MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Pharmacovigilance

Edition 3.0

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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 from 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 serious 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.
Chemotherapy agent	Medicines used to inhibit the uncontrolled growth and proliferation of cancer cells directly or indirectly. Also called antineoplastic agent. In the context of this Guideline, refers to medicines with indications for use in cancer treatment only.
Council for International Organizations of Medical Sciences (CIOMS)	CIOMS is an international, non-governmental, non-profit organisation established jointly by WHO and UNESCO.
Dear Healthcare Professional (DHPC) letter	A communication intervention by which important safety information is delivered directly to individual healthcare professionals, to inform them of the need to take certain actions or adapt their practices in relation to a medicine. Also called 'Direct healthcare professional communication'.

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. The EMA also produces the Guideline on Good pharmacovigilance practices (GVP). These are a series of modules to facilitate pharmacovigilance in the European Union.
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.
Guideline on the Regulation of Therapeutic Products in New Zealand (GRTPNZ)	Medsafe produces the GRTPNZ documents to assist industry meet the legislative and regulatory requirements for marketing a therapeutic product in New Zealand
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 the EMA's 'Inclusion/exclusion criteria for the Important Medical Events (IME) list', available in the 'References sources and services' section of the EudraVigilance system overview webpage.
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)	The ICH works with regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Responsible for the ICH Guidelines.
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 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 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. Medical assessors at the Centre for Adverse Reactions Monitoring (CARM) review causality of serious reports.

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 outside of the approved use as outlined in the prescribing information (for example the data sheet).
Other safety issues (OSIs)	OSIs are confirmed safety issues that do not meet the significant safety issue (SSI) criteria. OSIs must be reported to Medsafe (by email or CMN submission) within 30 days of the New Zealand sponsor's awareness of the issue.
PHARMAC	A government agency that is accountable to the Minister of Health and responsible for funding of medicines in New Zealand.
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).
Post-authorisation safety study (PASS)	A study that is carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management activities.
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.

Significant safety issues (SSIs)	SSIs are safety issues that require urgent attention due to the potential impact on the benefit-risk balance of the medicine and/or on patients' or public health. There may also be a need for prompt regulatory action and communication to patients and healthcare professionals. SSIs must be reported to Medsafe within 72 hours of the New Zealand's sponsor's awareness of the issue.
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 Administration (TGA)	The TGA is responsible for evaluating, assessing and monitoring medicines, medical devices and biologicals in 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 their medicines that they supply and distribute in New Zealand.

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

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 in New Zealand

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 New Zealand Pharmacovigilance Database. These reports are a source of safety information.

Medsafe, through the Ministry of Health, contracts CARM to assist with the collection and 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 (MARC)

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 applies to any 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 is 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 all their medicines that are distributed and supplied in New Zealand.

Sponsors have a responsibility to:

- notify Medsafe of the contact person for pharmacovigilance (as outlined in section 3.2.1.1).
- submit ICSR reports to the NZ Pharmacovigilance Database (as outlined in section 4)
- notify Medsafe when they become aware of safety issues (as outlined in 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 also confirm the products that they are responsible for.

The pharmacovigilance contact person does not have to be the person who conducts pharmacovigilance activities.

The expertise of a medically qualified person should be available 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.

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

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

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

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.

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.

Collection, use and disclosure of personal information should be undertaken in line with relevant privacy legislation.

4.2 What to report to the New Zealand Pharmacovigilance Database

4.2.1 Types of reports

Medsafe expects sponsors to report valid ICSRs of **all serious adverse reactions** to any of their medicines (including vaccines) occurring in a patient in New Zealand (ie, the medicine was dispensed, purchased or obtained 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 healthcare 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 (eg, 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.

4.2.2 Validation of reports

Valid serious ISCRs that are reported to Medsafe must contain the four mandatory items as shown in Table 2.

