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

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MANATU HAUORA

Contents

Section 1: Legislation

Section summary

This section identifies the legislation and guidance documents to be read by the sponsor in conjunction with this part of the regulatory guideline.

1.1 Legislation relating to pharmacovigilance

The following legislation should be read by the sponsor in conjunction with this part of the guideline.

- Medicines Act 1981 (the Act):

Section 8	Advisory and technical committees
Section 35	Revocation and suspension of consents
Section 36	Control of established medicines
Section 41	Duty of importer or manufacturer to report untoward effects of medicines

- Official Information Act 1982
- Privacy Act 1993

This guideline includes recommendations to the sponsor that are not currently underpinned by medicines legislation. These recommendations aim to provide guidance on best practice 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.

As described in other parts of this guideline, 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. 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 between benefit and risk of harm 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 Medsafe

Section 41 of the Medicines Act 1981 requires the Director-General of Health to receive reports of untoward effects from sponsors of medicines. Medsafe is the regulatory unit of the Ministry of Health that has been delegated authority by the Director-General to receive these reports. It is one of Medsafe's functions 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.

Post-market reports of suspected adverse reactions to medicines are collected in New Zealand. This activity 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 (eg, a Dear Healthcare Professional letter)

- a change to the product information (data sheet)
- 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 may be 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 Act 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 MARC are experts in various fields of clinical medicine, clinical pharmacology, pharmacy, pharmacovigilance, epidemiology and other medical specialties such as cardiology, biostatistics, and medicines regulation. The MARC 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). Reports presented to the MARC are also published on the Medsafe website (www.medsafe.govt.nz/committees/MARC/Reports.asp). Information provided by companies and private information is removed prior to publication.

Further information about the MARC is available on the Medsafe website (www.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
Online	https://nzphvc.otago.ac.nz/

Further information about CARM is available on the New Zealand Pharmacovigilance Centre's website (https://nzphvc.otago.ac.nz/carm).

2.5 Sponsors

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 Act, 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 (see also Section 5: Significant Safety Issues).

Sponsors have a responsibility to:

- notify Medsafe of the person responsible for fulfilling the sponsor's obligations described in this document
- submit adverse reaction reports to CARM (as specified in this document)
- notify Medsafe when they become aware of any significant safety issues
- ensure that any request from Medsafe for the provision of additional information is answered fully and within the requested timeframe.

When establishing their pharmacovigilance monitoring and reporting systems, sponsors should follow the guidance in the ICH guideline E2E *Pharmacovigilance Planning*.

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.

Where the contact person is located overseas, it is expected that the contact person will keep the New Zealand sponsor informed of pharmacovigilance and quality issues.

Details of the nominated contact person, including name, role, telephone number and email address should be sent to Medsafe at: medsafeadrquery@moh.govt.nz

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 prevent duplication of reporting of the same case report.

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 subcontracts 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 the responsibilities of sponsors (including innovator and generic pharmaceutical companies) for reporting suspected adverse reactions to medicines.

The Privacy Act 1993 allows the collection of information for a lawful purpose, such as the determination of adverse reactions occurring with 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 events or any medicine-related problem.

An adverse drug reaction is an unexpected or unintended effect suspected to be caused by a medicine.

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 to the sponsor 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 guideline E2D *Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*.

Sponsors must report all spontaneous reports of suspected serious adverse reactions to CARM 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 clinical trial or investigation
  - approved medicines in a blinded study, after all the blinded medicines have been identified and the identity of the suspected medicine(s) has been determined.
- All serious 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 the Guideline on the Regulation of Therapeutic Products in New Zealand, Part 11: *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 direct supply of a medicine to a patient has been terminated, or is no longer required by the patient, unless the termination of supply is associated with a serious adverse event.

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 document EMA/ 606246/2017 *Inclusion/exclusion criteria for the "Important Medical Events" list*.

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. Non-serious adverse reactions should not be routinely reported regardless of whether the reactions were expected or not, and regardless of whether the report was unsolicited or solicited. 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 come from sources such as:

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

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 reports, 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 event 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 other 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 one or more of the following:
  - physician, consumer etc,
  - name
  - initials
  - contact details (eg, telephone number, address or email address)

  Whenever possible, contact details should be collected in the sponsor's pharmacovigilance database 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 to CARM. However, invalid cases should still 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, death or new safety concerns.

