identified by the sponsor as a result of the sponsor’s own signal management process (see Section 4) once assessment has been completed and actions are proposed
- significant safety results from post-marketing clinical studies
- safety issues due to misinformation in the product information
- safety issues related to use outside the terms of the product information or directions for use
- safety issues in relation to any raw materials used in the medicine
- issues for which the sponsor is considering sending a “Dear Healthcare Professional” (or DHCP) letter in any country where the medicine is being marketed.

### 5.3 Timeframe for reporting significant safety issues

Sponsors must report any identified significant safety issue to Medsafe as soon as possible. This is generally within 72 hours of awareness of the issue by the sponsor (eg, from the time a sponsor concludes after review of data that a significant safety issue exists).

Sponsors should provide as much information as possible when reporting to Medsafe.

Sponsors must provide any additional information to assist with the evaluation of the impact of the safety issue on the benefits and risks of the medicine, when requested by Medsafe.

### 5.4 How to report

Significant safety issues should be reported to Medsafe:

Post            Clinical Risk Management Branch  
                  Medsafe  
                  PO Box 5013  
                  Wellington 6415

Fax             + 64 (04) 819 6806

Telephone    + 64 (04) 819 6800

Email          [medsafeadrquery@moh.govt.nz](mailto:medsafeadrquery@moh.govt.nz)

Medsafe's preference is for reporting via email.

Do NOT report significant safety issues identified with a medicine to CARM.

## Section 6: Submission of Safety Monitoring Documents

---

### Section summary

*This section provides information on Medsafe's routine safety reporting requirements for providing Periodic Benefit Risk Evaluation Report (PBRERs) and Risk Management Plans (RMPs).*

### 6.1 Introduction

A Periodic Benefit Risk Evaluation Report (PBRER) is a comprehensive, concise, and critical analysis of new or emerging information on the risks and benefits of a medicine compiled by the sponsor. The PBRER replaces the PSUR (Periodic Safety Update Report).

These ongoing appraisals aid both the sponsor and the regulator in maintaining confidence in the benefit-risk balance of the medicine based on the regulatory options currently imposed (such as approved indications, warnings, labelling) and those yet available (eg, limiting the indications, expanding warnings and precautions, creating contraindications, rescheduling, relabelling or restricting use to a subset of the population).

Medsafe recommends that sponsors follow the guidance in relation to PBRERs found in the ICH guideline *ICH E2C (R2)* ([www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E2C/E2C\\_R2\\_S tep4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_S tep4.pdf)).

### 6.2 Submission of PBRERs

Medsafe does not require routine submission of PBRERs for most medicines. The types of medicines for which PBRERs should routinely be submitted are:

- ☞ all biologicals
- ☞ all biosimilars
- ☞ all vaccines that are included in the immunisation programme.

In addition PBRERs should also be routinely submitted where a specific requirement for the submission of PBRERs has been imposed as a condition of approval. However, it is acceptable for sponsors to submit PBRERs routinely for their medicines if they wish to do so.

Medsafe may occasionally request the submission of a PBRER for a specific medicine if closer monitoring of its safety is required.

Medsafe will advise the sponsor when submission is no longer necessary.

### 6.2.1 Format of a PBRER

PBRERs should be prepared according to ICH guideline *ICH E2C (R2)*. A PBRER that has already been prepared for submission in Europe is acceptable. The period covered by the PBRER should remain in line with EU requirements.

## 6.3 Risk Management Plans

Medsafe does not require routine submission of Risk Management Plans (RMPs). However, Medsafe may request these for specific medicines during the evaluation of a new medicine application as a condition of approval or in response to a safety issue. It is acceptable for sponsors to submit RMPs outside of these circumstances if they wish to do so.

## Section 7: Safety Communications

---

### Section summary

*This section provides guidance on communications about safety issues to the health sector and consumers.*

### 7.1 Introduction

High levels of public interest are anticipated when new safety concerns arise. High quality safety communication can support public confidence in the regulatory system by providing timely, evidence-based information.

Safety communication should deliver relevant, clear, accurate and consistent messages using the appropriate level of language for the audience. Sponsors should keep in mind these principles:

- ☞ transparency and openness
- ☞ nature of the message and the target audience
- ☞ information on risks in context to benefits
- ☞ appropriate quantitative measures for risk comparisons
- ☞ recommendations on managing risks
- ☞ using a range of different and appropriate means of communication.

### 7.2 Dear Healthcare Professional letter

Information that impacts a change in the severity or incidence of adverse reactions in the general population or a specific section of the population may necessitate a letter to healthcare professionals and relevant organisations (eg, district health boards, pharmaceutical wholesalers, pharmacies, professional societies) in order to advise them of the overall impact on safety. Common examples of changes that have to be communicated are the imposition of new warnings, precautions, contraindications, a limitation of indications, or restriction on use.