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

Table 2: Mandatory items for a valid ICSR report

Mandatory item	Description
(1) Identifiable reporter	Characterised by **one or more** of the following. • Reporter type (eg, physician, consumer, etc) • Name • Initials • Contact details (eg, telephone number, address or email address)
(2) Identifiable patient	Characterised by **one or more** of the following. • Initials • Name • Patient identification number • Date of birth • Age or age group • Gender
(3) Suspect medicine(s)	Medicine(s) suspected to have caused the reaction(s)
(4) Suspect reaction(s)	Reaction(s) suspected to be caused by the medicine(s)

The interpretation of valid ICSR in Table 2 aligns with the EMA's Guideline on good pharmacovigilance practices: Annex 1 – Definitions, and the ICH guideline E2D: Post-approval safety data management.

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

Whenever possible, sponsors should collect the reporter's contact details in their pharmacovigilance system to enable follow-up activities. Medsafe does not need to be provided with the reporter's contact details.

4.3 Timeframe for reporting

Sponsors should submit valid ICSRs of serious adverse reactions within 15 calendar days of receipt. Day 0 is the day that the New Zealand sponsor receives the information.

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 How to report

Sponsors may use any of the following methods outlined in Table 3 below to report valid serious ICSRs.

Table 3: How to report valid serious ICSRs to Medsafe

Types of reporting	Directions
Online via the New Zealand Adverse Reaction Reporting Form with CIOMS[a] attachment *(Preferred)*	New Zealand Adverse Reaction Reporting form:[b] https://pophealth.my.site.com/carmreportnz/s/ Complete the following sections of the webform only: • Reporter details • A patient detail • At least one medicine • At least one reaction • Attach CIOMS reporting form Medsafe will add the information from the CIOMS form into the New Zealand Pharmacovigilance Database to complete the report. Sponsors will be provided with a reference number on submission of the report to the New Zealand Pharmacovigilance Database.
Email	Email CIOMS form to carmreport@health.govt.nz Information from the CIOMS form will be transferred into the New Zealand Pharmacovigilance Database by Medsafe. Sponsors will be provided with a reference number when Medsafe has transferred the report to the New Zealand Pharmacovigilance Database.
Electronic file transfer system (EFT)[c]	Submit CIOMS form via Medsafe's electronic file transfer system (EFT). Information from the CIOMS form will be transferred into the New Zealand Pharmacovigilance Database by Medsafe. Sponsors will be provided with a reference number when Medsafe has transferred the report to the New Zealand Pharmacovigilance Database.

Notes:

a. CIOMS: Council for International Organizations of Medical Sciences (CIOMS) reporting form (PDF, 108 KB, 1 page).

b. The New Zealand Adverse Reactions Reporting Form is an online webform that can be used to submit valid ICSRs to the New Zealand Pharmacovigilance Database. This webform can be used by anyone in New Zealand to submit suspected adverse reaction report, including sponsors.

c. 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).

4.4.1 Downgrading the seriousness of a case report

A valid serious 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.

4.4.2 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 healthcare professional for further information.

If the consumer refuses permission to contact a nominated healthcare professional, sponsors should record this refusal in their own pharmacovigilance database. This information is not required to be reported to the New Zealand Pharmacovigilance Database.

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.

4.4.3 Additional information for special situations

4.4.3.1 Clinical trials

For adverse reaction reporting requirements for approved and unapproved medicines used in clinical trials, see GRTPNZ: Clinical trials – Regulatory approval and good clinical practice requirements (available on Medsafe website).

4.4.3.2 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 healthcare professional.
- Sponsors should make reasonable attempts to obtain sufficient information to ascertain the nature and seriousness of the reaction.
- Sponsors must document all consumer ICSR reports, and take these into account, when assessing the safety of their medicines.

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 required 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.

4.4.3.3 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.

4.4.3.4 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 New Zealand Pharmacovigilance Database. A reference and/or copy of the publication should accompany the report.

4.4.3.5 Media reports

ICSRs for medicines marketed in New Zealand and originating from a non-medical source, such as the lay media, should be considered spontaneous reports.