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.

If permission is denied, it is recommended that this is recorded in the sponsor's own pharmacovigilance database. It can also be recorded in the report, but it is not mandatory to do so.

Where sponsors receive 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 should clearly identify the additional information being forwarded.

If sponsors submit the initial case report online (see Section 3.6), CARM's online reporting tool issues an acknowledgement of receipt and a number that can be used to cross-reference subsequent additional information back to the initial case report.

If sponsors submit an initial case report by other means and have not yet received a CARM reference number, sponsors should use the report number assigned to the initial report by their company's own pharmacovigilance system (see Section 2.5.1) for submitting additional information to CARM. CARM will use the sponsor's report number to link subsequent additional information back to the initial case report.

3.3.4 Downgrading the seriousness 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.

3.4 Reporting timeframe for adverse reaction reports

Valid ICSRs should be submitted to CARM within 15 calendar days from receipt of the 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 to valid adverse reaction reports 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.
- If the information is insufficient or incomplete, sponsors should contact the consumer or obtain permission to allow contact with their primary healthcare professional to obtain additional relevant medical information, as described in Section 3.3.3.
- If permission to seek further information is denied or explicitly withheld, the sponsor should note this in their pharmacovigilance system.
- 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 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.

3.5.3 Lack of efficacy

A lack of therapeutic efficacy for medicines should be reported to CARM within the standard time frame of 15 calendar days. Cases of a lack of therapeutic efficacy are considered to be serious for:

- vaccines
- contraceptives
- antibiotics
- medicines used in critical conditions or life-threatening situations
- medicines used for off-label purposes
- sole-supply generic medicines.

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

Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, sponsors are not required to report lack of efficacy of antibiotics used in life-threatening situations where the medicine was not appropriate for the infective agent. However, sponsors should report any cases of life threatening infection where the lack of efficacy seems to be due to the development of a resistant strain of a bacterium previously regarded as susceptible.

A lack of efficacy may also be related to, but is not necessarily considered to be, a quality issue. There may be reasons for a lack of efficacy not necessarily related to quality defects, such as a patient being on a concomitant medication or being prescribed a sub-therapeutic dose.

If a report of a lack of efficacy is associated with a report of a quality defect, this should be reported directly to Medsafe even if the case has previously been reported to CARM (see Section 5.3).

When a report of lack of efficacy is investigated and is not found to be associated with a quality defect, the lack of efficacy does not have to be reported to Medsafe.

3.5.4 Misuse or abuse

Misuse or abuse may occur with any medicine. Reports of intentional misuse or abuse where no suspected 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 serious adverse reactions are associated with valid ICSRs of misuse or abuse, they should be forwarded to CARM.

3.5.5 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
- age group
- dosage
- route or form of administration.

Off-label use itself does not have to be reported to CARM, but reports of off-label use associated with a suspected reportable adverse reaction(s) 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 suspected serious adverse reactions until the identity of the medicine has been confirmed (see also Section 3.5.7).

3.5.6 Medicines supplied under section 25 or section 29 of the Act (unapproved medicines)

Supply of medicines under the exemption provisions in section 25 or section 29 of the Medicines Act 1981 is considered to be similar to named patient use or 'compassionate' supply in other countries. Valid ICSRs detailing serious unexpected suspected adverse reactions to these medicines should be reported.

3.5.7 Clinical trials

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

Suspected adverse reactions in relation to clinical trials investigating approved medicines (eg, for an unapproved use) should be reported to CARM according to the process described in Section 3.2.

3.5.8 Post authorisation studies

Sponsors should report valid ICSRs of serious adverse reactions which are suspected by the principal investigator to be related to an approved medicine used in studies for which they are responsible for sponsoring.

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.

Sponsors receiving reports of medication error associated with a suspected serious adverse reaction should forward these to CARM provided they are valid unsolicited reports.

Sponsors receiving reports of medication error with the potential to be associated with a suspected adverse reaction are encouraged to forward these 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/

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 serious reports. These reports 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 to CARM.

Reports of overdose due to a medication error and with the potential for an adverse reaction are encouraged to be forwarded to MERP.

