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

Joint TGA and Medsafe Workshop

Early Warning System for Potential Safety Signals associated with Therapeutic Products

Summary of themes identified by participants

Contents

Introduction

TGA and Medsafe jointly hosted three workshops designed to obtain feedback from stakeholders on the proposal for a joint early warning system for safety signals associated with therapeutic products. The workshops were held on:

- Monday 16 April 2012 in Sydney, Australia
- Tuesday 17 April 2012 in Melbourne, Australia
- Tuesday 24 April 2012 in Wellington, New Zealand.

The aim was to identify basic principles and themes that would be important to such a scheme and enable the scheme to meet stakeholders' needs. The purpose of the workshops was not to decide on a particular methodology for an early warning system.

Participants were asked to provide feedback based on three possible scenarios.

Scenario one

To alert health professionals and consumers to **all** safety signals as soon as possible after detection. To include all (serious and non-serious) potential safety issues identified from spontaneous reporting and other sources.

Scenario two

To alert health professionals and consumers to all **serious** safety signals as soon as possible after detection. To include all serious potential safety issues identified from spontaneous reporting and other sources.

Scenario three

To alert health professionals and consumers to safety signals **requiring a change of behaviour** to ensure safe use of a therapeutic product. To include all serious issues after initial review and those which are likely to result in significant changes to the product information or the way the product is used.

Participants were asked to discuss a number of aspects, with respect to the different scenarios. Feedback was sought on when a safety signal should be communicated, what information should be communicated and how warnings should be sent to stakeholders. Participants were also asked how an early warning scheme should be promoted and how the success of the scheme could be measured.

This document summarises the comments and the themes identified by participants at the workshops.

Question 1: When to communicate?

Participants were asked to consider three main points.

- What are the advantages/disadvantages of communicating at this stage for consumers, health professionals and industry?
- Should the timing of communications differ for known information (i.e. an increased rate of reporting of an adverse event in the product information) vs. unknown information (i.e. reports of an unusual adverse event not associated with the therapeutic product)?
- Should the timing of communications differ for medicines and medical devices?

The following themes were identified.

Advantages

Several advantages were identified which were common for all scenarios.

- Improved patient safety and health outcomes: Early warning of safety signals would assist clinical decision making around the benefits and risks of treatments for individual patients. Adverse reactions may be avoided by changes in use of therapeutic products by health professionals and consumers.
- Enhanced interactions between health professionals and patients: Participants considered that publication of early warnings would increase and improve interactions between health professionals and patients.
- Increased transparency: Participants considered that an increase in transparency will improve confidence and trust in the health system. Consumers and health professionals will be better informed which could reduce the risk of the impact of emotive based media stories. Participants considered that poor media reporting of issues could result in patients stopping treatments which would be detrimental to their health. Participants noted that if everyone has access to all the information this would enable them to make informed decisions around their treatment choices.
- Improved interactions between the regulator and stakeholders: An early warning system may provide regulators with additional data. Participants considered that an early warning system would stimulate reporting of adverse events to therapeutic products. Alerting industry to potential safety signals would mean that industry would investigate/validate them and provide further information.
- Improved health literacy: An early warning scheme should lead to an improved understanding of the benefits and risks of therapeutic products. Participants thought that an early warning system would result in more responsible and accurate media reporting of these issues.
- Improved communication: Participants considered that the scheme would allow dissemination of proactive messages which would better counter misinformation and alarmist reporting than reactive messages.

Disadvantages

A number of disadvantages to an early warning system were highlighted. In general the disadvantages were considered to be most pertinent to scenario one.

- Risk of anxiety for consumers: Participants felt that there is a risk of panic/confusion/anxiety for consumers if early warnings for *all* potential safety signals are widely publicised. There is also a risk that patients will consequently stop using therapeutic products with the possibility of subsequent harm. Participants felt that it might be difficult to grade the importance of issues for consumers.
- Burden for health professionals: There may be an increase in workload from patients being directed to health professionals for advice following an early warning. Health professionals may need additional education so they could inform patients about warnings. Participants felt that health professionals may be confused about what to tell patients. It was also felt that there could be resource implications if changes in clinical practice were required.
- Impact on Regulators: Participants considered that an early warning system may impact on credibility if false signals are repeatedly publicised. The scheme will mean that the regulator will require additional resources. Participants questioned if there were legal implications for signals that subsequently were not verified.
- Impact on Industry: Participants noted that there may be a commercial disadvantage for companies whose products are highlighted by the scheme and that follow up communications should be provided particularly for signals which are communicated early or turn out to be false, to allay concerns.
- Communication issues: Participants considered that stakeholders may require additional education in order to understand the context and messages of an early warning system. Participants warned that there is a risk of information overload/alert fatigue resulting in important messages being ignored. The risk of inconsistent messages/reactions was also raised. It was noted that delays in communication could allow poor quality information to circulate from alternate sources.