Medsafe recommends that sponsors follow the guidance in the *European Guideline on good pharmacovigilance practice (GVP) Module XV – Safety Communication* ([www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/01/WC500137666.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137666.pdf)).

Dear Healthcare Professional (DHCP) letters should follow the EU template.

Drafts of DHCP letters should be provided to Medsafe for review and the final wording agreed prior to distribution, to ensure that the safety issue has been appropriately covered and managed.

DHCP letters may be published on the Medsafe website with the sponsor's agreement.

### **7.3 Other safety communications**

Sponsors may choose to place risk minimisation and safety communications about their medicines in bulletins and newsletters, company websites or using internet-based communications (eg, Twitter®, Facebook®) or mobile phone apps.

Medsafe recommends that before doing so, sponsors should consider involving consumers and healthcare professionals in preparing and field-testing their communications in order to ensure that the scientific evidence supporting the safety messages are easily and clearly understood by the target audience(s).

### **7.4 Other educational materials**

It is desirable that any communications materials (eg, publications, brochures, flyers) on matters relating to medicines safety should be made available to Medsafe prior to distribution.

## Section 8: Glossary

---

Adverse effect	An <b>adverse effect</b> , or <b>adverse event</b> (AE), is taken to mean any untoward medical occurrence in a patient administered a medicine, and which may or may not have a causal relationship between the event and the treatment. Examples are the patient being involved in an accident, or catching a cold while on the treatment. However, many reports of similar adverse events occurring may provide a signal regarding causality.
Adverse event	Alternative term for <b>Adverse effect</b> .
Adverse drug reaction	The term <b>adverse drug reaction</b> (ADR) is used to describe an unwanted, unintended, or unexpected effect to a medicine that has been taken. This term is synonymous with <b>adverse medicine reaction</b> and <b>adverse reaction</b> (AR).  Some adverse reactions may involve a known reaction, or an unexpected scale of effect to a known reaction. Other types of reactions may have been unforeseen, based on the medicine's known pharmacology. The onset of reactions may be sudden, or develop over a period of time, or after completion of treatment (such as withdrawal symptoms).
CARM	The Centre for Adverse Reactions Monitoring, based at the New Zealand Pharmacovigilance Centre at the University of Otago in Dunedin.
Case report	Alternative term for Individual Case Safety Report (ICSR).
Causality	The relationship between cause and effect.
CIOMS	Council for International Organizations of Medical Sciences. CIOMS is an international, non-governmental, non-profit organisation established jointly by WHO and UNESCO.  See: <a href="http://www.cioms.ch/">www.cioms.ch/</a>
EMA	The European Medicine Agency. The EMA is responsible for the scientific evaluation of applications for marketing medicines in the European Union (EU).
EU	European Union. An economic and political partnership between 28 European countries.
ICH	International Conference on Harmonisation. The ICH is an international approach towards making recommendations for achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.
ICSR	Individual Case Study Report is an adverse event report for an

	individual patient.
MARC	Medicines Adverse Reactions Committee.
Medication error	Any unintentional error in the process of prescribing, preparing, dispensing, administering or clinical monitoring of a medicine or vaccine while under the control of a healthcare professional, patient or consumer.
Important medical event	An <b>important medical event</b> (IME) is considered to be one where intervention of some form is required to prevent a life-threatening situation or death, or leading to disability, incapacitation, hospitalisation, serious morbidity or birth defect or congenital anomaly. The term is synonymous with <b>medically important event</b> .
PBRER	A Periodic Benefit-Risk Evaluation Report ( <b>PBRER</b> ) is a common standard developed for periodically reviewing the risks of a medicine in light of its benefits, which emphasises the cumulative knowledge and focus on new information. Replaces the PSUR.
PSUR	A Periodic Safety Update Report ( <b>PSUR</b> ) is a pharmacovigilance document intended to provide a safety update resulting in an evaluation of the impact of the reports on the risk-benefit balance of a medicine. Replaced by the PBRER.
Side effect	An alternative use of the term <b>Adverse effect</b> , when the effect is judged to be secondary to a main or therapeutic effect.
Signal	A <b>signal</b> is a new safety finding within safety data that requires further investigation.
Spontaneous reporting	Spontaneous reports are reports of an adverse reaction that are voluntarily submitted by clinicians, pharmacists, other healthcare professionals, patients and the general public.
TGA	Therapeutic Goods Administration. The TGA is Medsafe's counterpart in Australia. It is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products.
WHO	World Health Organization. The WHO is the directing and coordinating authority for health within the United Nations system.