MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Pharmacovigilance

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Definitions

Advanced therapy medicinal products (ATMPs)	Medicines for human use that are based on genes, tissues or cells. ATMPs are classified into three main types: gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines.
Adverse drug reaction (ADR)	All noxious and unintended responses to a medicinal product should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.
Adverse event (AE)	Any untoward medical occurrence in a patient, consumer or clinical investigation subject administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse event following immunisation (AEFI)	Any untoward medical occurrence which follows immunisation, and which does not necessarily have a causal relationship with the usage of the vaccine.
Biological medicines	Medicines that are made by living organisms or cells (eg, therapeutic proteins).
Biosimilar medicines	Biological medicines that are highly similar to already approved biological medicines (the reference or innovator medicine).
Centre for Adverse Reactions Monitoring (CARM)	Medical assessors at CARM review causality of spontaneous case reports. CARM is 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.
Council for International Organizations of Medical Sciences	Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organisation established jointly by WHO and UNESCO.
Established medicine	An established medicine (also referred to as a grandfathered medicine) is one that was in existence in New Zealand before the Medicines Act 1981.
European Medicines Agency (EMA)	The EMA facilitates development and access to medicines in the European Union, evaluates medicine applications for

	marketing authorisation, monitors the safety of medicines across their lifecycle and provides information to healthcare professionals and patients.
Expected adverse drug reaction	An adverse reaction known to be associated with use of the medicinal product, as reflected in the data sheet or label warning statement.
Individual case safety report (ICSR)	The complete information provided by a reporter at a certain point in time to describe an event or incident of interest. The report can include information about a case involving one subject or a group of subjects.
Important medical event (IME)	Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent serious outcomes. Refer to European guidance document Inclusion/exclusion criteria for the "Important Medical Events" list (PDF 181 KB, 6 pages).
Medicines Adverse Reactions Committee (MARC)	A technical advisory committee established under section 8 of the Medicines Act 1981 to provide expert advice to the Director-General of Health and Minister of Health on the safety of approved medicines.
Medicinal cannabis products	Medicines that consist of dried cannabis or are products that contain ingredients that are extracted from the cannabis plant. They are prescription medicines and, with the exception of CBD (cannabidiol) products (as defined in section 2A of the Misuse of Drugs Act 1975), also controlled drugs.
Medication error	Any unintentional error in the process of prescribing, preparing, dispensing, administering or clinical monitoring of a medicine including vaccines while under the control of a health care professional, patient or consumer.
New Zealand (NZ) Pharmacovigilance Database	The digital solution for collecting, storing and processing of post-market reports of suspected adverse reactions in New Zealand. The database and initial processing of reports is centred in Medsafe. The Centre for Adverse Reactions Monitoring (CARM) assesses serious reports and enters Medical Warnings.
Non-serious adverse drug reaction	An adverse reaction that does not meet the definition of a serious adverse drug reaction.
Off-label use	Use of an approved medicine different to recommendations outlined in the prescribing information (for example the data sheet)
Periodic Benefit-Risk Evaluation Report (PBRER)	A common standard for periodic benefit-risk evaluation reporting on marketed products. It includes a comprehensive, concise and critical analysis of new or emerging information on the risks and benefits of a

	medicine compiled by the sponsor. PBRER replaces the Periodic Safety Update Report (PSUR).
Quality defect	Includes 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.
Risk Management Plan (RMP)	Developed by the sponsor for the approval application and updated during the lifetime of the medicine. Includes information on a medicine's safety profile, how its risks will be prevented or minimised in patients, plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine and measuring the effectiveness of risk-minimisation measures.
Serious adverse event or adverse drug reaction	In accordance with the ICH guideline E2A a serious adverse event or reaction is 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.
Signal	Information that arises from one or more sources, that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.
Solicited report	Reports derived from organised data collection systems, which include clinical trials, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or health care providers, or information gathering on efficacy or patient compliance.
Sponsor	An individual, company, institution, or organisation that is responsible for the medicinal product in New Zealand.
Spontaneous report	An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (eg, National Poisons Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme.
Therapeutic Goods	The TGA is responsible for evaluating, assessing and monitoring medicines, medical devices and biologicals in

Administration (TGA)	Australia.
Unexpected adverse drug reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable data sheet or label warning statement.
Unsolicited report	Another term for a spontaneous report.
World Health Organization (WHO)	The directing and coordinating authority for health within the United Nations system.

1 Introduction

Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any medicine-related problem.

New Zealand is a member of the WHO International Drug Monitoring Programme based in Uppsala, Sweden.

Medsafe has an established pharmacovigilance system for collecting and evaluating information relevant to the benefit-risk balance of approved medicines in New Zealand.