Timing of warnings

Participants had a number of comments around the point at which warnings should be issued.

- Nature of the safety concern: Participants considered that the timing should be linked to whether a change in behaviour is required, the risk and seriousness of the safety concern and whether there was prior knowledge around the concern. There was a difference of opinion as to whether known risks or new risks should be communicated earlier. Concerns with new products may need to be communicated earlier and there should be a higher index of suspicion for these products. Risks

arising from long-term use may need different considerations. Participants also highlighted off-label use as a consideration for the timing of communications.

- Staged Communication. There was some disagreement as to who should be notified when. Some participants thought industry should be informed of very early signals, then health professionals, and then consumers. It was suggested that the process should be that once a signal was identified (by TGA/Medsafe), the information should be reviewed and passed to states/territories/other relevant government organisations as well as sponsors and regulators. The balance of benefits and risks would then be decided by TGA/Medsafe prior to communication with health professionals (so they can prepare to respond and support consumers) and then consumers. TGA and Medsafe should then provide follow up when available. Other participants considered that all stakeholder groups should be notified at the same time, as early as possible or that sponsors and health professionals should be notified at the same time followed by consumers.
- Speed: Participants suggested that communicating early warnings only after the issue has been reviewed will result in fewer warnings about non-valid signals. However if there is a delay in communication this will attract criticism. The regulator will need to progress and inform stakeholders about issues in a timely fashion.
- Caveats: Participants pointed out the need to consider the consequences of the warning e.g. reduction in vaccination. If the signal is communicated too early there may not be enough information. Regulators will need to consider if there has been stimulated reporting for known risks before issuing a warning.

Differences between medicines and medical devices

Participants commented on whether there were differences between medicines and medical devices that meant that the timing of early warnings would need to be different. There were some differences of opinion in this area. Whilst, in principle, participants thought there should be no differences, a number of potential differences pertinent to an early warning system were identified.

- Inherent differences: Participants noted that replacement costs may be more significant for medical devices as medicines are often easier to change than medical devices. In addition there are more alternatives for medicines.
- Monitoring differences: It may be more difficult to provide early warnings for medical devices as monitoring systems are not as mature as those for medicines. There are differences in the types of investigations performed for medicines and medical devices. Warnings with implantable medical devices require more information and validation prior to communication. The response time to suggested actions in any communication may be different.

- Risk based approach: Participants recommended a risk based approach to medical devices to account for differences between low risk products and high risk products such as implantable medical devices.

Other comments

A number of other comments to this question were provided by participants.

- Education: Participants considered that there was a need for clear definitions e.g. safety signal, serious signal, signal vs. noise to assist understanding of the system. The role of TGA and Medsafe will need to be clearly explained.
- Differences between Australia and New Zealand will need to be considered for the scheme to be successful.
- Content: Participants considered that there will need to be continuous updates to warnings, information should be provided regardless of whether further action is required and if no advice is available this should be stated. Communications will need to allow appropriate risk management for individual patients where possible.
- Advice, especially if clinical advice is needed, could come from recognised experts other than TGA or Medsafe.
- Any communications will need to provide a balanced view.
- Better liaison with the media is required to educate journalists and work towards more balanced reporting.
- The benefits of establishing registries for high risk therapeutic devices which could form both the source of the 'safety signal' and the data for informing the affected population.
- Need to ensure that significant non-serious signals are not missed.

Question 2: What to Communicate?

Participants were asked to consider three main points.

- What information would be required for the different stakeholder groups (consumers, health professionals and industry)?
- Should communications differ for known information (i.e. an increased rate of reporting of an adverse event in the product information) vs. unknown information (i.e. reports of an unusual adverse event not associated with the therapeutic product)?
- Should the information communicated differ for medicines and medical devices?

Information for Consumers

Participants considered that the following information should be communicated to consumers.

