Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

Early Warning System for Potential Safety Signals Associated with Therapeutic Products

Workshop Briefing Document

Contents

Background

You have been invited to a workshop hosted jointly by the Australian therapeutic products regulator: TGA and Medsafe the equivalent New Zealand regulator. This workshop is an important step in aligning the processes of the two regulators prior to the creation of a joint regulator; currently known as the Australia New Zealand Therapeutic Products Agency (ANZTPA).

ANZTPA

The Prime Ministers of Australia and New Zealand agreed on 20 June 2011 to proceed with a joint scheme for the regulation of therapeutic products. The creation of a joint regulatory scheme across both countries will safeguard public health and safety, while encouraging economic integration and benefitting industry in both countries.

A 3 stage approach over a period of up to 5 years will be adopted to progressively achieve this goal.

1. Medsafe and the TGA will immediately begin a program of work-sharing and increased joint operations. This will enable the separate regulatory systems of each country to be enhanced by sharing of data and information, training, and establishing centres of expertise in each country.

2. Building on this, a single entry point for industry will be established and a common trans-Tasman regulatory framework will be agreed.

   During these two preliminary phases, each country will retain its own regulator and continue to make its own regulatory decisions, but business will benefit from a significant reduction in red tape with only one set of requirements to operate in two countries.

3. As business operations become increasingly integrated and following a review of progress, the single regulator will be established.

A number of initial joint Medsafe/TGA projects have been agreed to begin the alignment of procedures. One of these projects is to establish a single trans-Tasman early warning system of potential safety issues around therapeutic products (further information can be found at: http://www.tga.gov.au/about/international-anztpa.htm & http://www.medsafe.govt.nz/hot/anztpa.asp)

This workshop is being held to give key stakeholders the opportunity to help shape this early warning system and ensure it brings benefits to health professionals and consumers. Following this workshop, Medsafe and the TGA will use your input to formulate the design and develop the early warning system.

To help you understand our current systems this briefing document provides:

- A background to the activities undertaken by Medsafe and the TGA in relation to safety signal detection;
- A summary of the communication of safety signals in Australia and New Zealand;
- A summary of the communication of safety signals in other countries;
- Proposed models for how a system might look in Australia and New Zealand;
- Questions to think about before the workshop which will be used to stimulate discussion.

Further information about the processes and safety signals can be found on both the TGA (http://www.tga.gov.au/safety/index.htm) and Medsafe (http://www.medsafe.govt.nz/) websites.

Introduction

Need for Therapeutic Products Regulation

The purpose of a therapeutic products regulator is to manage the risk associated with the use of therapeutic products. This need was highlighted back in the 1960's by the thalidomide tragedy at which point there was very little regulation of medicines or safety monitoring. The only method by which safety concerns could be raised was in the medical literature.

The community using therapeutic products expects that these will be efficacious, of high quality and safe. The role of the regulator is to ensure that the therapeutic products available in their country are of acceptable safety, quality and efficacy (performance). The regulator needs to enable timely access to new, potentially life-saving therapeutic products whilst ensuring that there is evidence that these therapeutic products have adequate safety by determining the benefit risk balance.

Benefit risk balance

Factors which need to be considered in determining the balance of benefits and risks include the:

- Level of absolute benefits;
- Level of absolute risk and the potential health consequences;
- Seriousness of the disease the therapeutic product is intended to treat;
- Benefit risk balance for alternative therapeutic products/treatment options (this may include no treatment);
- Perspective of the individual.

In practice, the benefits and risks are balanced at two levels: the population level and the individual level. The benefit risk balance at the population level is the regulator's task and considers the overall picture. The benefit risk balance for the individual is a decision made by health professionals in consultation with each patient and takes into account additional factors such as previous treatment, disease severity and patient preferences.

The process of balancing benefits and risks remains a judgement and for some issues where the benefits and risks are finely balanced, it is possible for different regulators of therapeutic products to come to different conclusions.

Once a product is approved the regulator continues to monitor its effects. This process can be referred to as Therapeutic Product Vigilance.

Therapeutic Product Vigilance

Therapeutic Product Vigilance consists of continuous product vigilance throughout the therapeutic product life cycle. This includes information collection, monitoring, evaluation, and risk management from the development stage through to initial marketing and continual supply of a therapeutic product. In order for patients to have access to new therapeutic products in a timely manner, new products on the market may have limited safety information in regards to rare or uncommon adverse events and long-term effectiveness. Where this is the case, the regulator relies on adverse event reporting to determine whether further investigation, such as post-marketing studies is required.