This Pharmacovigilance guideline provides information for sponsors about their pharmacovigilance obligations and responsibilities for medicines that are approved by Medsafe and for medicines imported under s29 of The Act. The guideline also includes recommendations to sponsors that are not currently underpinned by medicines legislation and provides guidance on best practice of pharmacovigilance.

2 Legislation

Table 1 provides New Zealand legislation relating to pharmacovigilance. Sponsors should read the legislation in conjunction with this guideline.

Table 1: New Zealand legislation relating to pharmacovigilance

Legislation	Relevant section(s)
Medicines Act 1981	Section 8: Advisory and technical committees Section 25: Exemptions for practitioners and others Section 29: Exemption for medicine required by a medical practitioner 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	All
Privacy Act 2020	All
Therapeutic Products Act 2023	Applicable on commencement of this Act (on or by 1 September 2026), at which point provisions in the Medicines Act 1981 and it secondary legislation and guidelines there to will be repealed.

3 Roles and responsibilities

3.1 Medsafe

Medsafe detects, investigates and takes regulatory action on safety issues of approved medicines to ensure that the benefit-risk balance remains favourable.

Section 41 of the Medicines Act 1981 requires sponsors to report any substantial untoward effects of their medicines to the Director-General of Health. Medsafe is the regulatory unit of the Ministry of Health that has been delegated authority by the Director-General to receive these reports.

At the time of approval of a medicine, the evidence of safety is usually limited. It is not until the medicine begins to be used widely that the full safety profile becomes apparent. For this reason, New Zealand has a spontaneous reporting programme to gather information on the post-market safety of medicines.

3.1.1 Collection of spontaneous reports of adverse reactions

Post-market reports of suspected adverse reactions to medicines including vaccines that occur in New Zealand are reported to Medsafe and collected and stored in the NZ Pharmacovigilance Database. These reports are a source of safety information.

Medsafe, through the Ministry of Health, contracts CARM to assist with the evaluation of spontaneous reports. CARM medical assessors evaluate the likelihood of the association between the adverse reaction(s) described and the medicine(s)/vaccine(s) involved for serious reports. CARM uses the WHO causality assessment criteria for this evaluation.

3.1.2 Evaluation of safety issues

Medsafe detects and/or is notified of potential safety issues relating to medicines from a number of sources, including New Zealand case reports, sponsor notification of safety issues, overseas regulatory action and the literature.

After evaluation of the information on a safety issue, Medsafe will decide on the most appropriate regulatory action to take. This may include:

- no action 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
- requesting a data sheet update
- an instruction to sponsors to communicate to health care professionals (eg, a Dear Health Care Professional letter)
- seeking advice from the MARC
- publishing a safety communication
- suspending the distribution of the medicine while investigations are ongoing
- advising the Minister of Health to revoke consent for the medicine to be distributed.

3.1.2.1 Medicines Adverse Reaction Committee

The MARC provides expert advice on medicine 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 MARC is also provided with a quarterly review of adverse reactions reported in New Zealand.

The Chair and other members of the MARC are experts in various fields of specialist medicine, general practice, clinical pharmacology, pharmacy, pharmacovigilance, epidemiology and nursing. The MARC also holds a position for a lay person (non-health care 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, with out-of-session meetings as required. Medsafe provides secretariat support to the committee. Minutes of the meetings and reports presented to the MARC are published on the Medsafe website. However, Medsafe removes (redacts) information provided by sponsors and private information prior to publication.

Further information about the MARC is available on the Medsafe website.

3.1.2.2 Efficacy and safety review of established medicines

Section 36 of the Medicines Act 1981 makes provision for a review of the safety or efficacy of an established 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.

Medsafe will inform sponsors in writing if a section 36 review will be conducted. Sponsors will be requested to provide evidence to support the efficacy or safety of their product(s) and will 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 about a section 36 review should contact Medsafe (email: medsafeadrquery@health.govt.nz).

Section 35 of the Medicines Act 1981 allows the Director-General of Health to revoke or suspend any consent given under Section 20 or Section 23 of the Medicines Act 1981. This section of the Act may apply for medicines where the safety, efficacy or quality can no longer be regarded as satisfactory. In practice, the sponsor will be given the opportunity to provide information to justify the safety, efficacy, and quality of the medicine, similar to the process for section 36.

3.1.2.3 Medsafe safety communications

Medsafe identifies potential safety concerns through a signal management process. If a safety concern is identified, Medsafe will communicate this to consumers and health care professionals via a safety communication. There are two types of Medsafe safety communications: monitoring and alerts.

