LEADING ARTICLE

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Risk Management from an Asian/ Pacific Rim Regulatory Perspective

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Abstract

This article reviews the state of adverse drug reaction monitoring in five Asian/ Pacific Rim countries (Australia, Japan, Malaysia, New Zealand and Singapore). Each country has an active pharmacovigilance programme managed by a national regulatory agency. Current methods for assessing risks and current methods used for risk management and communication are compared with the 'tools' used by the US FDA. Major positive attributes of the programmes in all five countries include active involvement of independent expert clinical advisory committees in identifying and evaluating risks through the assessment of reports of serious and unusual reactions, and regular communications about risks from the national agencies to doctors and pharmacists by means of pharmacovigilance bulletins. Most components of the risk-management toolbox are currently used, in some instances without legislated support. Variations in the way risk-management tools are implemented within individual national health systems are illustrated.

Medicines are given approval for marketing after a regulatory agency has decided that the benefits of a product outweigh the risks of its use. Often, the control or limitation of risks relies heavily on what advice is included in the approved labelling, data sheet and associated documentation for the medicine. During the postmarketing period, more information emerges about the risks of the medicine. Risk management has been described as the overall and continuing process of minimising risks throughout the lifecycle of a product to optimise its benefit/ risk balance.[1] Risk management involves:[2]

- risk assessment – identification, estimation and evaluation of risk;
- risk confrontation – determination of acceptable levels of risk in a societal context;
- risk interventions – actions to control risk;
- risk communication – a process for exchanging risk information;
- risk management evaluation – measurement of the effectiveness of the aforementioned activities.

Against this background, this paper aims to review the current state of risk management in five countries in Asia and the Pacific Rim. This region includes a large number of countries, ranging in population from the People's Republic of China (1284 million in 2002) to small independent Pacific Island countries with populations numbered in the thousands. The regional perspective is not uniform, but there are several common themes, as can be illustrated by consideration of the five countries that have been chosen because they are amongst those with the best-developed pharmacovigiliance sys-

Table I. Demographic and reporting information for five countries

Country	Population (millions)	Number of adverse drug reaction reports per year[a]			Frequency of expert advisory committee meetings (per year)	Frequency of bulletin sent to healthcare professionals (per year)
		health professionals	industry	consumers		
Australia	20.0	7324	3180	391	8	6
Japan	126.9[b]	4195	24221	0	10	12
Malaysia	23.0	875	130	0	6	3
New Zealand	4.0	3245	268	11	4	3
Singapore	4.18	1059	46	0	4	3

a Australia, Malaysia and Singapore: calendar year 2003; Japan: fiscal year 2002; New Zealand: July 2002–June 2003.

b Data from year 2000.

tems – Australia, Japan, Malaysia, New Zealand and Singapore.

An obvious characteristic shared by all of these countries is that they are not part of a multi-national drug regulatory system as exists in the European Union (EU) and, with the exception of Japan, are not members of the International Conference on Harmonisation. Malaysia and Singapore are members of the Association of South East Asian Nations (ASEAN), which is active in promoting harmonisation of pharmaceutical regulation amongst its members. The major ASEAN emphasis is currently on harmonised technical documents and assessments for drug registration.[3] The intention to create a single regulatory agency for Australia and New Zealand was recently announced;[4] however, currently, all five countries conduct their regulatory activities as individual countries and resources for postmarketing regulatory activities are generally limited.

Australia, New Zealand and Japan established spontaneous reporting schemes in 1964, 1965 and 1967, respectively.[5-7] The New Zealand centre was established at a university and is contracted by the national regulatory agency to collect and analyse adverse drug reaction (ADR) reports. In Japan, a new agency (Pharmaceuticals and Medical Devices Agency) commenced operations in April 2004 and may refine the current Japanese ADR reporting arrangements.

The centres in Malaysia and Singapore were established in 1987 and 1993, respectively. Both are vigorous centres and, like the other three countries, are active members of the WHO Collaborative Program for International Drug Monitoring. Table I summarises some basic information about each centre.