Sponsors should regularly screen internet or digital media under their management or responsibility 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 New Zealand 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.

4.4.3.6 Suspected adverse reactions related to quality defects or falsified medicines

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

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

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

Contact the Medsafe Product Safety Team via email: recalls@health.govt.nz

4.4.3.7 Unapproved medicinal cannabis products

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

Valid ICSRs, where a serious adverse reaction was suspected and occurred in New Zealand, should be reported to the New Zealand Pharmacovigilance Database.

4.4.3.8 Other reports

Table 4 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 4: Guidance on what to report in certain situations

Safety concern	What to report within 15 calendar days
Lack of therapeutic effect[a]	Cases where the lack of therapeutic effect is considered to be serious for the individual using the medicine for the approved indication. Examples include: • vaccines • contraceptives • antibiotics (with sensitivity in *in vitro* testing). Use clinical judgement when considering whether or not to report other cases of lack of therapeutic effect.
Misuse or abuse	Cases with an associated serious adverse reaction.
Off-label use of an approved medicine	Cases with an associated serious adverse reaction.
Unapproved medicines (Section 29)	Cases with an unexpected[b] serious adverse reaction.
Post authorisation safety studies	Cases with a serious adverse reaction and considered related by the principal investigator. Cases with a serious adverse reaction and considered related by the sponsor.
Medication error	Cases with an associated serious adverse reaction.
Overdose or occupational exposure	Cases with an associated serious adverse reaction.
Period after suspension, revocation of consent to distribute, or company-initiated removal from the market	Cases with an unexpected serious adverse reaction.

Notes

a. For vaccines, cases of a lack of prophylactic efficacy may highlight signals of reduced immunogenicity in a subgroup of vaccines, waning immunity, or strain replacement. Such a signal may need prompt action and further action as appropriate. For COVID-19 vaccines, lack of therapeutic effect reports 3 months post vaccination should be reported.

   For antibiotics, a lack of therapeutic effect may indicate newly developing resistance, making further study necessary. Antibiotics used in life-threatening situations where the medicine was not appropriate for the infective agent do not require reporting to Medsafe. However, sponsors should report any cases of life-threatening infection where the lack of therapeutic effect seems to be due to the development of a resistant strain of a bacterium previously regarded as susceptible.

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

   Clinical judgement should be used when considering if other cases of lack of therapeutic effect qualify for reporting.

b. An unexpected adverse reaction is an adverse reaction that is not currently listed in the Company Core Data Sheet.

4.5 What not to report to the New Zealand Pharmacovigilance Database

Table 5 describes the types of cases that sponsors should not report to the NZ Pharmacovigilance Database.

Table 5: What not to report to the New Zealand Pharmacovigilance Database

Sponsors should not report
Non-serious adverse reactions
Invalid serious adverse reactions
Cases occurring outside New Zealand, unless the sponsor is aware that the medicine was dispensed or purchased in New Zealand
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.

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 two months (ie, if the database was updated in September, the search results will include cases reported up to the end of June).

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 New Zealand 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 New Zealand Pharmacovigilance Database.

5 Signal management

5.1 Introduction

Signal management is a set of activities performed to identify whether new risks have been identified with a medicine or 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 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.

Section 6 outlines information for sponsors about notification of safety issues to Medsafe.

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's GVP: Module IX – Signal Management (Rev. 1) (PDF, 284 KB, 25 pages).

5.2 Signal management process

The signal management 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 reporting or in published scientific literature in any part of the world.

6.2 Types of safety issues

6.2.1 Significant safety issues (SSIs)

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

Types of SSIs include:

- those that may lead to withdrawal of the medicine from the market
- change of an approved indication for safety reasons
- those that may lead to an addition of a contraindication
- where a Dear Health Care Professional letter may be needed
- where additional risk management measures may be needed.

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.

6.2.2 Other safety issues (OSIs)

Other safety issues are those confirmed safety issues that do not meet the SSI criteria.