The safety of a therapeutic product is dependent on two factors: the intrinsic safety which is how the therapeutic product interacts with the body and user-dependent safety. By monitoring the therapeutic product in use the intrinsic safety is more clearly defined and recommendations to improve user dependent safety can be identified.

The aim of therapeutic product vigilance is to continually monitor and evaluate the safety and efficacy (performance) profile of therapeutic products and to manage any risks associated with individual products.

Information from many sources is used in therapeutic product vigilance including:

- Clinical and observational studies;
- Published medical literature;
- Therapeutic Products Industry;
- Other International Regulators;
- Disease or Product Registries;
- Spontaneous adverse event reports from consumers and health professionals;
- (Mandatory) adverse event reports from sponsors/manufacturers.

The aim of monitoring these sources of information is to detect a signal of a safety issue. A safety signal could be a previously unknown adverse event or a change in the frequency or severity of a known adverse event. It is important to note that not all safety signals are real and therefore these signals require further investigation before any action is taken.

Spontaneous reporting

The method of spontaneous reporting was developed in the 1960's as an early warning system for regulators. Health professionals and consumers can report any suspicions of an adverse event with a medicine or medical device to the appropriate body. This part of therapeutic product vigilance is the one most familiar to health professionals.

The strengths of the spontaneous system are that it applies to all therapeutic products all the time and can rapidly detect safety signals. The main limitations are the unquantifiable under-reporting and the potential for the data to be misunderstood. Also associations between a therapeutic product and an adverse event that take a long time to develop (e.g. cancer) are generally poorly reported. The data is biased with reports being more likely to be submitted for serious unrecognised adverse events and in response to publicity. These biases make interpretation of adverse event data difficult. For example reports of fatal adverse events reported with a particular product can cause concern. However, these reports need to be considered in the context of the condition the therapeutic product is used to treat, the nature of possible adverse events, the presence of other factors that could explain the effect and the number of people treated with the therapeutic product.

All databases of spontaneous adverse events for therapeutic products contain many reports where the adverse event was not actually caused by the therapeutic product these reports provide background noise. Therefore, most regulators use mathematical tools for detecting safety signals.

If a safety signal is detected the regulator will investigate further using the available information. The signal review may include obtaining further information from the therapeutic product sponsor or manufacturer, investigation of published literature, information from other regulators and/or other data sources such as registries and linked datasets (if available). For some issues expert advice will be sought from either the regulator's expert advisory committee(s) or individual independent experts.

The key issues considered when evaluating a safety signal are:

- Causality – does the balance of evidence support cause and effect? Is there a plausible mechanism?
- Frequency – what are the public health implications?
- Clinical implications- what are the consequences for the patient i.e. seriousness and severity of the problem?

- Detectability/Repeatability - is the event or type of problem detectable before use and is the event easily repeatable?
- Preventability – are there ways to prevent the adverse event?

It is important to remember that an initial safety signal may turn out to be incorrect.

Taking action

Whilst the vast majority of safety signals do not require any action there are a number of steps that can be taken if a signal is confirmed, including:

- Providing information to prescribers and consumers e.g. through publications or media releases.
- Changing the warnings in the product information.
- Restricting the indications for the therapeutic product.
- Changing the legal status of the medicine e.g. from over-the-counter to prescription only.
- Requesting further study of the issue by the sponsor/manufacturer of the therapeutic product.
- Removal of the therapeutic product from the market.

Clearly communication is very important when action is taken on a safety signal. This is discussed in more detail below.

Communication

Principles of Communication

There are a number of difficulties in communicating risk issues as they tend to be complex, involve scientific information and often have no simple conclusion. A number of principles have been developed internationally to guide these communications.
Communications should:

- Be science based;
- Provide context and be adapted to perceived audience needs;
- Describe the benefits as well as risks;
- Be results orientated.

One of the factors determining whether communications on risk are successful is trust in the source of information. It is generally considered that information coming from governments and their agencies is trusted less than that from individual credible professionals such as doctors. The power of the media to influence consumers is also greater than that of the regulator.