1. Monitoring of Reactions

At all of these five centres there is an emphasis on monitoring the adverse reactions reported in that country ('domestic reports') and a recognition that agencies with limited resources cannot, by themselves, gather and analyse large numbers of individual case reports of reactions in other countries ('foreign reports'). A marked preponderance of direct reports from healthcare professionals is a feature of all centres except Japan, where reports from industry predominate. All centres except Japan now have online electronic reporting available to healthcare professionals, while an online reporting system from pharmaceutical companies started in Japan in October 2003. Incoming individual case reports of reactions occurring within each country are reviewed on receipt by the professional staff (doctors, pharmacists) at the national pharmacovigilance centres.

2. Identifying Risks

A feature of all five countries is the existence of independent expert advisory committees actively involved in assessing drug safety, particularly the scrutiny of incoming ADR reports. For more than three decades, members of the Australian Adverse Drug Reactions Advisory Committee (ADRAC) have reviewed allocated batches of copies of incoming reports as part of their preparation for meetings,

which are held eight times a year. Members comment on reports of interest or concern during these meetings. The increased volume of reports in Australia in recent years now limits this individual case review to reports involving new drugs, serious reactions and a small number of other categories, but still amounting to about two-thirds of all incoming reports.

In Japan, the advisory committee has 64 members, comprised of 12 members who attend the regular meetings and 52 members who review case reports. Committee review is targeted at reports of reactions that may warrant labelling changes.

Although somewhat less exhaustive than in Australia, there is detailed review in Malaysia, New Zealand and Singapore by the expert ADR advisory committees of essentially similar types of individual domestic ADR reports – those describing fatal reactions, serious reactions, unusual reactions and, in Malaysia, reactions to newly marketed drugs.

Data-mining of domestic report databases is not used for routine review of reports in any of the countries, but has been used as a research tool in Australia.[8] New Zealand is the home of a long-standing form of prescription event monitoring (PEM) known as the Intensive Medicines Monitoring Programme (IMMP),which involves the prospective identification of cohorts of patients who have had prescriptions either issued or dispensed for the medicine being monitored.[9] There have been steps by a nonprofit organisation towards establishing PEM in Japan.[10] There is no programme in any of the five countries that is broadly equivalent to the US FDA's Cooperative Agreement Program for Pharmacoepidemiology, which funds epidemiological studies of identified risks with medicines.[11] These studies are usually undertaken using health maintenance organisation or similar databases which permit linkage of drug use, diagnoses and laboratory test results. Agency funding of research into specific safety issues has been limited to occasional research grants, such as a study of the safety of third-generation oral contraceptives in New Zealand and the exploration of the usefulness of a small medical record database in Australia.

The advent of periodic safety update reports (PSURs) has been a mixed blessing for the regional regulatory agencies. On the positive side, information in the same standard format that is provided to large agencies, such as the European Agency for the Evaluation of Medicinal Products, is also available to smaller regulatory agencies. On the negative side, the regular submission of PSURs in line with the European schedule can pose an overwhelming workload for a small agency. This has resulted in four agencies (Japan, Malaysia, New Zealand and Singapore) being selective in requirements for submission (table II). Australia has more extensive requirements for PSUR submissions and more detailed review of their content, but this review is still targeted at key information. Japan has the most intensive review, which includes a review of all labelling changes in countries other than Japan.

3. Estimating and Evaluating Risks

To date, none of the countries have required the submission of a company-prepared Council for International Organizations of Medical Sciences (CIOMS) IV or similar format benefit-risk assessment, although in a small number of instances companies have chosen to volunteer such a report. There are few examples of published CIOMS IV-style benefit-risk assessments undertaken by regulatory agencies.[12] To date, none of the agencies has undertaken a CIOMS IV-style assessment of its own volition, but all agencies have, of course, made their own assessments using other formats and criteria.

In making a benefit-risk assessment, information about national exposure to a medicine is an important resource, enabling assessments (albeit crude) of incidence of adverse effects. All five agencies are able to obtain sales information from sponsor companies, but are generally not able to use this in the public domain. In Australia and New Zealand, national data on dispensing of Government-subsidised prescription medicines are available, but these are

Table II. Registration (related activities)