Types of OSIs include:

- updates to the safety information section of the company core data sheet and therefore the New Zealand data sheet
- product information safety-related changes received by the sponsor from recognised regulatory authorities[1] whether or not the sponsor agrees with the safety-related change.

[1] Recognised regulatory authorities are defined in section 5.4 of GRTPNZ: New Medicine Applications (PDF, 1234 KB, 43 pages).

6.2.3 Responsibility for reporting safety issues

Sponsors of approved innovator products are responsible for notifying Medsafe of SSIs and OSIs.

Sponsors of approved generic products where the New Zealand innovator product is not approved are responsible for notifying Medsafe of SSIs and OSIs.

The above applies irrespective of marketing status.

For products that are approved in another country and are currently under a New Medicine Application (NMA) in New Zealand, the sponsor is responsible for notifying Medsafe of SSIs only. It is likely that this will apply mainly to sponsors of innovator medicines.

Exceptions:

- Sponsors of innovator products that are not marketed in New Zealand and there is no generic product available in New Zealand (ie, there is no approved product of the active substance on the New Zealand market) are not required to notify Medsafe of any safety issues.
- If a generic product is marketed in the future and the innovator is still approved, the sponsor of the generic medicine is not required to report safety issues.

6.3 How to report

Appendix 1 (significant safety issues) and Appendix 2 (other safety issues) provides a summary flowchart for the process of reporting safety issues to Medsafe.

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 OSIs, as outlined in section 6.4.2.1).

- Email: medsafeadrquery@health.govt.nz

6.4 Timeframe for reporting safety issues

Medsafe acknowledges that safety information may be received and processed by global counterparts before it is distributed to the local New Zealand sponsor. Medsafe expects that sponsors have appropriate processes in place to ensure timely communication of safety information.

Note that all reporting timeframes include weekends and public holidays.

6.4.1 Significant safety issues (SSIs)

SSIs require notification to Medsafe following the sponsor's initial awareness of a confirmed signal and that a safety investigation will be undertaken.

SSIs must be reported to Medsafe **within 72 hours** of the New Zealand sponsor's awareness of the issue. The sponsor must also inform Medsafe of an expected timeframe for investigation.

Additional follow up information and outcome of the safety information should be notified to Medsafe when available.

6.4.2 Other safety issues (OSIs)

Sponsors must report the results of completed safety investigations that require action to be taken. Medsafe does not need to be notified of completed safety investigations which have been refuted by the sponsor.

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

OSIs must be reported to Medsafe via email within 30 calendar days of the New Zealand sponsor's awareness. Alternatively, sponsors may submit a Changed Medicine Notification (CMN) within this time frame (30 calendar days (see section 6.4.2.1)).

6.4.2.1 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. 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.

Please note that CMNs are not required to be submitted within 30 days of completion of a safety investigation. This is an option for sponsors notifying Medsafe of OSIs instead of email notification.

For more information on CMNs:

- refer to GRTPNZ: 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@health.govt.nz if you are unsure of the CMN category.

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 Products for which PBRERs should be submitted

Medsafe requires sponsors to routinely submit PBRERs for the innovator products described in Table 6.

Table 6: Innovator products* requiring routine submission of PBRERs

Vaccines that are included in the routine New Zealand National Immunisation Schedule
Marketed biological medicines (excluding vaccines) that have been approved in New Zealand for less than 5 years
Marketed biosimilars that have been approved in New Zealand for less than 5 years
Marketed chemotherapy agents used in cancer that have been approved in New Zealand for less than 5 years
Marketed advanced therapy medicinal products that have been approved in New Zealand for less than 5 years
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 safety is required

Note:

* Refer to the Definitions section for further information on the types of medicines listed in Table 6.

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.

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.

7.1.3 Duration of submission of PBRERs

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

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 EMA's 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 (DHCP) letters

New information that significantly affects the risk-benefit balance of a medicine may require a letter to healthcare professionals and relevant organisations (eg, Te Whatu Ora (Health New Zealand), pharmaceutical wholesalers, pharmacies, professional societies) to advise them of the overall impact on safety and/or use of the medicine.

