Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Evaluating the feasibility of a new-to-market risk communication scheme for therapeutic goods

Public consultation paper

Version 1.0, May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

Version history

Version	Description of change	Author	Effective date
V1.0	Original Publication	Management and Co-ordination, Office of Product Review	06/05/2013

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Evaluating the feasibility of a new-to-market risk communication scheme for therapeutic goods

Background

In 2010, the TGA undertook a review of the way it communicates its regulatory processes and decisions, with the aim of improving its transparency. One of the recommendations of the review was that the TGA undertake a feasibility study of a new-to-market risk communication scheme for therapeutic goods. The panel who conducted the review noted that there appeared to be a lack of public awareness of the uncertainties about the safety profiles of medicines early in their lifecycles, and felt that a risk communication scheme for new products could help to encourage public understanding of safety profiles.[1]

The TGA is currently evaluating the feasibility of implementing a new-to-market risk communication scheme, and will provide its evaluation to Government for consideration.

About the consultation

The purpose of this consultation is to seek views from interested parties on the value, feasibility, design and impacts of a new-to-market risk communication scheme.

The TGA will also hold consultation workshops in May with peak bodies representing consumers, health professionals and the therapeutic products industry, and providers of therapeutic product information. Workshop outcomes will be published on the TGA website. Organisations represented at the stakeholder workshops are not expected to also provide a written submission.

Timetable

Document released for consultation on **13 May 2013**.

Interested parties should respond by close of business **13 June 2013**.

Feedback will be released following consideration of submissions.

Content of submissions

Submissions may address any issues relating to a new-to-market risk communication scheme. In particular, the TGA invites comment about:

[1] Panel to Review the Transparency of the Therapeutic Goods Administration. Review to improve the transparency of the Therapeutic Goods Administration: final report. June 2011.

- whether or not you support the idea of a new-to-market risk communication scheme,
- the potential value and uses of a new-to-market risk communication scheme,
- how a new-to-market risk communication scheme might best be designed, promoted and evaluated, and
- how a new-to-market risk communication scheme will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.

How to respond

All submissions should be accompanied by a TGA submission cover sheet, available from the TGA website <http://www.tga.gov.au/newsroom/consult-opr-ntm-scheme-130513.htm#coversheet>. Submissions must include full personal or organizational contact details (including address, telephone number and email).

Electronic submissions are preferred and should be emailed to complianceconsultation@tga.gov.au. Please include 'New-to-market risk communication scheme' in the subject line of the email.

Alternatively, hard copy submissions may be mailed to:

Management and Co-ordination Section
Office of Product Review
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

What will happen

Submissions will be reviewed by the TGA and feedback on submissions will be provided through the TGA's Internet site.

Content of submissions will inform the further development of a model for a new-to-market risk communication scheme and the evaluation of its feasibility, including impacts on the regulated industry.

The TGA's evaluation report will be provided to Government by June 2014.

Confidentiality

All submissions will be placed on the TGA website unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked 'IN CONFIDENCE'. Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet.

For submissions made by individuals, all personal details other than your name will be removed from your submission before it is published on the TGA's website.

In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

Enquiries

Any questions relating to submissions should be directed by email to complianceconsultation@tga.gov.au or by telephone to 02 6232 8660.

Product lifecycle

The process for registering new products requires a balance to be struck between providing prompt access to new and potentially life-saving medicines and medical devices and conducting rigorous testing to gather comprehensive information about their benefits and risks. Once a product has been marketed, regulatory authorities continue to monitor it to ensure that new information that accumulates about it demonstrates that it meets acceptable standards of quality, safety and efficacy (performance). Early in a product's lifecycle, information about its safety profile, in particular, is relatively limited. The longer a product is on the market, and the more people who use it, the more comprehensive our understanding of its safety profile.

Development and testing of new products

Potential new medicines are tested first in animals, before being cautiously tested in a small number of healthy people (usually 50–150 people). If these tests are successful, the candidate medicine is then tested in a larger number of people (100–200 people) with the target condition. These early phases of testing help to build a picture of the medicine's side effects and beneficial effects at various doses. The medicine is then tested in hundreds or thousands of people with the target condition to gather more information about its safety and efficacy. Often, a medicine that is already available to treat one condition is tested in trials for a different condition. For example, many medicines that were originally used to lower blood pressure were subsequently tested for heart failure.