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

3.5.11 Period after suspension or removal from the market

All valid serious ICSRs identified by the sponsor after suspension or withdrawal of consent to distribute, or after company-initiated withdrawal (such as discontinuation) of a medicine should be reported to CARM, as the medicine may still be in use for a time after the event. Sponsors should continue to report valid ICSRs for a period up to the date of expiry of the last batch that was distributed before the distribution ceased.

3.5.12 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 screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. This includes digital media that is owned, paid for and/or controlled by the sponsor. The frequency of the screening should allow for valid adverse reactions to be reported within the appropriate reporting timeframe based on the date the information was posted on the internet site/digital medium. Sponsors may also consider utilising their websites to facilitate the

collection of reports of suspected adverse reactions.

If a sponsor becomes aware of a report of a suspected adverse reaction described in any non-company sponsored medium, the report should be assessed to determine whether it qualifies for reporting. If it qualifies, it should be considered to be a spontaneous report and handled according to the process described in this guideline, subject to the criteria for a valid report (see Section 3.3.2).

3.5.13 Reports from the scientific and medical literature

Sponsors should frequently review the scientific and medical literature and assess reports of suspected adverse reactions occurring in New Zealand, 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 only report to CARM cases occurring in New Zealand for a medicine they distribute. If the brand of medicine is not known, sponsors should only report if their medicine was in use in New Zealand at the time of the publication. This helps to reduce duplicate reporting. A reference and/or copy of the publication should accompany the report.

3.5.14 Suspected adverse reactions related to quality defect or falsified medicine

A report of a quality defect (see Section 9: Glossary) should be reported to Medsafe's Compliance Management Branch as soon as possible.

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 directly 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

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	carmnz@otago.ac.nz
Online	https://nzphvc.otago.ac.nz/

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 6140
Fax	+ 64 (04) 819 6807
Telephone	+ 64 (04) 819 6800
Email	recalls@moh.govt.nz

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 received from sponsors and considered by CARM to be causally related to the medicine. 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.

Case reports identified using SMARS should not be re-reported to CARM. However, if upon further analysis of these reports the sponsor identifies a significant safety issue, this should be communicated to Medsafe (see Section 5).

SMARS can be accessed at: www.medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp

The website contains information on how sponsors may choose to use SMARS data. If more information on using SMARS is required, please contact:

Post Clinical Risk Management
Branch Medsafe
PO Box 5013
Wellington 6140

Telephone + 64 (04) 819 6800

Email medsafeadrquery@moh.govt.nz

3.9 Release of information under the Official Information Act

Occasionally Medsafe is required under the Official Information Act 1982 to release information regarding individual case reports. When this occurs, the information is anonymised so that individuals are not identified. These cases should not be re-reported to CARM.

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 Medicines Act 1981.

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 European Medicines Agency document EMA/827661/2011, Guideline on good pharmacovigilance practices (GV) Module IX – *Signal Management (Rev 1)*.

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. However, sponsors should not solely rely on local reports for signal detection.

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 suggests 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 has 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 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 to sponsors on what constitutes significant safety issues which may need to be reported to Medsafe under section 41 of the Medicines Act 1981.

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:

- modification or removal of an approved indication for safety reasons
- addition of a contraindication
- major changes to 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
- a lack of efficacy associated with a serious suspected adverse reaction report

- quality defect, adulteration, contamination or falsified medicine associated with a serious adverse reaction report
- issues for which the sponsor is considering sending a Dear Healthcare Professional (or DHCP) letter in any country where the medicine is being marketed (see Section 7.2).

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, or from the time a New Zealand sponsor is advised by a parent company 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 6140
Fax	+ 64 (04) 819 6806
Telephone	+ 64 (04) 819 6800
Email	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 sponsors 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 E2C (R2).

6.2 Submission of PBRERs

PBRERs are required to be routinely submitted for the following types of medicines.

- Biological medicines
- Biosimilars
- Vaccines that are included in the immunisation programme
- Medicines where a specific requirement for the submission of PBRERs has been imposed as a condition of approval.

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

PBRERs should be submitted in line with the European Union reporting timetable. If the PBRER was produced for another jurisdiction, such as the Therapeutic Goods Administration (TGA), the reporting timeframe of that jurisdiction may be used.

Medsafe will advise sponsors when routine submission is no longer necessary.

Retrospective submission of PBRERS is not required.