Common examples of changes that should be communicated are the imposition of new warnings, precautions, contraindications, a limitation of indications or restriction on use, or changes related to formulation or appearance of the product.

Medsafe recommends that sponsors follow the guidance in the EMA's GVP: Module XV – Safety Communication (Rev. 1) (PDF, 189 KB, 20 pages). This includes situations where a DHCP letter should be disseminated and other situations where dissemination of a DHPC letter should be considered.

A DHCP letter may be disseminated by the sponsor's own initiative or at the request of Medsafe.

Use the template in the EMA's guideline for DHCP letters.

Medsafe recommends that sponsors send drafts of DHCP letters relating to pharmacovigilance issues to Medsafe for review (email: medsafeadrquery@health.govt.nz). 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 (email: medsafeadrquery@health.govt.nz).

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 (email: medsafeadrquery@health.govt.nz).

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
- 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, 2066 KB, 144 pages)

ICH Efficacy/Clinical safety guidelines:

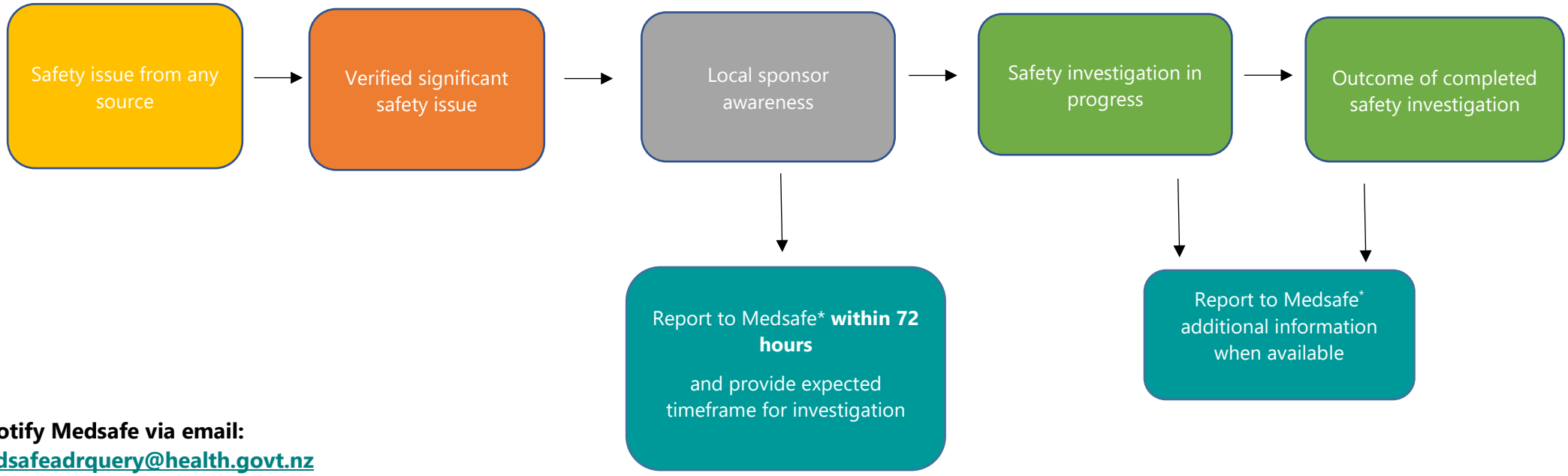
- ICH E2D: Post-approval safety data management
- ICH E2B (R3): Electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide reports
- ICH E2A: Clinical safety data management: definitions and standards for expedited reporting

Therapeutic Goods Administration:

- Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements

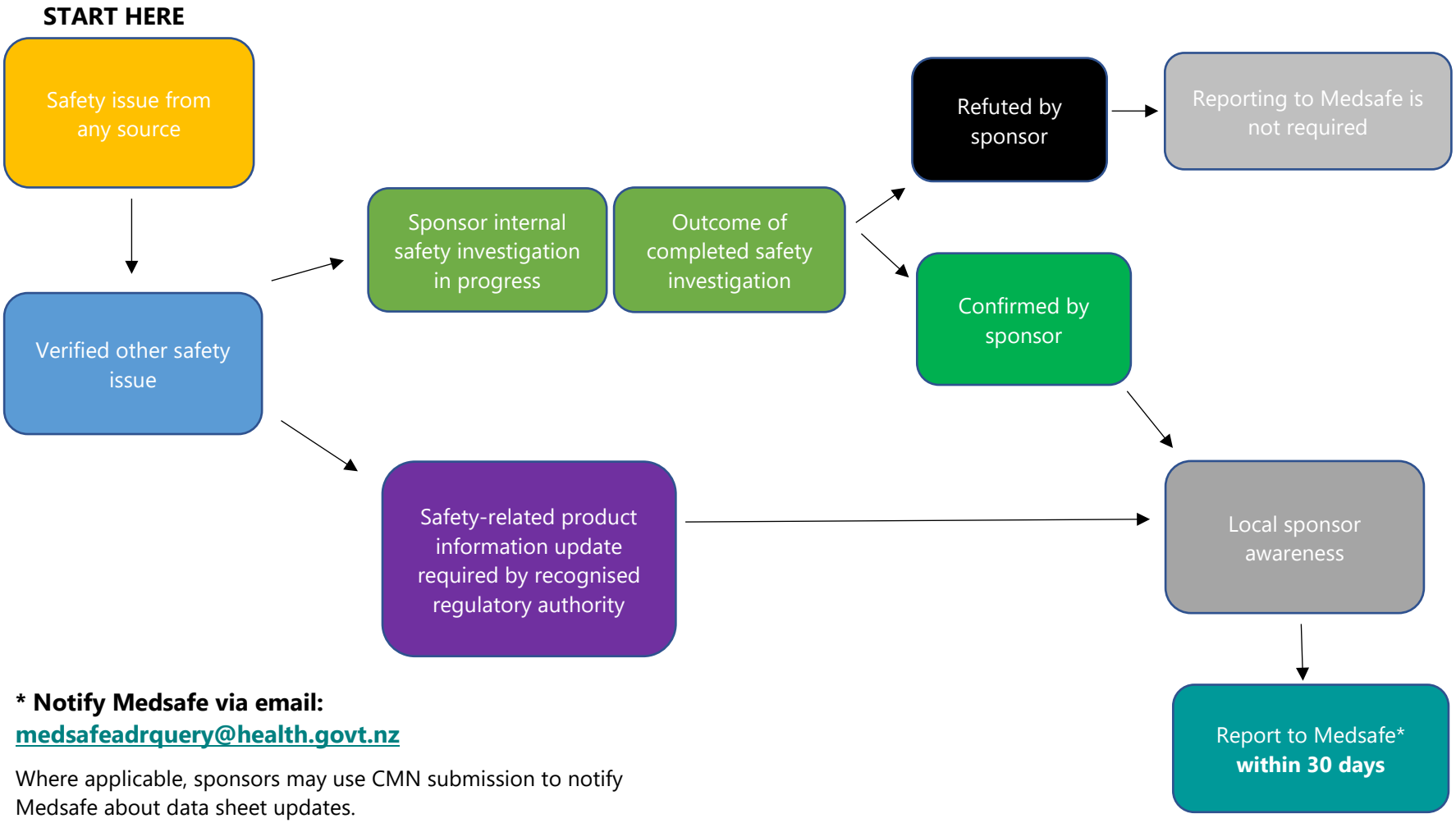
Appendix 1: Summary flow chart for reporting of significant safety issues (SSIs)

START HERE



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

Appendix 2: Summary flow chart for reporting of other safety issues (OSIs)



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

Where applicable, sponsors may use CMN submission to notify Medsafe about data sheet updates.

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
March 2024	3.0	Revised and expanded guideline