Monitoring communications outline newly identified safety concerns that are under review and, on completion of a safety review, may not require any action. Safety concerns for which

Medsafe is actively seeking further reports display this symbol M. Sponsors should note these safety concerns, and that no action is currently required on their part. This is because, after an investigation, Medsafe may consider that there currently no evidence to support a link between the adverse event(s) and the medicine.

In contrast to monitoring communications, Medsafe will issue an alert communication if the review of the safety concern identifies a causal link between the adverse event(s) and the medicine.

Safety communications are published on the Medsafe website. Before publication, Medsafe will send the safety communication to the relevant sponsor(s) for review.

3.2 Sponsors

Medsafe expects sponsors to have a pharmacovigilance system to collect and review new safety information on their medicines.

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

3.2.1 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.

Sponsors should continuously monitor the safety of their medicines and inform Medsafe of any significant changes to the safety profile, as outlined in this guideline.

Sponsors have a responsibility to:

- notify Medsafe of the person responsible for fulfilling the sponsor's obligations
- submit ICSR reports to the NZ Pharmacovigilance Database (see section 4)
- notify Medsafe when they become aware of safety issues (section 6)
- ensure that any request from Medsafe for the provision of additional information is answered fully and within the requested timeframe.

3.2.1.1 Contact person for pharmacovigilance

For all approved medicines, sponsors should 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, Medsafe expects that the contact person will keep the New Zealand sponsor informed of pharmacovigilance and quality issues.

Send details of the nominated contact person, including name, role, telephone number and email address to Medsafe at: medsafeadrquery@health.govt.nz

If there are any changes to the pharmacovigilance contact, notify Medsafe as soon as possible using the same email address.

3.2.2 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. However, sponsors may 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 have processes in place to prevent duplicate reporting of the same case report.

3.2.2.1 Subcontracting pharmacovigilance functions

Sponsors may choose to subcontract their pharmacovigilance responsibilities to specialised pharmacovigilance organisations. When subcontracting tasks to another provider, the sponsor should have 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 a pharmacovigilance system is in place.

3.2.3 Emergency planning

Medsafe expects sponsors to have plans for dealing with critical incidents. These may include product recalls or new urgent safety information that alters the benefit-risk balance of their medicines.

3.2.4 Failure to comply with responsibilities and obligations

If a sponsor refuses or fails to meet their responsibilities, consent to distribute their medicine may be suspended or revoked under section 35 of the Act. Alternatively, the sale of the medicine may be prohibited or conditions imposed on supply of the medicine under section 36 of the Act.

4 Individual Case Safety Reports (ICSRs)

4.1 Collection of reports

The sponsor's pharmacovigilance system should allow for collection and collation of all reports of suspected adverse reactions associated with their medicines from unsolicited and solicited sources. The system should also collect sufficient information for the evaluation of these reports.

4.1.1 Validation of reports

Valid ICSRs must contain the four items as shown in Table 2.

Table 2: Mandatory items for a valid ICSR report

Mandatory item	Description
Identifiable reporter	Characterised by one or more of the following: • physician, consumer etc, • name • initials • contact details (eg, telephone number, address or email address). Whenever possible, sponsors should collect the reporter's contact details in their pharmacovigilance system to enable follow-up activities.
One single identifiable patient	Characterised by one or more of the following: • initials • name • patient identification number • date of birth • age or age group • gender.
One or more suspect medicines	
One or more suspect reactions	

Where necessary, sponsors should attempt to follow up cases to obtain information that meets the minimum criteria for reporting.

If any of these four items is missing from the report, the case is invalid and it should not be submitted to the NZ Pharmacovigilance Database. However, invalid cases should still be recorded in the sponsor's pharmacovigilance system for use in product safety evaluation activities.

This interpretation of valid ICSR aligns with the EMA Guideline on good pharmacovigilance practices: Annex 1 – Definitions and the ICH guideline E2D: Post-approval data safety management.

4.2 How to report

Sponsors may use any of the following methods to report valid ICSRs that meet the reporting criteria (as described in section 4.4).

- Completing the Council for International Organizations of Medical Sciences (CIOMS) reporting form (PDF 108 KB, 1 page), and either emailing it to carmreport@health.govt.nz or submitting via Medsafe's electronic file transfer system (EFT).
- Online via the New Zealand Adverse Reactions Reporting Form.

EFT information can be located on the Medsafe website.

Note that direct E2B transfer to the NZ Pharmacovigilance Database will be available in the future. Medsafe will notify sponsors once this functionality is available. If required, please contact Medsafe for more information (email: medsafeadrquery@health.govt.nz).

4.3 Timeframe for reporting ICSRs

Sponsors should submit valid ICSRs within 15 calendar days from receipt of the information (day zero).

If a report was originally classified as 'non-serious', but follow-up information, such as review by a health care professional, indicates that the case should be reclassified as 'serious', the ICSR must be reported within the 15 calendar days of the ICSR now being a serious report.