Country	Submission of PSURs required?	Extent of review of PSURs	Registration includes phase IV study commitments?	Registration subject to regular review?	Pharmacovigilance department of agency involved in pre-marketing planning?
Australia	Yes – broadly similar to European Union	All reviewed – review targeted by pro-forma	Occasionally sponsor required to submit results of ongoing studies – rare for studies in Australia to be required	No – registration continues unless an issue provokes review	No – but anticipated in 2004
Japan	NCEs only	Detailed review including labelling changes outside Japan	Yes	Yes – after 6 years registration for NCE, after 4 years for new indication, and after 10 years for a new orphan medicine	No
Malaysia	NCEs only	All reviewed – focussed on key details, including overseas studies	No	Re-registration required after 5 years	No
New Zealand	No – sponsor company in NZ must hold and submit on request	Not applicable	Sponsors may be required to submit results of ongoing studies – full registration may depend on results. May also require IMMP monitoring	No – registration continues unless an issue provokes review	Only with regard to possible inclusion in IMMP
Singapore	Targeted drugs only	Detailed review only if there are major safety concerns	No	No	Yes

IMMP = Intensive Medicines Monitoring Programme; **NCE** = new chemical entity; **PSURs** = periodic safety update reports.

not comprehensive as they may not include such items as public hospital dispensing, medicines with a cost below the patient co-contribution or the Government subsidisation, or medicines not chosen for subsidisation. In Malaysia and Singapore, some insights are available from information about products supplied to government hospitals through tenders and contracts.

4. Use of Risk Communication and Risk Management Tools

Currently available risk communication and risk management tools have been broadly categorised as follows:[13]

- product labelling (warnings, black box, medication guides);
- 'Dear Healthcare Provider' letters (previously known as 'Dear Doctor' letters);
- educational programmes organised by sponsors;
- restricted distribution;
- drug withdrawal (product licence withdrawal).

All five countries have a national product monograph document for prescribers (variously known as the package insert, product information, summary of product characteristics or data sheet) which includes warning statements. In Australia, Japan, Malaysia and Singapore there is provision for boxed warnings in the product information document. In New Zealand, warning statements are usually highlighted in bold print.

Availability of a separate consumer medicines information (CMI) document has been a gradually introduced requirement in Australia. A CMI reflecting the content of the product information is now required for all prescription medicines and all of the pharmacist-only category of over-the-counter medi-

cines approved for registration since 4 July 1995. In New Zealand, the CMI is not required under legislation, but sponsors have been actively encouraged to prepare CMIs. There are 450 CMIs accessible through the website of the New Zealand regulatory agency (Medsafe). In Japan, the agency may request a company to provide a leaflet for patients. In Malaysia, the requirement for a CMI-like document has recently been introduced for new chemical entities, but is not compulsory. In Singapore, a somewhat different approach has been taken; a patient information leaflet (PIL) is required for all pharmacy and general sale list medicines, but only the package insert (patient information) is generally mandatory for prescription-only medicines. However, in some instances where information for the patient is deemed important because of the safety profile of the drug, a PIL is required for a prescription-only medicine. Isotretinoin is an example of such a medicine.

All of the agencies are able to request pharmaceutical companies to send a letter to doctors and pharmacists concerning a safety problem with a medicine. In addition, in Malaysia, Singapore and New Zealand, the regulatory agencies are able to issue their own 'Dear Healthcare Professional' letters to all doctors, dentists and pharmacists. All five agencies enjoy sufficient financial support to be able to send their own national pharmacovigilance bulletins to all doctors and pharmacists with frequencies between 3 and 12 times a year (table I).

To date, little formal regulatory use has been made of educational materials prepared by the sponsoring pharmaceutical companies. The recent registrations for restricted indications of thalidomide in Australia and New Zealand have been conditional upon the implementation of the 'Pharmion Risk Management Programme' (PRMP), which incorporates registration of prescribers, pharmacies and patients, and requirements for data collection. The PRMP is based on the 'System for Thalidomide Education and Prescribing Safety' (STEPS) programme that operates in the US.[14] Thalidomide is not currently registered in Japan, Malaysia or Singapore.

All of the agencies can take steps to restrict the classes of medical practitioners who can prescribe a particular medicine. In Japan, the restrictions are described in the package leaflet, but are not legally binding. In Australia, which is a federation with both Federal, State and Territory Governments, such a restriction may not be enforceable under Federal legislation, but has been achieved for a small number of drugs through the introduction of essentially identical controls in each State and Territory under the poisons and drugs control powers of each jurisdiction. These restrictions have sometimes been reinforced by limiting the national prescription subsidy to authorised prescribers. In New Zealand, a provisional approval for distribution of a medicine can include conditions as to who can prescribe the medicine and be reinforced through subsidy restrictions under the New Zealand prescription subsidy scheme.