- Information about the safety concern: Any communication should include information that the government/regulator has reviewed reports, that there may/may not be a causal relationship, what action is being taken by authorities in Australia/New Zealand and internationally, provide full details of the affected product, context to the issue and state the benefits of the product, to provide a balanced approach.
- Include actions to take: Consumers should be directed to see a health professional if they have concerns. Advice on whether to continue taking/using the product should be provided as well as direction on where to find additional information. It was also considered to be helpful to provide information for carers.
- Style: The level of information will depend on the seriousness of the signal. The text should provide a simple clear message in layman's terms. Fright factors should be avoided.
- General: Participants considered that there was a need to explain the regulatory system. Some participants thought that early signals should not be communicated to consumers. When communicating with consumers consumer advocacy groups could be utilised.

Information for Health Professionals

Participants considered that the following information should be communicated to health professionals.

- Information about the safety concern: Communication should include detailed information on the signal i.e. what is known, whether it is considered serious/non-serious. The risk should be outlined with specific figures, the context and any confounding factors, the benefit/risk outlined and all information on the product identification provided. Participants considered that it would be helpful to provide a

copy of all publicly available information (or references), although not necessarily in the main document. In addition, participants thought it would be helpful to state the source of information, what steps the regulator is taking and an outline of what is not known. Participants considered it important that health professionals were advised of the communication to consumers.

- Include actions to take: Health professionals should be advised of any actions they need to take. This should include whether health professionals need to contact patients, this is anticipated to only be necessary for significant urgent risks. Direction on where to find additional information should be provided.
- Style: Participants recommended a clear bulleted format. The main messages should be stated at the beginning and further details near the end with links to additional information if needed. Catchy titles are helpful to stimulate busy professionals to read the contents.
- General: Participants considered that an aim would be to stimulate reporting. Participants also thought it would be helpful to provide information in electronic patient records. Participants considered that there would be a need to explain the regulatory system. Health professionals should also be aware of the communication plan and the communication should be consistent with that provided to other groups. It was also noted that it may be helpful to utilise health professional bodies.

Information for Industry

Participants considered that the regulator should seek early clarification/confirmation of potential safety signals with industry. It was considered that all information should be shared and further information requested. Participants recommended that the communication plan should be shared and the actions to be taken by the regulator should be stated. A question was raised as to whether all sponsors for medicines with generics should be contacted or only the sponsor of the innovator/brand product.

Differences for known events vs. unknown events

Participants considered that there may be some differences for known events compared with new risks. For known events it should be possible to reference existing information whereas for new risks, the evaluation will need to start from first principles. Participants considered that the reliability of the data source was more important for new risks. It was also noted that the types of patients involved may also be important. Finally participants noted that, especially for new risks, it was important to identify what additional research is underway.

Differences between medicines and medical devices

Participants considered that what to communicate remains the same, although implantable medical devices require special consideration. It was considered important to be able to provide batch numbers for medical devices. As previously discussed, the timing and actions may differ for medical devices, specifically implantable medical devices.

Other comments

Participants made the following other comments to this question.

- TGA and Medsafe should consider joint communications with other bodies and advice could come from recognised experts.
- Warnings could be linked to ARTG (Australian Register of Therapeutic Goods) entry/NZ approved product database, product information and consumer information.
- Participants considered that ways of making communications relevant to the recipient should be investigated. It was considered helpful to only inform relevant stakeholders for each issue rather than everyone for all issues. Participants considered that a two tier system might be helpful. It was proposed that there would be two types of issues, those the regulator is looking into and those requiring action. In this respect participants noted that a traffic light system may be useful.
- Participants considered that having a set lay out/template for communications is helpful as it makes it easier to determine if the issue is relevant and what actions are required.
- The information to be communicated and the mechanisms to communicate, may differ for prescription medicines, over the counter medicines and complementary medicines.
- Participants considered it would be important to state who was taking responsibility for actions.
- For some issues participants suggested that regulators may need to consider if there are alternative products available.
- There is a need to consider how communication is coordinated as health professionals do not like to read about issues in the media first.
- Updates to warnings will need to be provided as more information becomes available and where possible stakeholders should be advised when the next update will be communicated.

Question 3: How to Communicate?

Participants were asked to consider three main points.

- Which method/s would be used most by the consumers, health professionals and industry?
- Would the method/s of communication differ for known information vs. unknown information?
- Would the method/s of communication differ for medicines and medical devices?

Consumers

Participants considered that the following communication methods would be used by consumers. It was noted that forms of communication may change according to patient demographic.