Manufacturers of medical devices must be able to demonstrate that devices they make perform as intended and produce benefits that outweigh their risks for the expected lifetime of the product. For new medical devices that are versions of existing medical devices, manufacturers can use information about the performance of the existing devices to help to demonstrate that a device meets the requirements for marketing. For novel types of medical device, however, manufacturers need to undertake testing to gather evidence to support an application for marketing. Prototypes of new types of medical device are usually tested in laboratories and/or in animals to refine and improve them before they are tested in clinical settings. The scale of testing in people can vary widely depending on what the medical device is to be used for. A device might be tested in fewer than 100 patients with no comparison group, or it might be subjected to a rigorous randomised controlled trial of hundreds of patients.

Before a medicine or medical device can be supplied in Australia for a particular use, its sponsor must make an application to the TGA demonstrating that the product meets the requirements for marketing - particularly that it meets acceptable standards of quality, safety and efficacy (performance) for the intended use. If the application is successful, then the product can appear in the Australian Register of Therapeutic Goods (ARTG). The ARTG records the therapeutic products that can be imported into, supplied in, or exported from Australia.

Safety monitoring of marketed products

Regulatory authorities monitor the safety of products once they have been made available for use. Monitoring is most intensive for newly available products. Post-marketing

monitoring is important because information accumulates about the benefits and risks of a product throughout its lifecycle. Information gathered before a product is registered is limited by the way in which products are tested.

For example, trials of new medicines:

- do not include all of the different types of people who might eventually use the product and who might be more susceptible to some adverse reactions, such as older people, children, pregnant women, or people with other medical conditions or who are taking other medicines;
- usually do not continue for long enough to detect problems that might develop after a long time; and
- do not include enough people to detect problems that happen rarely.

Testing of medical devices before marketing might not uncover, for example:

- failures of products that are intended to be used for a long period of time;
- problems with the way health professionals or consumers use the device; or
- interactions between different medical devices.

Below is a summary of the main safety monitoring methods used by the TGA. The approach taken by the TGA to safety monitoring is further described in the *Therapeutic Product Vigilance*, which is available from the TGA website <www.tga.gov.au/safety/tga-therapeutic-product-vigilance.htm>.

Adverse event reports from users

An important method used for monitoring all types of therapeutic products is collecting and analysing reports of problems from health professionals and the public. The TGA, like other regulators, encourages users of therapeutic products to report suspected problems with them. Reports are used to identify potential safety issues with therapeutic products, which can then be investigated to establish the possible role of the product in causing the adverse event.

Risk management plans for medicines

Sponsors of certain prescription medicines are required to provide risk management plans as part of applications for registration of these medicines. Risk management plans set out the risks known or thought to be associated with the medicine and the plan for monitoring and collecting more information about them. Such information might be collected from adverse event reports, clinical trials, observational studies, or other methods. Risk management plans also outline the required risk minimisation activities for the medicine. Implementing the risk management plan becomes a condition of approval. The risk management plan and its updates cover the entire life cycle of the prescription medicine. The TGA can request that a sponsor provides a risk management plan for a medicine that is already marketed.

Sponsors' obligations

Sponsors are required to report to the TGA adverse events of which they become aware. For medicines and vaccines, sponsors are required to report serious adverse reactions and significant safety issues within designated timeframes, and must report non-serious adverse reactions on the TGA's request. For medical devices, sponsors are required to report adverse events associated with their medical device that led to or might lead to death or serious injury.

Sponsors of certain new medicines and medical devices are also required to supply regular reports to the TGA of their products' safety. Periodic safety update reports (PSUR) must be prepared annually by sponsors of prescription medicines for at least the first three years of a medicine's registration. PSURs aim to establish whether safety information collected during the reporting period is consistent with previous knowledge of the medicine's safety profile. Sponsors or the TGA may identify changes required to the Product Information or other actions required to address safety issues arising in the PSUR.

Sponsors of higher risk medical devices (defined as active implantable medical devices, class III medical devices, or implantable class IIb medical devices) are required to submit three consecutive annual reports to the TGA following inclusion of the device in the Australian Register of Therapeutic Goods. The reports must include all complaints received by the manufacturer relating to problems with the use of the device that have been received by them over the year. Annual reports are reviewed by the TGA and any issues arising are discussed with the sponsor.