Medsafe does not require routine submission of PBRERs for other medicines. However, it is acceptable for sponsors to submit PBRERs routinely for all their medicines if they wish to do so.

6.2.1 Format of a PBRER

PBRERs should be prepared according to ICH guideline E2C (R2). A PBRER that has already been prepared for submission in Europe is acceptable.

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.

Where a RMP has been requested, the European format described in the guideline EMA/838713/2011 Rev 2 EMA Guideline on Good Pharmacovigilance Practices (GVP) *Module V – Risk management systems (Rev 2)* is acceptable. It is acceptable for sponsors to submit RMPs outside of these circumstances for all their medicines if they wish to do so.

6.4 RMPs and risk management tools

Some sponsors may already include risk management tools such as safety communications and educational materials in their RMPs. When RMPs include safety communications or other educational material these should be made available to Medsafe prior to distribution of the materials.

Where a RMP is not routinely submitted or available, safety communications and educational materials may be provided to Medsafe separately, as described in Section 7.

6.5 How to submit a PBRER or RMP

PBRERs should be submitted to:

Post	Clinical Risk Management Branch Medsafe PO Box 5013 Wellington 6140
Fax	+ 64 (04) 819 6806
Telephone	+ 64 (04) 819 6800
Email	medsafeadrquery@moh.govt.nz

Section 7: Safety Communications

Section summary

This section provides guidance on sponsors' 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 letters

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 should 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 EMA guideline EMA/1184654/2012 Rev 1 European Guideline on good pharmacovigilance practices (GVP) *Module XV* – Safety Communication (Rev 1).

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

Although it is not mandatory, drafts of DHCP letters relating to pharmacovigilance issues should be provided to Medsafe for review as good practice, and the final wording should be 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 (www.medsafe.govt.nz/safety/DHCPLetters.asp).

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).

Medsafe recommends that any communication materials (eg, Twitter®, Facebook® or mobile phone apps) on matters relating to medicines safety are provided to Medsafe prior to distribution.

7.4 Other educational materials

Medsafe recommends that any educational materials (eg, publications, brochures, flyers) on matters relating to medicines safety are provided to Medsafe prior to distribution.

Section 8: Best Practice Guidelines

8.1 Other New Zealand guidance

The following New Zealand guidance documents may also be of interest to sponsors.

- Medicines New Zealand Inc. Code of Practice
- National Ethics Advisory Committee Streamlined Ethical Guidelines for Health and Disability and Research
- Pharmacy Council of New Zealand Code of Ethics
- Medical Council of New Zealand Good Medical Practice

8.2 International best practice guidance

- EMA Guideline on Good Pharmacovigilance Practices (GVP) *Module V – Risk management systems (Rev 2)*
- EMA Guideline on Good Pharmacovigilance Practices (GVP) *Module VI – Management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)*
- ICH guideline E2D Post-approval safety data management (CPMP/ICH/3945/03)
- ICH guideline E2B (R2) Data elements for transmission of individual case safety reports
- ICH guideline E2A Clinical safety data management: Definitions and standards for expedited reporting (CPMP/ICH/377/95)
- Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines

Section 9: Glossary

Adverse event (AE)	Any undesirable effect in a patient or clinical trial subject administered a medicine and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 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. The term **adverse effect** may sometimes be used synonymously with adverse event by some parties.
Adverse reaction (AR)	An adverse reaction is an unexpected or unintended effect suspected to be caused by a medicine. 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). The terms **adverse drug reaction (ADR)** or **adverse medicine reaction** may sometimes be used synonymously with adverse reaction by some parties.
Biological medicine	A biological medicinal product is a product, the active substance of which is a biological substance. (www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001832.jsp). For the purposes of the Guideline for the Regulation of Therapeutic Products in New Zealand, biological medicines include biotechnological medicines.
Biological substance	A substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. (www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004447.pdf).