- Media: Articles in newspapers, on TV and radio would be accessed by consumers.
- Electronic communication. Participants considered that consumers would access websites, sign up to RSS feeds, read emails, listen to podcasts and read blogs.
- Social media. Consumers were considered by participants to use social media forums such as Facebook and twitter.
- Smart phone apps. For example an app where patients can register their medicines and medical devices and then only receive relevant warnings that involve the medicines and medical devices used by them.
- Consumer organisations, cultural groups, other government organisations or patient registries may have links to consumers and be able to disseminate information.
- Elderly may need to be contacted through GP or consumer groups.

Health Professionals

Participants considered that the following communication methods would be used by health professionals.

- Electronic communication: Participants recommended that GPs are contacted by fax for urgent issues. Prescribing/dispensing software could be used to display warnings.
- Existing alert systems: Participants recommended using professional bodies' communication systems and existing alert systems. In New Zealand the Healthlink email system could be used for urgent warnings.
- Web based and email: Participants suggested that emails to procurement departments and state health departments could be used; an email subscription/ distribution list could be created. TGA and Medsafe websites could allow health professionals to subscribe to alerts and/or RSS feeds.
- Smart phone apps.

- Other systems: Participants mentioned that warnings could be communicated at conferences, though MIMS, treatment guidelines, New Zealand Formulary and announcements from the Chief Medical Officer.

Industry

Participants considered that industry could be informed directly through phone/email but a point of contact would need to be established. Other communications could be through the industry associations, websites and email subscription.

Differences for known events vs. unknown events

Participants did not identify any differences.

Differences between medicines and medical devices

Participants did not identify any differences.

Other comments

Other comments were provided by participants to this question.

- An early warning system should be a graded system dependent on risk to public, that is targeted i.e. alert the right people at the right time. It will require robust contact databases.
- An early warning system will require regulator infrastructure and a dedicated team.
- An early warning system should have a brand/recognisable visual style to aid in the communication and promotion of the system.
- Participants recommended that TGA and Medsafe look how other systems put out alerts i.e. European Medicines Agency.
- Participants considered that the system will need a trial run.
- Participants recommended following up an immediate alert with paper back-up e.g. *Medicines Safety Update*/*Prescriber Update*.
- Participants considered that a specific website (or page) should be the primary source of information that all systems link back to.
- The M^2 scheme currently run by Medsafe was considered by participants to be valuable and a positive step in helping to keep stakeholders informed.
- Participants considered that a scheme will be helpful to improve relationship with media.
- The recommendations of recent reviews regarding the communication by the regulator should be considered.

Promotion of the Scheme

Participants considered that there were two main aspects to promoting a scheme. Firstly to create a brand as a brand name/recognisable visual style will aid communication and promotion. Branding should also be considered for the priority of the warning e.g. a traffic light system.

Secondly participants made suggestions on how to raise awareness of a scheme.

- Ministerial Announcement: Interviews with relevant Ministers on TV, radio or in newspapers.
- Education: For example, include information on the scheme in education programmes e.g. health literacy initiatives, undergraduate health science curricula and professional education schemes.
- Face to Face communication: Participants suggested promoting via 'in–person' mechanisms e.g. have credible ambassadors as spokespeople, regulators to attend health conferences, use road-shows and have demonstrations in pharmacies or supermarkets.
- Use existing information sources: Participants recommended providing information about the scheme on existing systems that health professionals access for information on therapeutic products e.g. pathology request forms, prescribing software, dispensing software, health records, Medicare online systems, New Zealand Formulary, medicines labels, medical device information sheets.
- Use existing groups: Promote via professional and consumer groups e.g. Colleges, Pharmaceutical Society, regional healthcare organisations, health charities, consumer advocacy groups. Promotion could be via the group's electronic communication systems, local meetings, conferences or via the group's print media.
- Print Media: Participants suggested placing an advertisement in different print media e.g. newspapers, professional journals and medical press. Provide promotional pamphlets/posters to doctor's surgeries and pharmacies. Have pharmacists include a leaflet with the product information given with dispensed medicines. Write directly to health professionals.
- Television/Radio: Place an advertisement on TV and radio. Also use health TV playing in doctor's surgeries. Use sports personalities to promote the scheme.
- Publicise benefits of the scheme. Use a case study where the early warning system benefited a person and promote to TV/radio news/current affairs programmes. Promote a similar good news story to glossy magazines. Get reference to the scheme included in TV programmes such as soap operas.
- Internet and email: Send emails to current subscribers promoting the scheme. Include information on the scheme on regulators' websites and ask other relevant websites (e.g. professional groups other government agencies) to link to the information. Run a webinar on the scheme.

- Social media. Post a story about the scheme on Facebook and twitter.