There are biases involved when consumers think about risk. These include:

- Awareness bias - when increased awareness of an issue leads to an exaggerated perception of risk;
- Optimistic bias - when individuals rate their chance of avoiding mishap as 'better than average';
- New risk bias - new risks generate more fear than risks that have been experienced for some time;
- Catastrophic bias - where events happening at once in one place are feared more than chronic on-going events.

In general, risks are perceived as more worrying if they include a 'fright factor', such as:

- Involuntary rather than voluntary;
- Inequitably distributed;
- Inescapable by taking personal precautions;
- Arising from an unfamiliar source;
- Man-made rather than natural;
- Causing hidden and irreversible damage;
- Posing danger to small children or pregnant women;
- Threatening a form of illness associated with dread;
- Damaging to identifiable rather than anonymous victims;
- Poorly understood by science;
- Subject to contradictory statements from responsible sources.

Uncertainty and debate about an issue has the potential to increase public concerns, but is a common situation when new safety issues are identified for therapeutic products.

The traditional systems in place for communicating safety issues to health professionals and consumers include:

- Updates to the product information and consumer information;
- Letters/faxes sent by the regulator to health professionals;
- Letters sent by the sponsor/manufacturer to health professionals;
- Media releases;
- Including information in drug safety bulletins (Medicines Safety Update in Australia and Prescriber Update in New Zealand);
- Posting information on the regulator's website such as Safety alerts regarding therapeutic products.

Current Communication Systems in Australia and New Zealand

In Australia the TGA issues alerts for safety issues associated with therapeutic products. The TGA issues alerts to advise consumers, health professionals and industry about new safety information about therapeutic products. A TGA alert does not necessarily mean that a product is considered to be unsafe.

A TGA alert may explain the outcome of an investigation or a change to the availability of a product, or may advise that counterfeit or illegal therapeutic products have been detected in Australia.

These alerts tend to be issued following review of the safety signal once a recommendation and advice can be provided. Alerts are posted on the TGA website with information about the issue and TGA recommendations. For urgent, serious issues TGA also issues letters to health professionals.

The TGA publishes the Medicines Safety Update, a medicines safety bulletin, which provides practical information and advice on drug safety and information about emerging safety issues.

Product information and consumer medicine information for medicines is published on the TGA website. Updates are made to the product information once a safety issue has been confirmed. In addition AusPARs (Australian public assessment reports) detailing the information evaluated for a prescription medicine approval have been published since October 2009, for new prescription medicines and major changes to existing prescription medicines.

The TGA shares therapeutic product vigilance data with state and territory health departments and other partners such as the National Centre for Immunisation Research and Surveillance, the World Health Organisation and overseas regulatory agencies through the Global Harmonization Task Force National Component Authority Reports.

In New Zealand, Medsafe alerts are found on the website either in the section on alerts/letters, recall notices or as media releases. Information is usually only posted after review of the safety signal has been completed. For urgent, serious issues Medsafe issues letters to healthcare professionals electronically or by fax.

Medsafe runs an additional scheme known as M squared (M²). This scheme is designed to highlight potential safety issues, identified from reports of suspected adverse reactions to medicines. The aim is to stimulate further reports to assist in the evaluation of the signal. Data sheets for medicines on the M² list have the logo published next to the data sheet list on the Medsafe website. Full details are available on the Medsafe website (http://www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp).

Medsafe also sends a list of medicines for which there have been data sheet changes to subscribers. Data sheets are published on the Medsafe website and are updated once a safety issue has been confirmed.

Communication Systems in Other Countries

Some examples of the communication systems in place in other countries are outlined below.

United States

The United States currently has the most advanced early warning communication system. The FDA issues safety advisories, highlights potential safety signals arising from spontaneous reports and provides information on updates to product information.

Safety advisories are e-mailed to subscribers and cover all therapeutic products. Advisories can be issued at any stage, however, those issued for early signals are normally updated with further

information as it becomes available. The aim of these advisories is to inform health professionals and consumers early, so that they can make fully informed decisions on the benefits and risks of medicines. Advisories are issued for serious issues where an early change in health professional behaviour or consumer behaviour is likely to result in safer use of the therapeutic product. The aim is to benefit the consumer at an early stage.

Highlighted potential safety signals identified from spontaneous reports are detailed on the FDA website. These safety signals are generally important events and/or affect a significant number of patients. Not all potential signals are listed.