Limiting prescribing rights to certain specialist groups may disadvantage patients, either because of a limited number of such specialists in a country or because of physical remoteness of the patient. Subsidy restrictions, rather than direct limitations on the right to prescribe, have limited usefulness if nonsubsidised private prescriptions are affordable, as can happen when generic versions of a product enter the market.

The nature of controls on prescribing in four of the countries is illustrated by the regulation of isotretinoin (table III). It may be noted that the controls implemented to achieve essentially the same goals are different in each country.

An important element in the contemporary approach to risk management is the measurement of the impact of the various regulatory tools that have been adopted. This has been an area of limited research in the Asian/Pacific Rim region principally because of the lack of comprehensive medicine usage databases. A study of the impact of changes in the approved indications and the national subsidisa-

Table III. Risk-management strategies: the example of oral isotretinoin[a]

Australia
Prescribing limited under individual State and Territory drugs and poisons control laws, consistent with a national recommendation:
available only on prescription of a specialist physician or dermatologist who must, for female patients of child-bearing age, exclude pregnancy and advise avoidance of pregnancy during or for 1 month after treatment
dispensed product must be labelled with warning statements about teratogenicity, avoidance in pregnancy
Pregnancy warning highlighted in consumer medicines information
Innovator provides consent from – other (generic) sponsors do not
National prescription subsidy limited to approved indication and to prescriptions complying with State and Territory law
Malaysia
Supply limited to:
dermatologist gazetted with the Ministry of Health, Malaysia or registered with the Academy of Medicine, Malaysia, Specialist Registry and approved by the Drug Control Authority
a hospital or institution maintained by the government having the services of a skin specialist or a registered medical practitioner with experience in dermatology and approved by the Drug Control Authority
Product container must be conspicuously and distinctly labelled with warnings that product is teratogenic and that pregnancy must be avoided during treatment and for at least 4 weeks after treatment
Detailed records of quantities received and supplied must be kept by prescriber and suppliers (importers/manufacturers/wholesalers), and submitted or made available for audit
New Zealand
No registration restriction on who can prescribe. However, statement in data sheet that "isotretinoin should only be prescribed by doctors who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risks of teratogenicity if isotretinoin is used during pregnancy"
Highlighted (boxed) pregnancy information in consumer medicines information
National prescription subsidy limited to prescriptions written by dermatologists
Singapore
The licence holder must ensure the signing of consent forms by prescribing physicians undertaking to:
exclude pregnancy before initiating treatment for female patients of child-bearing potential, and to ensure that these patients use an effective method of birth control during treatment and for a specific period after ending treatment
ensure that patients who have been prescribed the product receive a copy of the patient information leaflet
ensure that the product is only used for the approved indications
The licence holder must ensure the signing of consent forms by patients to:
undertake the responsibilities of keeping the prescribed product for their own use
undertake that they will not conceive during treatment and for a specified period after ending treatment (for female patients of child-bearing potential)

a Isotretinoin is not marketed in Japan.

tion on the dispensing of cisapride is in progress in Australia (Boyd I, personal communication).

5. Discussion and Summary

Risk management has been practised by medicine regulatory agencies in an increasing number of Asian and Pacific Rim countries for many years. All five countries reviewed have expert advisory committees which review important individual ADR case reports as part of their work, providing each agency with expert and practical clinical advice. These expert committees are valued greatly within each country. A high proportion of direct reporting from healthcare professionals occurs in four of the five countries. In Australia and New Zealand, it is felt that follow-up of potentially important reports, to obtain further information such as laboratory test results and outcome details, is more successful when dealing directly with reporters. The contributions of expert advisory groups and of direct reporting warrant formal assessment in terms of their contributions to identification of risks.

In all five countries reviewed, most components of the risk management toolbox exist and are used. Increased support in law for some tools may be valuable in some countries. The example of isotretinoin shows how countries need to adapt their approach to make what is essentially the same tool work within their own national healthcare system.

An important positive attribute in all five countries is that each centre is able to send bulletins and, in some instances, letters directly to doctors and pharmacists, promoting the existence of the national pharmacovigilance programme and highlighting contemporary risk issues with medicines. An important opportunity exists to evaluate the impact of this direct form of risk communication.

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