4.4 What to report

4.4.1 Criteria for standard ICSRs

Medsafe expects sponsors to report valid ICSRs of serious expected and/or serious unexpected adverse reactions to any medicine (including vaccines) occurring in a patient in New Zealand (ie, the medicine was dispensed, purchased or administered in New Zealand), even if the sponsor disagrees with the reporter's causality assessment.

Spontaneously reported adverse events meet the definition of an ICSR, even if the relationship is unknown or unstated.

Therefore, all spontaneous reports of suspected adverse reactions notified by health care professionals or consumers to the sponsor are considered to be ICSRs, unless the reporter specifically states that the events are unrelated or that a causal relationship can be excluded. This interpretation aligns with the ICH guideline E2D: Post-approval safety data management.

Sponsors should also report solicited reports where causality assessment conducted by the sponsor, investigator or reporter indicates a positive correlation.

Where the sponsor is aware that the suspected adverse reaction may have been reported to another body (e.g., National Poisons Centre), the report is still considered a valid ICSR and should be reported to the NZ Pharmacovigilance Database if it meets the criteria. Where possible, the sponsor should name the other agency to help identify possible duplicate reports.

4.4.2 Criteria for special situations

4.4.2.1 Clinical trials

For adverse reaction reporting requirements for approved and unapproved medicines used in clinical trials, see the Guideline on the Regulation of Therapeutic Products in New Zealand: Clinical trials – Regulatory approval and good clinical practice requirements (available on Medsafe website).

4.4.2.2 Consumer reports

Sponsors should use the following as a guide when they receive adverse reaction reports or complaints directly from consumers.

- Regard unsolicited reports received directly from consumers as spontaneous reports, irrespective of any subsequent medical confirmation.
- Encourage consumers to discuss adverse reaction(s) with their health care 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 health care professional to obtain additional relevant medical information.
- 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 ICSR reports, and take these into account, when assessing the safety of their medicines.
- Additional follow-up may not be necessary for non-serious adverse reactions.

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 if it meets the above criteria.

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.

4.4.2.3 Adverse events following immunisation (AEFI)

Sponsors should report serious AEFIs to the NZ Pharmacovigilance Database.

Clusters of non-serious AEFIs may indicate a safety issue and should be reported to Medsafe as specified in section 6.

4.4.2.4 Reports from the scientific and medical literature

Sponsors should frequently review the scientific and medical literature to identify and record

ICSRs. Reviews should only commence from the time that the medicine is marketed in New Zealand, not when the new medicine application is submitted or approved.

Sponsors should review the literature at a minimum of three-monthly intervals.

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

Valid ICSRs, where the serious adverse reaction was reported in the literature and occurred in New Zealand, should be reported to NZ Pharmacovigilance Database within the standard timeframe of 15 calendar days (with day zero being the day the case was identified in the literature). A reference and/or copy of the publication should accompany the report.

4.4.2.5 Media reports

ICSRs originating from a non-medical source, such as the lay media, should be considered spontaneous reports.

Sponsors should regularly screen internet or digital media for suspected adverse reaction reports. This includes digital media that is owned, paid for and/or controlled by the sponsor.

Sponsors should screen the media at a frequency that allows for identification of valid adverse reaction reports and reporting them within the standard timeframe (see below). Sponsors may also consider using their websites to facilitate the collection of suspected adverse reaction reports.

If a sponsor becomes aware of a suspected adverse reaction report described in any non-company-sponsored medium, the sponsor should assess that report to determine whether it should be reported to the NZ Pharmacovigilance Database.

Valid ICSRs, where the serious adverse reaction was reported in the media and occurred in New Zealand, should be reported to the NZ Pharmacovigilance database within the standard timeframe of 15 calendar days (with day zero being the day the case was identified in the media).

4.4.2.6 Suspected adverse reactions related to quality defects or falsified medicines

A report of adverse reactions associated with suspected or confirmed quality defects, including adulteration or contamination, or falsified medicines (such as counterfeit or tampering) constitutes a safety issue and should be reported to Medsafe (see section 6)

A report of a quality defect without an adverse reaction should be reported to Medsafe's Product Safety Team as soon as possible via email: recalls@health.govt.nz

4.4.2.7 Unapproved medicinal cannabis products

Suppliers of medicinal cannabis products should have systems in place to comply with this Pharmacovigilance guideline.

Valid ICSRs, where an adverse reaction was suspected and occurred in New Zealand, should be reported to the NZ Pharmacovigilance Database within the standard timeframe.

4.4.2.8 Other reports

Table 3 provides further guidance on how sponsors should respond to valid adverse reaction reports in other special situations, and what should be reported to the NZ Pharmacovigilance Database.