Measuring the Success

Participants suggested different methodologies and outcome measures that would be useful to measure the success of an early warning system.

- Market research: Participants considered that this can provide useful qualitative information through the use of focus groups and surveys. These tools could be used to determine if the information provided is useful.
- Surveys: A feedback form or Survey Monkey could be used to obtain information on the usefulness of the scheme and whether stakeholders changed their behaviour. These tools could be provided in doctors' surgeries, pharmacies, with recalls or displayed on the website.
- Studies: Participants suggested using epidemiological study methods to measure outcomes such as changes in prescribing. Study changes in numbers and quality of adverse reaction reports. For example, ACC (Accident Compensation Corporation) and PBS (Pharmaceutical Benefits Scheme) data could potentially be used to measure changes in patient harm.
- Measure awareness: Participants considered that awareness could be measured using read receipts on emails, measuring the number of media articles and quality of these articles, using Google ads or measuring an increase in health literacy.
- Review accuracy of the scheme: Participants suggested identifying if any safety signals were missed and how many false positives were communicated. Another measure would be to compare the output from the system with other regulators.

Other comments included that a successful scheme would lead to decreased crisis response activities and that measurement should continue over time.

Glossary

Term	Definition
Adverse event	Any untoward medical occurrence in a patient who has used a therapeutic product and which does not necessarily have to have a causal relationship with this therapeutic product.
Adverse reaction	An unintended and noxious effect that is attributable to a therapeutic product used correctly.
Generic product	A therapeutic product comparable to the innovator/brand product.
Health literacy	An individual's ability to read, understand and use healthcare information to make decisions and follow instructions for treatment.
Innovator product	The product first authorised for use. When a substance has been available for many years it may not be possible to identify an innovator product.
Medsafe	New Zealand medicines and medical devices safety authority. Medsafe is a business unit of the Ministry of Health and is the authority responsible for the regulation of therapeutic products in New Zealand.
Safety signal	New information that suggests a new potentially causal association, or new aspect of a known association, between an intervention and an event(s) that is judged to be of sufficient likelihood to justify further action to verify.
Serious (safety signal)	Any untoward medical occurrence that results in: death, hospitalisation (or prolonged hospitalisation), persistent or significant disability, a congenital abnormality, or is life threatening, or is medically significant.
Sponsor	The company responsible for distributing a therapeutic product.
Spontaneous report/notification	An unsolicited communication to a company, regulatory authority, or organisation that describes an adverse reaction in a patient given one or more therapeutic products and which does not derive from a study or organised data collection scheme.
TGA	The Therapeutic Goods Administration is Australia's regulatory authority for therapeutic goods. TGA carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard with the aim of ensuring that the Australian community has access within a reasonable time to therapeutic advances.
Therapeutic product	Any product for which therapeutic claims are made.

List of Participating Organisations

Australia

Apotex Pty Ltd
Arthritis Australia
Audiology Australia
AusBiotech
Australian and New Zealand College of Anaesthetists
Australian College of Cosmetic Surgery
Australian Competition and Consumer Commission
Australian Consumers Association (Choice)
Australian Homeopathic Association
Australian Medical Association
Australian Orthopaedic Association
Australian Self-Medication Industry Inc.
Australian Society of Plastic Surgeons Inc.
Boehringer Ingelheim Pty Ltd
Cancer Voices Australia
Clinical Oncology Society of Australia
Complementary Healthcare Council of Australia
Consumer Health Forum of Australia
Department of Health and Ageing
Department of Health New South Wales
Department of Health Queensland
Department of Health South Australia
Department of Health Victoria
Department of Health Western Australia
Ensign Laboratories Pty Ltd
Generic Medicines industry Association of Australia
Medicines Australia
National Prescribing Service
NSW Therapeutic Advisory Group
Pharmacy Guild of Australia
Public Health Association of Australia
Royal Australasian College of Physicians
Royal Australian and New Zealand College of Psychiatrists
Royal College of Pathologists of Australasia
Therapeutic Guidelines Ltd

New Zealand

Best Practice Advocacy Centre
Canterbury District Health Board
Capital and Coast District Health Board
Health Quality Safety Commission
Immunisation Programme
Medicines Adverse Reactions Committee
Medicines New Zealand
Medical Technology Association of New Zealand
New Zealand Formulary
New Zealand Pharmacovigilance Centre
New Zealand Self Medicating Industry
PHARMAC
Pharmaceutical Society of New Zealand
Roche Products NZ Ltd
Royal Australasian College of Physicians