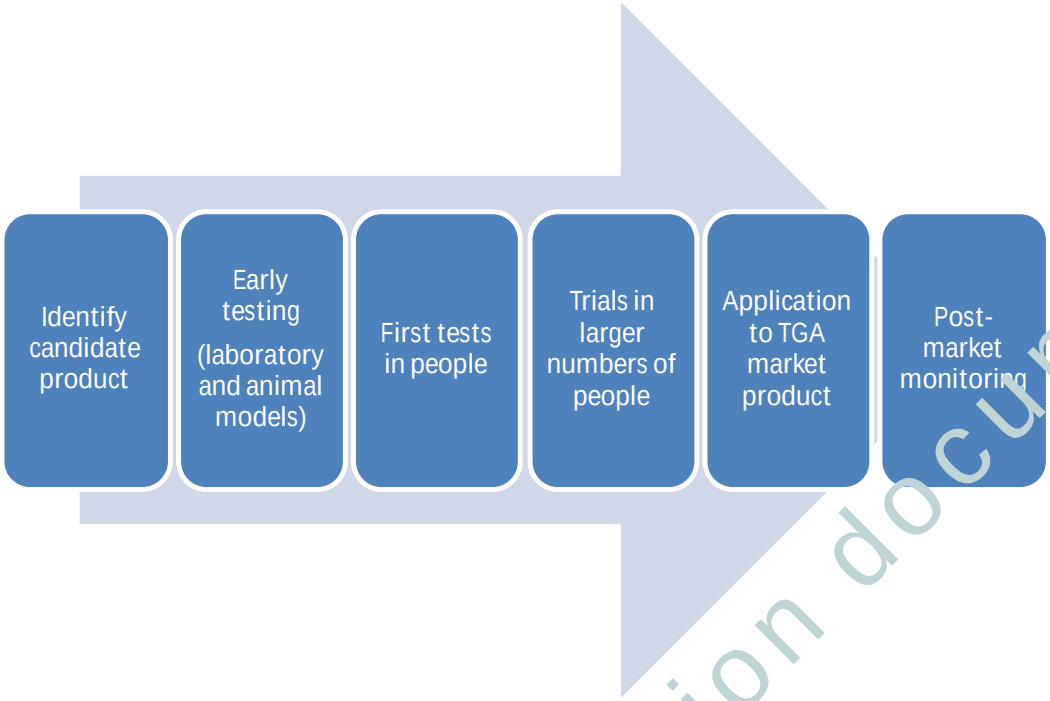
Addressing new information about a therapeutic product

As information about a new product accumulates, new problems might become apparent. For example, a previously unknown side effect to a medicine might be identified, or a medical device might be found to fail under certain conditions. The regulator must ensure that accumulating evidence demonstrates that the product meets acceptable standards of quality, safety and efficacy (performance), and that users of therapeutic products have access to complete information about their possible risks and benefits, so that they can make informed choices.

The TGA can address newly identified concerns relating to quality, safety and efficacy (or performance) of therapeutic products in various ways. For example:

- the TGA and/or sponsor might alert health professionals and consumers to a suspected safety issue that is being investigated,
- a side effect might be added to the Product Information and Consumer Medicines Information,
- the Instructions for Use for a medical device might be updated with new warnings,
- a new contraindication might be added to the Product Information and Consumer Medicines Information if the balance of benefits and risks is found to be unfavourable in particular types of patients (such as those with certain other medical conditions),
- the inclusion of a medical device in the ARTG might be suspended so that the device cannot be supplied while a problem with its performance is addressed, or
- a medical device might be recalled so that the manufacturer or sponsor can undertake repairs to prevent or fix a fault.

Figure 1: Product lifecycle



What is a 'new-to-market risk communication scheme'?

A new-to-market risk communication scheme is designed to signal to people that a particular therapeutic product is new or is newly available for a particular use. In other schemes, this has been done by placing a symbol next to the name of the product when it appears in certain information sources. For example, in the United Kingdom, a small black triangle is placed next to the name of new medicines in books and databases that are commonly used by doctors, pharmacists and nurses (see *International examples*).

A new-to-market risk communication scheme is not intended to alert people to specific known or suspected risks associated with a product. The Product Information and Consumer Medicines Information provide information about known risks associated with a medicine. The Instructions for Use provide information about known risks associated with medical devices. The TGA is currently developing a design for an Early Warning System to alert the public to potential safety concerns with medicines and medical devices. Box 1 sets out the differences between the Early Warning System and a new-to-market risk communication scheme.