Table 3: Guidance on what to report in certain situations

Safety concern	What to report within 15 calendar days
Lack of therapeutic effect	Reports considered to be serious. Cases that report a lack of therapeutic effect are considered to be serious for: • vaccines • contraceptives • antibiotics • medicines used in critical conditions or life-threatening situations • sole-supply generic medicines. Use clinical judgement when considering whether or not to report other cases of lack of therapeutic effect. If the lack of therapeutic effect report is associated with a quality defect, report the ICSR directly to Medsafe's Product Safety Team (and not to the NZ Pharmacovigilance Database).
Misuse or abuse	Reports with an associated serious adverse reaction.
Off-label use	Reports with an associated serious adverse reaction.
Supply of medicines under the exemptions provisions in section 25 or section 29 of the Medicines Act 1981	Reports with an unexpected serious adverse reaction.
Post authorisation studies	Reports with a serious adverse reaction and considered related by the principal investigator.
Medication error	Reports with an associated serious adverse reaction.
Overdose or occupational exposure	Reports with an associated serious adverse reaction.
Period after suspension, revocation of consent to distribute, or company-initiated removal from the market	Reports with a serious adverse reaction. Continue to submit reports up to the date of expiry of the last batch that was distributed before the distribution ceased.

4.4.3 Downgrading the seriousness of a case report

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

4.4.4 Follow-up reports

The information in ICSRs 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 or for new safety concerns.

If incomplete information is received directly from a consumer, sponsors should attempt to contact the consumer directly or obtain consent to contact a nominated health care professional for further information.

If the consumer refuses permission to contact a nominated health care professional, sponsors should record this refusal in their 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 an already-reported ICSR, sponsors should quote the reference number and the date of the original report when sending further information. Sponsors should clearly identify the additional information being submitted.

4.5 What not to report

Table 4 describes the types of cases that sponsors should not report to the NZ Pharmacovigilance Database.

Table 4: What not to report to the NZ Pharmacovigilance Database

Sponsors should not report
Non-serious adverse reactions
Cases occurring outside New Zealand, unless the sponsor is aware that the medicine was dispensed or purchased in New Zealand
Blinded clinical trial cases for approved medicines when the identity of the suspected medicine or the patient has not been identified
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. For example, where the sponsor may be aware when supply of a medicine has been terminated, such as in compassionate use programmes, named patient use programmes or electronic database monitoring programmes.

All adverse reactions that do not meet the 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 own pharmacovigilance database and use them for signal detection and evaluation activities. These should be included in the PBRER, if one is required.

4.6 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 in New Zealand.

The SMARS database is updated once a month.

SMARS does not include:

- any report where the patient may be identified (eg, due to the rareness of the reaction)
- reports from the last three months (ie, if the database was updated in September, the search results will include cases reported up to the end of May).

SMARS contains information on how sponsors may choose to use the data. See the Understanding the information in SMARS section and Advice for industry section.

Case reports identified using SMARS should not be re-reported to the NZ Pharmacovigilance Database. For more information on using SMARS, please contact medsafeadrquery@health.govt.nz

4.7 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 the NZ Pharmacovigilance Database.

5 Signal management

5.1 Introduction

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

Medsafe must be notified of safety signals that sponsors are investigating (see section 6).

In order to identify safety signals, sponsors should have a signal management process for their medicines. Medsafe recommends that sponsors follow the guidance in the EMA document: Guideline on good pharmacovigilance practices (GVP): Module IX – Signal Management (Rev. 1) (PDF 284 KB, 25 pages).

5.2 Signal management process

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

- examination of 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.

There may need to be some flexibility in the sequence of these steps. 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.

5.2.1 Signal detection

Signal detection is the process of looking for and/or identifying signals from any source.

Signal detection is a multidisciplinary approach. As a general principle, signal detection should follow a recognised methodology, which may vary depending on the type of medicine. The detection method should also be appropriate for the data set. Sponsors should consider data from all appropriate sources, and have systems in place to ensure the quality of the detection activity and timely review of the data. Sponsors should adequately document

the whole process, including the rationale for the method and the frequency of the signal detection activity.

5.2.2 Signal validation

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

This process considers 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. Sponsors should also consider other factors, such as medicine interactions, occurrence in various populations and previous awareness of a signal.

If it is not possible to validate a signal, further monitoring may provide additional data for subsequent analysis. Therefore, sponsors should use tracking systems to capture the signal validation outcome. These systems should include the reasons why signals were not validated, information that would facilitate further retrieval of ICSRs and validation of signals.

5.2.3 Signal analysis and prioritisation

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

The 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.

Medicines with high media or stakeholder interest may also need to be prioritised.