Whilst the FDA provides as much information as possible, often recommendations cannot be made as the issue is at an early stage and the review is on-going. A number of methods of communication are used including:

- MedWatch Safety Alerts;
- Twitter and Facebook;
- Podcasts;
- Letters to Editors or Perspective articles in medical journals;
- Stakeholder conference calls;
- Question and Answer documents;
- Website feature postings.

In addition the FDA also provides regular summary lists of changes to product information which includes more minor changes not requiring a safety alert.

Europe

The European Medicines Agency (EMA) publishes media statements on its website (available as RSS feeds), normally when an issue has been reviewed. However an alert may also be published at the start of a review process. A list of all the major changes made to the authorisation of medicines recommended to improve patient safety is published on the EMA website. For all medicines a European Public Assessment Report (EPAR) outlining the information considered at approval and a summary of changes post approval are also published in the EMA website.

Individual regulators within Europe also publish alerts and media releases on their websites. For example, the MHRA (UK regulator) runs the black triangle scheme which is designed to highlight new medicines for which safety information may not be fully characterised, rather than any specific issue with the medicine and issues safety warnings to health and social care providers and other users of medical devices which warn of particular problems and risks and recommend appropriate action to minimise them.

Canada

Health Canada publishes safety alerts for therapeutic products to which interested persons can subscribe and receive via email. These alerts can be published at any point following the detection of a safety signal. Health Canada also publishes the Canadian Adverse Reaction Newsletter (CARN). This is slightly different to other regulator's bulletins in that the aim is to communicate information on adverse event reports for therapeutic products rather than the results of safety reviews.

Review of the success of Regulatory Communication

A recent review of FDA communications [1] concluded that:

[1] Dusetzina SB, Higashi AS, Dorsey ER et al 2012 'Impact of FDA Drug Risk Communications on Health Care Utilization and Health Behaviours: a systematic review' Med Care [Epub ahead of print]

- Advisories recommending greater monitoring do not result in long-term changes to prescriber behaviour;
- Warning information is adopted more quickly for new rather than continuing medicine users;
- Warnings were more effective when the message was specific and there are acceptable alternatives and the message is reinforced over time;
- Most physicians appeared aware of general safety concerns but many disagreed with the content and did not act upon the advisory;
- There is the potential for unintended consequences such as being taken for non-targeted populations. For example, restrictions on use of a medicine in children may result in lower use in all patients.

What might an early communication system for Australia and New Zealand look like?

Three proposals for possible schemes are outlined below. An example of how the schemes might work and their differences is shown using the hypothetical new medicine for treating insomnia called Noxuout.

Proposal one:

To alert health professionals and consumers to all safety signals as soon as possible after detection.

The criteria would be all (serious and non-serious) potential safety issues identified from spontaneous reporting and other sources are published.

Communications would emphasise the preliminary nature of these signals. The communication will explain that most of these issues will not result in any action as they were not considered to be associated with the therapeutic product upon further evaluation. Follow up communication will be provided on issues where action is required. This follow up communication will need to be more extensive and should include the following elements:

- Current known benefits and risks;
- Details of the possible new risk;
- Information on the knowledge base such as reliability of the data source, limitations of the data, how the issue will be evaluated;
- Any changes in behaviour required to improve the safe use of the product;
- Where appropriate that no conclusions have been made on the issue, that patients should not stop using the therapeutic product;
- Information on how to report suspected adverse reactions;
- That the information will be updated if more data becomes available and when a decision has been finalised;

This proposal is likely to result in the communication of numerous 'false' signals and it may be difficult to focus healthcare professional and consumer attention on the most important/serious issues. Also, it is likely to lead to increased concern by users and clinicians in the use of the therapeutic product/s. However, all issues will be highlighted very early and allow more complete decision making.

Proposal two:

To alert health professionals and consumers to all serious safety signals as soon as possible after detection.

The criteria would be all serious potential safety issues identified from spontaneous reporting and other sources are published.

Communications would emphasise the preliminary nature of these signals. The communication will explain that many of these issues will not result in any action as they were not considered associated with the therapeutic product upon further evaluation. Follow up communication will be provided on issues where action is required. This follow up communication will need to be more extensive and should include the following elements:

- Current known benefits and risks;
- Details of the possible new risk;
- Information on the knowledge base such as reliability of the data source, limitations of the data, how the issue will be evaluated;
- Any changes in behaviour required to improve the safe use of the product;

- Where appropriate that no conclusions have been made on the issue, that patients should not stop using the therapeutic product;
- Information on how to report suspected adverse reactions;
- That the information will be updated if more data becomes available and when a decision has been finalised.