Biosimilar	Also known as a similar biological. A biological product that is similar to another biological medicine that has been granted consent to be marketed in New Zealand (the biological reference). (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf) The active substance of a biosimilar is similar, but not identical, to that of the biological reference. Approval is based on pharmacokinetic and pharmacodynamics studies as well as comparative clinical studies.
CARM	The Centre for Adverse Reactions Monitoring, part of 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. www.cioms.ch/
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 certain European countries.
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 **important medical event** (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 **medically important event**.
PBRER	A Periodic Benefit-Risk Evaluation Report (**PBRER**) 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 (**PSUR**) 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.
Quality defect	Can include but not limited to one or more of the following attributes associated with a product: faulty manufacture, contamination, product deterioration, detection of falsification, non- compliance with the product specification file, labels or approved product information, failure of sterility assurance.
Signal	A **signal** is a new safety finding within safety data that requires further investigation.
Solicited report	A report derived from organised data collection systems, which include clinical trials, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.
Sponsor	The New Zealand entity — agent, distributor, exporter, importer or local manufacturer — responsible for the medicine.
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.
Unsolicited report	Another term for a spontaneous report.
WHO	World Health Organization. The WHO is the directing and coordinating authority for health within the United Nations system.

Summary of Changes Made in the Updated GRTPNZ Part 8: Pharmacovigilance Edition 2.1

The pharmacovigilance guideline has been updated as part of the review of Medsafe's quality system documents. The following changes have been made.

Section	Summary of changes
Cover page	Edition number updated to Edition 2.1.
1	Addition of a reference and a hyperlink to the Official Information Act 1982.
2.1	Rephrased to better reflect that the balance is between benefit and risk of harm.
2.3	Addition of a hyperlink to the reports to the MARC that are published on the Medsafe website. Addition of advice that information provided by companies and private information is removed prior to publication.
2.4	Correction to the New Zealand Pharmacovigilance Centre website address.
2.5.2	Addition of guidance that where the contact person is located overseas, it is expected that the contact person will keep the New Zealand sponsor informed of pharmacovigilance and quality issues.
3	Clarification made that sponsors include innovator and generic pharmaceutical companies.
3.1	Explanation of adverse drug reaction has been revised to reflect updated language style. The hyperlink address for the ICH E2D guideline document has been corrected.
3.2	Addition of 'approved medicines in a clinical trial or investigation'.
3.2.1	Correction made to the title of the Guideline on the Regulation of Therapeutic Products in New Zealand, Part 11.
3.5.3	Final paragraph has been rephrased to reflect updated language style.
3.5.6	Section 3.5.10 relating to medicines supplied under section 25 or section 29 has been moved up the guideline to this position and renumbered as Section 3.5.6. This puts the guidance in logical juxtaposition with the guidance relating to other forms of supply of medicines. Subsequent section numbers are renumbered accordingly.
3.5.7	Addition of a new paragraph – 'Suspected adverse reactions occurring in clinical trials investigating new medicines should be reported as detailed in the *Guideline on the Regulation of Therapeutic Products in New Zealand Part 11: Clinical trials – regulatory approval and good clinical practice requirements.*'
3.8	The last paragraph has been revised to include a caution that reports identified using SMARS should not be re-reported to CARM.
3.9	Addition of a new section on advice on private information in relation to the Official Information Act.
4.5	Removed the reference to the Therapeutic Goods Administration of Australia (TGA).

6.1	Amended the name of the link to the ICH guideline E2C (R2).
6.2	Added 'Therapeutic Goods Administration' as an example of a jurisdiction.
6.2.1	Removed the redundant words ICH guideline.
6.3	Updated the guideline reference EMA/838713/2011 to Rev 2 (ie, revision 2).
7.2	Updated the title of the EMA guideline EMA/118465/2012 Rev 1 – *Guideline on good pharmacovigilance practices (GVP) Module XV – Safety Communication (Rev 1)*. Addition of a hyperlink to the published Dear Healthcare Professional letters on Medsafe's website.
7.3	Revised wording of the last paragraph to reflect updated language style.
7.4	Revised wording to reflect updated language style.
8.1	Change of guideline title National Ethics Advisory Committee Streamlined Ethical Guidelines for Health and Disability Research to reflect the new title of this guideline.
8.2	Updated the EMA guideline document to EMA/838713/2011 Rev 2 – *Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (Rev 2)*. Updated the hyperlink to the EMA guideline EMA/873138/2011 Rev 2 – *Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 2).*
9	Corrected the EC reference for the definition of biological medicine, biological substance and biosimilar and added the hyperlink. Revised explanation of adverse event to reflect updated language style. Revised explanation of adverse reaction to reflect updated language style.