5.2.4 Signal assessment

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

Assessments should be as complete as possible and include all available information from pharmacological, non-clinical and clinical data, and other sources. Other information sources include 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 need extending to other products of the class and to other adverse reactions (ie, a broader level assessment).

If any stage of the signal assessment supports the conclusion that a potential risk is present, sponsors should take appropriate action to prevent or minimise the risk in a timely manner.

5.3 Outcomes of signal management process

Following the signal management process the sponsor should consider what action is most appropriate, including:

- no further action necessary
- periodic review of the signal

- requesting additional information to confirm plausible links
- post-market safety studies
- updating product safety information
- taking immediate measures (temporary or otherwise) including voluntary suspension of distribution by the sponsor, or the possibility of imposed suspension or withdrawal of consent
- communicating to health professionals.

Sponsors should propose an appropriate timeframe for initiation or completion of the action, including requirements for the provision of progress reports and interim results.

5.4 Quality requirements

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

6 Safety Issues

6.1 Introduction

It is a statutory requirement that sponsors must report any untoward effects for their medicines and indicate what action they are proposing to take on these issues.

Medsafe interprets 'untoward effects' as any safety issue relating to the medicine.

Safety issues may be identified in ongoing or newly completed clinical trials, post-registration studies, non-clinical studies, spontaneous reported or in published scientific literature in any part of the world. In addition, communications from regulatory authorities or within the media.

Sponsors must report safety issues to Medsafe for their medicines with consent for distribution (ie, approved medicines) in New Zealand.

Sponsors of innovator products must notify Medsafe of any safety issues. However, if the innovator product is not marketed in New Zealand or the approval has lapsed, then notification to Medsafe is not required. In this situation, the sponsor of the PHARMAC-funded generic product must notify Medsafe of any safety issues.

Appendix 1 provides a summary flowchart for reporting of safety issues to Medsafe.

6.1.1 Significant safety issues

Significant safety issues are those that sponsors are aware of that require **urgent** attention by Medsafe because of the potential major impact on the benefit-risk balance of the medicine and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Types of significant safety issues include:

- those that may led to withdrawal from the market, change of an approved indication or which may lead to a contraindication
- serious quality-related safety issues that are an immediate risk to public health, including adulteration, contamination or falsified medicine.

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

6.1.2 Other safety issues

Other safety issues are those that do not require urgent attention from Medsafe.

These safety issues are unlikely to significantly alter the benefit-risk balance of the medicine.

Types of other safety issues include:

- signals internally assessed by the sponsor that result in updates to the company core data sheet and/or other risk mitigation strategies
- quality-related safety issues that are not considered to be significant safety issues

- safety-related changes requested by recognised regulatory authorities[1].

6.2 How to report

Sponsors should report safety issues to Medsafe by email (except in circumstances where submission of a Changed Medicine Notification (CMN) is considered appropriate for notification for other safety issues as outlined in section 6.3.2).

- Email: medsafeadrquery@health.govt.nz

6.3 Timeframe for reporting safety issues

Note that all reporting timeframes include weekends and public holidays.

6.3.1 Significant safety issues

Sponsors must report significant safety issues to Medsafe **within 72 hours of identification.**

6.3.2 Other safety issues

Sponsors must report confirmed other safety issues (i.e., a safety investigation by the sponsor is completed and action is to be taken) to Medsafe within 30 days via email. If changes to the data sheet are planned, Medsafe may be notified through a Changed Medicine Notification (CMN) submission, as opposed to email, within the same timeframe (see section 6.3.2.1).

Medsafe does not need to be notified of completed safety investigations for other safety issues which have been refuted by the sponsor. However, if the other safety issue has been confirmed by a recognised regulatory authority[1], the sponsor must notify Medsafe within 30 days of the sponsors completed safety investigation.

6.3.2.1 Submission of a Changed Medicine Notification for data sheet updates for other safety issues

When the CMN is submitted, sponsors must submit supporting information for the proposed changes, such as the clinical overview for the safety issue and the company core data sheet. Medsafe may also issue a request for further information (RFI) to the sponsor as part of the CMN evaluation, especially if the supporting information is not sufficient to support the proposed data sheet changes.

For more information on CMNs:

- refer to Guideline on the Regulation of Therapeutic Products in New Zealand: Changed Medicine Notifications and Non-Notifiable Changes (PDF, 316 KB, 18 pages)
- download the Changed Medicines Notification Forms from the Forms and Templates section of the Medsafe website
- contact medsafeapplications@healthgovt.nz if you are unsure of the CMN category.

[1] Recognised regulatory authorities are defined in section 5.4 of the Guideline on the Regulation of Therapeutic Products in New Zealand: New Medicine Applications (PDF, 1,234 KB, 43 pages).