Box 1: Comparison of a new-to-market risk communication scheme and an early warning system

New-to-market risk communication scheme	Early warning system
Selected new products (or products used in new populations or for selected new indications) Alerts public to uncertainty about overall safety profile of a product. Appears as symbol next to product name in various sources. Product would remain in the scheme for years, until overall risk–benefit profile better understood. Action for consumers / health professionals is identical for all included products: to report adverse events and to be aware of uncertainty.	Any therapeutic product, regardless of point in lifecycle, for which a signal has been detected. Alerts public to a safety signal in relation to a product Appears as alert-type communications published on websites, etc. Signal would remain in system for duration of investigation (probably months in most cases). Actions for consumers / health professionals are tailored to the specific safety signal and product in regards to taking specific action to avoid or detect a possible safety issue. All communications will include the action of reporting suspected adverse events.

Why might it be important to tell people which products are new?

There are a number of possible benefits of implementing a new-to-market risk communication scheme.

Transparency

A new-to-market risk communication scheme is a way to signal to users of therapeutic products which products have been available for a relatively short time. It could also be used to indicate to users which products are subject to certain monitoring activities (for example, a requirement to provide regular reports to the TGA).

Supporting quality use of medicines and medical devices

A new-to-market risk communication scheme could help to support quality use of medicines and medical devices by serving as an indicator to health professionals and consumers making choices about therapeutic products to consider 'newness' and potential uncertainty when weighing the benefits and risks of a product for an individual. Such a scheme could help to promote discussions about therapeutic product choices between health professionals and consumers.

A new-to-market risk communication scheme could assist in encouraging a more balanced view of the benefits and risks of new products by addressing misconceptions of some people that new products always provide a benefit over existing products.

Inclusion in a new-to market risk communication scheme for therapeutic goods could be a risk minimisation activity included in the risk management plan for a new medicine.

Better targeting of adverse event reporting

A new-to-market risk communication scheme could be used to encourage health professionals and the public to submit reports to the TGA about adverse events associated with new products.

Potential risks of a new-to-market risk communication scheme

Possible risks of a new-to-market risk communication scheme include that:

- some people might perceive a product's inclusion in the scheme as meaning that the product should be avoided, and
- there might be fewer adverse events reported that relate to products not included in the scheme if people perceive that the TGA is only interested in reports relating to new products.

International examples

The United Kingdom's Black Triangle Scheme indicates to health professionals which new drugs and vaccines are being intensively monitored by the national regulator (the Medicines and Healthcare products Regulatory Agency, or MHRA) to confirm their risk–benefit profiles. There has been no published evaluation of the Black Triangle Scheme, although the scheme has been in place for more than a decade. The Transparency Review panel heard that 80% of adverse drug reaction reports to the MHRA concerned 'black triangle' drugs.[2] The Belgian medicines regulator also publishes a list of 'black triangle drugs', which include medicines containing new active substances and new biological medicines for the first three years of marketing. The European Medicines Agency (EMA) intends to implement a similar scheme in 2013. Details of the UK and EMA schemes are in Table 1.

There are apparently no risk communication schemes for new medical devices operated by other regulators. However, a recent report from the UK House of Commons Science and Technology Committee[3] recommended that the UK adopt the Black Triangle Scheme or an equivalent system for medical implants where equivalence data has been used in place of clinical trials or evaluations of the specific implant, as a signal to health professionals that a particular product 'requires an intense level of reporting'. The committee felt that this would mean that devices approved on equivalence alone would be subject to stronger post-market monitoring. Although the committee did not specifically refer to the introduction of the Black Triangle Scheme as a transparency measure, they recommended that it be clear when medical implants have been approved using equivalence data and when clinical investigations have been conducted on that implant prior to market.

[2] Panel to Review the Transparency of the Therapeutic Goods Administration. Review to improve the transparency of the Therapeutic Goods Administration: final report. June 2011.
[3] House of Commons Science and Technology Committee. 'Regulation of medical implants in the EU and UK. Fifth Report of Session 2012-13. London: The Stationery Office Limited, 1 November 2012.