This proposal is likely to result in the communication of many 'false' signals and it may be difficult to focus healthcare professional and consumer attention on the most important issues. Also, it is likely to lead to increased concern by users and clinicians in the use of the therapeutic product/s. However, all potential serious issues will be highlighted very early.

Proposal three:

To alert healthcare professionals and consumers to safety signals requiring a change of behaviour to ensure safe use of a therapeutic product.

The criteria would be to include all serious issues that have been initially reviewed and are likely to result in significant changes to the product information and/or the way the product is used.

Communications for this issue would follow the principles outlined in proposal one.

This proposal has the potential to reduce the number of false signals and concern amongst users and health professionals, but means that safety issues are not highlighted as quickly.

The differences between the proposals are shown for the example of Noxuout.

Proposal one	**Proposal two**	**Proposal three**
After several months of use the following potential serious and non-serious safety issues are detected and communicated: Feeling of body temperature change Seizure Nightmare Pneumonia Tendonitis Increase in liver enzymes	After several months of use the following potential serious safety issues are detected and communicated: Seizure Pneumonia Tendonitis	No information is posted at this time
An update is posted for seizure as a review has started	An update is posted for seizure as a review has started	
		An alert is posted for seizure following initial review of the issues
Further communication is issued as when the review is complete	Further communication is issued when the review is complete	Further communication is issued when the review is complete

It is important to note when considering these proposals that both TGA and Medsafe have finite resources. Therefore in order for this scheme to operate effectively this must be considered. It will not be desirable to divert all the resource for detecting and evaluating safety issues to administering this scheme.

Workshop: Early warning system for Australia and New Zealand.

In order to help the workshop discussions you are asked to consider the proposals above and the following points and questions.

When should an early warning of a potential safety signal be issued?

- Should the M squared scheme be considered part of the early warning system?
- Should alerts be issued as soon as a safety signal has been identified?
- Should alerts be issued once a safety signal requires an extensive review or a risk benefit review?
- Should the alert be issued once a safety issue has been confirmed? Should this be before or after any change to the product information?
- When are the sponsor/manufacturer advised of the potential safety signal?

What kind of safety signals should be communicated?

- Everything (all serious and non-serious)?
- Only signals of serious adverse events? But what are the criteria for serious v non-serious?
- When do you know it is a safety issue?
- Issues which could cause a public health risk?
- What are the numbers/indications of a issue?
- Are summaries of routine changes to product information useful?
- Will it depend on the source of the signal?
- Who is involved in assessing the risk?
- Would it depend on whether any changes to behaviour ameliorate the risk?
- What are the risks of communicating potential safety issues that turn out to be false?
- Should the issue have the potential to affect a health professional's decision to prescribe the medicine?
- Should there be a difference in the stage at which a medical device alert is issued compared with a medicine? Particularly for implantable devices which cannot be easily removed.
- Similarly should safety issues with depot formulations of medicines be treated differently?
- What happens when the therapeutic product is only available in one country?

What kind of information should be provided?

- What is the best way of providing information without causing unnecessary alarm?
- What kind of information is useful?
- What was the basis for the decision?
- What is not known?
- Preliminary conclusions
- Why was another course of action not taken?
- Who reached the decision; it is more reassuring if an expert committee produces recommendations?
- Whether to stop using the therapeutic product?
- Where to get more information
- Advise consumers to talk to their health professional if they have concerns.
- Provide updates when more information is available - should these be early warnings or a different type of communication?
- Provide review outcomes - should these be early warnings or a different type of communication?

How should an early warning be communicated?

- Paper based?
- Fax or email?

- RSS feeds or email subscription?
- Website only?
- Social media?
- Media/press releases?
- Should these be issued at a set time or as soon as they are ready?
- Is there a bad time/ good time to issue alerts?

How should an early warning scheme be promoted?

- Does it need a name and logo?
- Does it need promotion?
- What is the best way of promoting a new scheme?

Post implementation of an early warning system

- Should the success be audited? How?
- How should questions and answers regarding the early warnings be managed?