7 Safety Monitoring Documents

7.1 Periodic Benefit Risk Evaluation Reports (PBRERs)

PBRERs 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 (eg, approved indications, warnings, labelling) and those yet available (eg, limiting the indications, expanding warnings and precautions, creating contraindications, rescheduling, re-labelling or restricting use to a subset of the population).

7.1.1 Submission of PBRERs

Medsafe requires sponsors to routinely submit PBRERs for the products described in Table 5.

Table 5: Products requiring routine submission PBRERs

Vaccines that are included in the routine New Zealand National Immunisation Schedule
Marketed biological medicines (excluding vaccines) that have been in use in New Zealand for less than five years
Marketed biosimilars that have been in used in New Zealand for less than five years
Marketed chemotherapy agents that have been in use in New Zealand for less than five years
Marketed advanced therapy medicinal products
Medicines where a specific requirement for the submission of PBRERs has been imposed as a condition of approval
Any other medicines specifically requested by Medsafe if closer monitoring of its safety is required

For vaccines that are funded for only a small group of patients and are not on the routine National Immunisation Schedule, there is no need to routinely submit PBRERs.

PBRERs should be submitted in line with the European Union reference date (EURD) list. If the PBRER was produced for another jurisdiction, such as the TGA, sponsors may use the reporting timeframe of that jurisdiction.

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

In situations where an approved medicinal product becomes marketed in the future, retrospective submission of PBRERs is not required.

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

7.1.2 Format of a PBRER

Sponsors should use the ICH guideline E2C (R2): Periodic benefit-risk evaluation report when preparing PBRERs. A PBRER that has already been prepared for submission in Europe is acceptable.

7.2 Risk Management Plans (RMPs)

Medsafe does not require routine submission of Risk Management Plans (RMPs).

However, Medsafe may request the RMP for a specific medicine during the evaluation of a new medicine application as a condition of approval or in response to a safety issue.

If Medsafe requests the RMP, the European format as described in the guideline EMA/838713/2011 Rev. 2, Guideline on good pharmacovigilance practices (GVP): Module V – Risk management systems (Rev. 2) (PDF 569 KB, 36 pages), is acceptable. There is no requirement to submit a local annex with the RMP, unless specifically requested by Medsafe.

Sponsors may also submit RMPs outside of these circumstances for all their medicines if they wish to do so.

7.3 Risk management tools

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

Where the RMP is not routinely submitted or available, sponsors may separately provide safety communications and educational materials to Medsafe, as described in section 8.

7.4 How to submit a PBRER or RMP

To submit a PBRER or RMP, sponsors can:

- upload the document to Medsafe's electronic file transfer (EFT) system. If using the EFT system, please also notify medsafeadrquery@health.govt.nz
- email the document directly to medsafeadrquery@health.govt.nz.

8 Safety Communications

8.1 Introduction

There is likely to be increased public interest when new safety concerns arise. High quality safety communication can support public confidence in the regulatory system by providing timely, evidence-based information.

Safety communications should deliver relevant, clear, accurate and consistent messages using the appropriate level of language for the target audience. Sponsors should follow these principles:

- be transparent and open about what is known and not known
- provide information on risks in context to benefits
- provide appropriate quantitative measures for risk comparisons
- Include any recommendations on managing risks
- use a range of different and appropriate means of communication for the different audiences.

8.2 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 require a letter to health care professionals and relevant organisations (eg, Te Whatu Ora, pharmaceutical wholesalers, pharmacies, professional societies) 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, Guideline on good pharmacovigilance practices (GVP): Module XV – Safety Communication (Rev. 1) (PDF, 189 KB, 20 pages).

Use the template in the EMA's guideline for Dear Health Care Professional (DHCP) letters.

Medsafe recommends that sponsors send drafts of DHCP letters relating to pharmacovigilance issues to Medsafe for review, 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.

8.3 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 or social media communications.

Medsafe recommends that before doing so, sponsors should consider involving consumers and health care 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).

Before publication or distribution, Medsafe recommends that sponsors send any communication materials relating to medicines safety to Medsafe for review.

8.4 Other educational materials

Before publication or distribution, Medsafe recommends that sponsors send any educational materials (eg, publications, brochures, flyers) relating to medicines safety to Medsafe for review.

9 Best Practice Guidelines

9.1 Other New Zealand guidance

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

- Medicines New Zealand: Code of Practice (edition 17) (PDF, 1,141 KB, 64 pages)
- National Ethics Advisory Committee: National Ethical Standards for Health and Disability Research and Quality Improvement (PDF, 4,648 KB, 250 pages)
- Pharmacy Council of New Zealand: Code of Ethics 2018 (PDF 911 KB, 17 pages)
- Medical Council of New Zealand: Good Medical Practice

9.2 International best practice guidance

In addition to the documents already mentioned in this guideline, the following international guidance documents may be of interest to sponsors.