Table 1: Summary of international risk communication schemes for medicines

Scheme	Criteria for inclusion	Actions / outcomes	Communications	Criteria for removal from scheme	Mandated by legislation?
UK Black Triangle scheme [Currently being phased out before introduction of European Medicines Agency's additional monitoring scheme.]	All newly licensed active ingredients* All biosimilars A product containing previously licensed active ingredients may be included if it is: a new combination, a new route of administration or drug delivery system, a significant new indication that may alter established risk–benefit profile, or an established medicine to be used in new patient population.	Health professionals and consumers are encouraged to report all suspected reactions to these products. Industry required to report all serious suspected adverse drug reactions to a black triangle product from within the UK and EU within 15 days.	Symbol (▽) appears next to drug name in: British National Formulary British National Formulary for Children Monthly Index of Medical Specialities, Association of the British Pharmaceutical Industry Medicines Compendium advertising material in *Drug Safety Update* (a monthly publication for health professionals from the MHRA).	Inclusion in the scheme is reassessed after 2 years. The symbol is removed when the safety profile of the drug is 'well established'.	No. Requirements for black triangle in advertising are in the industry code of practice.

Scheme	Criteria for inclusion	Actions / outcomes	Communications	Criteria for removal from scheme	Mandated by legislation?
EMA additional monitoring scheme [Will be introduced in September 2013 as a result of the 2010 EU pharmacovigilance legislation.]	New active substances (mandatory)* All biological medicinal products (mandatory) Products with marketing authorisation granted subject to particular conditions (optional).† After marketing authorisation, if sponsor required to undertake a post-authorisation safety or efficacy study or to put in place a risk management system (optional).	Health professionals and consumers encouraged to report all suspected adverse reactions to these products. Regulatory agencies are advised to review the statistical outputs from EudraVigilance (the central database for adverse reaction reports to medicines licensed in the European Union) every 2 weeks for drugs on list.	Drugs appear on 'additional monitoring' list Symbol (▽) will appear in the Summary of Product Characteristics and Package Leaflets (equivalents of PI and CMI), followed by a statement explaining that the medicine is under additional monitoring, and encouraging health professionals and consumers to report adverse reactions.	New products will initially included for 5 years. Initial period of inclusion for other products decided on a case-by-case basis. Time on list depends on need for increasing awareness about safe and effective use of product and additional information to evaluate of the product, knowledge of the safety profile, etc.	Yes. Article 23 of Regulation (EC) No 726/2004 sets out requirement for EMA and Member States to set up, maintain and make public a list of medicines subject to 'additional monitoring'.

* known in Australia as 'new chemical entities' †conditions for safe and effective use, measures for ensuring safe use to be included in risk management system, post-authorisation safety study, post-authorisation efficacy study, compliance with reporting of suspected adverse drug reactions stricter than in the Regulations, conditional approval, marketing authorisation under exceptional circumstances, existence of an adequate pharmacovigilance system.

How might a new-to-market risk communication scheme work in Australia?

Below is a possible model for a scheme designed to alert consumers and health professionals to newly marketed medicines and medical devices. This model is intended to serve as a basis for public comment. It is based on the Black Triangle scheme that operates in the United Kingdom, and has been developed through discussions internally at the TGA.

Figure 2 on page 15 provides an outline of the model.

1. Selection of products for inclusion in the scheme

Criteria could be used to determine which products should be included in the scheme.

For medicines, these criteria could include, for example:

- all new chemical entities
- previously registered active ingredients for which registration is sought in a new indication, or for a new route of administration, combination, or dose form
- newly registered biological medicinal products
- newly registered vaccines
- after registration, the sponsor is required to submit a risk management plan that includes additional pharmacovigilance activities
- one of the TGA's expert advisory committees has advised the TGA to include a product

For medical devices, these criteria could include, for example:

- the product is a new class IIa or above home use medical device, or an implantable class IIb, class III or active implantable medical device, AND
- a TGA evaluator considers that it has a sufficiently different or uncertain benefit–risk profile to warrant inclusion in the scheme, OR
- one of the TGA's expert advisory committees has advised the TGA to include a product, OR
- the product has previously been included in the ARTG and inclusion is now sought for a new intended purpose.

Criteria would be needed to select biological and in vitro diagnostic medical devices for inclusion, if a scheme was to be implemented and covered these types of therapeutic products.