EMA Guidelines on Good Pharmacovigilance Practices (GVP):

- Module V – Risk management systems (Rev. 2) (PDF 569 KB, 36 pages)
- Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2) (PDF 2,066 KB, 144 pages)

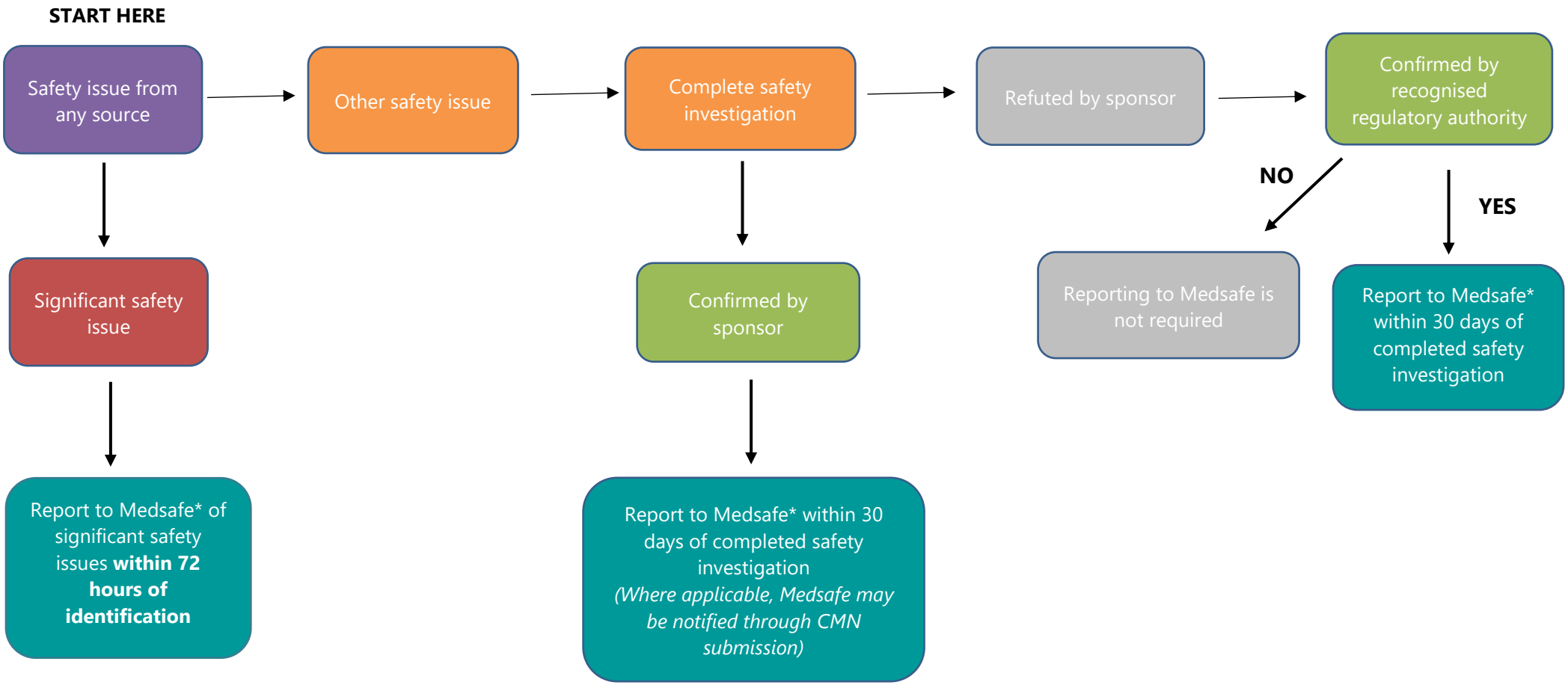
ICH Guidelines:

- ICH E2D: Post-approval safety data management
- ICH E2B (R3): Electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide reports
- ICH E2A: Clinical safety data management: definitions and standards for expedited reporting

Therapeutic Goods Administration:

- Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements

Appendix 1: Summary flow chart for reporting of safety issues



*** Notify Medsafe via email:**
medsafeadrquery@health.govt.nz

Document History

Revision Date	Edition number	Summary of Changes
August 2011	1.1	Publication of guideline
October 2014	1.1	Scheduled review
August 2015	2.0	Revised and expanded guideline
December 2017	2.1	Updated EMA and ICH guideline titles
August 2020	2.2	Scheduled review
September/October 2023	3.0	Revised and expanded guideline