2. Communication to health professionals and consumers

The fact that a particular product is included in the scheme could be communicated to health professionals and consumers using a symbol next to the name of the product whenever it appears in certain sources. For example:

· Magixa ›

[Please note, this symbol (›) is presented for illustration purposes only]

These sources might include:

- The Product Information and Consumer Medicine Information (for medicines)
- Instructions for use and patient information leaflets (for medical devices)
- Prescribing and dispensing software
- Promotional and educational materials produced by the sponsor
- Product packaging
- Information sources commonly used by health professionals (such as MIMS, Australian Medicines Handbook, NPS information)
- The Australian Register of Therapeutic Goods
- The National Product Catalogue

3. Removal of products from the scheme

Products could be removed from the scheme automatically after a certain period of time.

Alternatively, the TGA could consider whether a product should be removed from the scheme after a certain period of time, or if it should remain in the scheme for a certain additional period of time. To make this decision, the TGA could consider things like:

- how many people had used the product,
- whether the sponsor had undertaken any postmarketing monitoring activities it had committed to (such as activities specified in a risk management plan), and
- whether there were any significant potential safety issues being actively investigated.

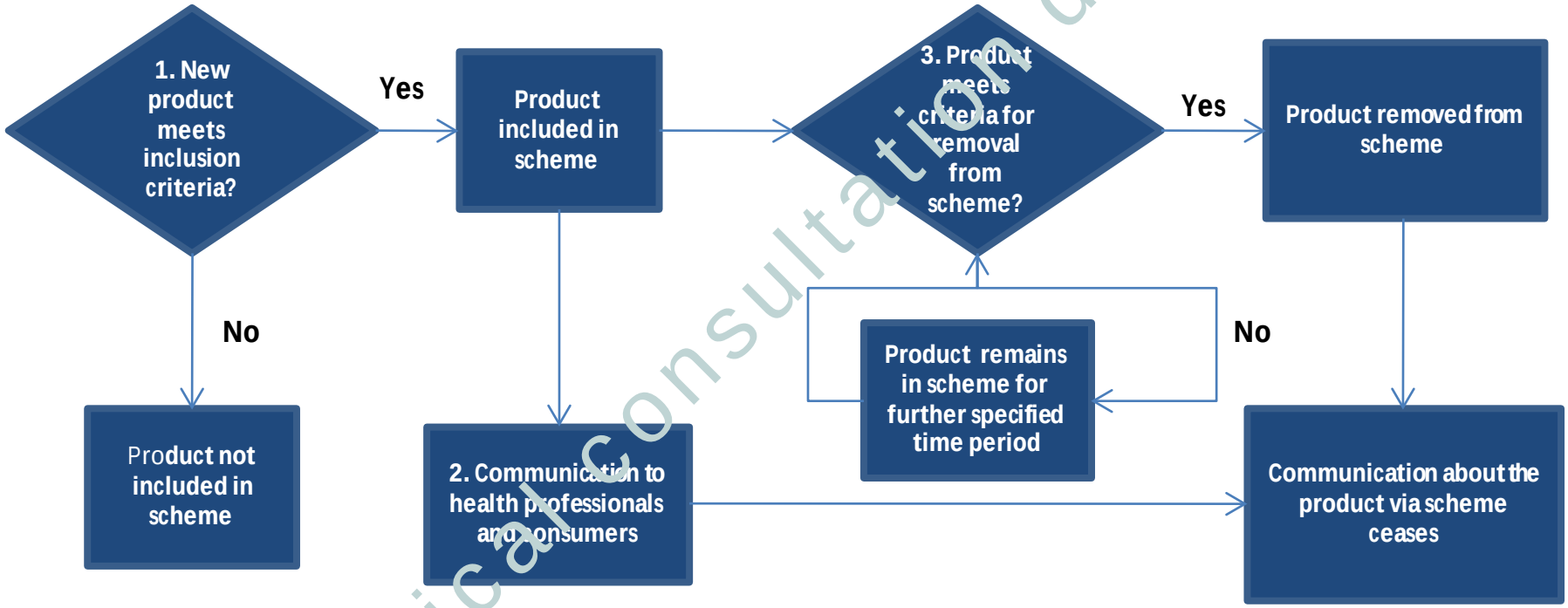
Communications about a scheme

If a scheme were to be implemented, it would need to be accompanied by activities to raise awareness of the scheme, and to explain its meaning.

Evaluation of a scheme

If a scheme were to be implemented, it would be advisable to evaluate whether people were aware of the scheme, and what effects it had on their knowledge, attitudes and behaviour.

Figure 2: Outline of a possible model for a new-to-market risk communication scheme



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Reference/Publication #