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# The Art and Science of Risk Management

## A US Research-Based Industry Perspective

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## Abstract

The research-based pharmaceutical industry in the US strongly supports the concepts of risk management and sees formal risk management as playing a major role in the development of safe medicines for the public, as well as providing a mechanism to ensure that decisions concerning individual drug benefit and risk are made based on scientific evidence. Safe medicines refer to those drugs whose benefits have been found to outweigh their risks when they are used according to the approved labelling. Risk management is the comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate and minimise risk throughout the life cycle of a drug so as to establish and maintain a favourable benefit-risk balance in patients. Although there are certainly a number of global risk management initiatives in place or being undertaken, harmonisation has yet to be achieved. Industry is faced with a variety of different risk management approaches and tools. There is a need to move the focus of risk management from the post-approval arena to earlier in the development process and tools need to be developed to support risk management throughout the lifecycle of a drug. The focus in the US on risk minimalisation strategies will also be an area for methodological development. A key factor in the success of overall risk management is the dialogue between industry and regulators throughout the development, review and marketing of the product. It is through such dialogue that appropriate, efficient and effective risk management strategies will be developed and implemented and the best decisions regarding the safe use of pharmaceutical products will be made.

Historically, the pharmaceutical industry has taken an active role in pharmacovigilance to assure the greatest benefit is derived from its products with the minimum risk to patients. Pharmacovigilance has evolved over time because of increased public awareness of the potential risks of drug therapy, through technology (such as the Internet), globalisation of the industry and changes in the regulatory environment. Greater expectations on the part of the regulators, along with advances in technology, have led to the development of different types of computerised databases for adverse event reporting. Further advances in technology have heightened interest and expectations in signal generation as well as hypothesis testing that is carried out through other tools. Consumers and the media have come to expect 'risk-free' medications, putting pressure on regulators and industry alike to ensure that pharmaceuticals 'do no harm'. Globalisation has resulted in the need to communicate with multiple regulatory bodies simultaneously, although the individual regulators may have different perspectives and requirements.

Recently, regulators have placed greater importance on the issue of the benefit-risk balance of pharmaceutical products, including a greater focus on recognising and, where possible, mitigating risk. In 1998 the Council for International Organizations of Medical Sciences (CIOMS) Working Group IV published the results of its efforts in a document entitled "Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals".[1] The document was intended to provide guidance to industry and regulators alike in establishing the balance between the benefit and risk of drugs in the post-approval timeframe. Particular emphasis was placed on evaluating safety signals that potentially impact the public's health by examining and analysing information from a variety of sources, including the evaluation of the safety of a drug in light of other available therapies.

Regulators in the US and elsewhere have long recognised the importance of the benefit-risk balance of pharmaceuticals. More recently, however, the need for risk management, as outlined in "Managing the Risks from Medical Product Use – Creating a Risk Management Framework: Report to the FDA Commissioner for the Task Force on Risk Management",[2] has been increasingly emphasised. In this document, the task force outlined changes that should be considered to improve the current passive system of postmarketing surveillance, which has as its core the voluntary spontaneous reporting system of the US FDA. The task force encouraged the development of a systems-based process in which the agency would have electronic access to safety information from a variety of sources. They envisioned a process where the FDA, with greater electronic tools available, would shift its role from passive risk assessment, with action through labelling, to a more proactive role that would include the re-evaluation of the benefit-risk balance in major, postmarketing decision making. Options that were discussed include: restrictions in use, restrictions in distribution, mandatory education programmes, slow rollouts of new products and review of other therapeutic alternatives. Some of these interventions have already been employed.

With the enactment of the 2002 reauthorisation of the Prescription Drug User Fee Act (PDUFA III), risk management now has a formal role in the development, review and approval of new drugs in the US. Under PDUFA III, for the first time revenue collected in the form of prescription drug user fees may be used for certain postmarketing risk assessment activities. In its goals for PDUFA III, the US Department of Health and Human Services included the development of formal risk management plans (RMPs) based on information developed on the new drug, to be submitted to the FDA during the pre-approval timeframe. Although such RMPs are voluntary, this recommendation brings risk manage-

ment into the pre-approval timeframe where potential safety signals can be explored, quantified and formally followed through the product's RMP. A well constructed and comprehensive RMP has the potential to result in earlier approval of drugs or approval of a drug that has a clearly defined safety risk. Both of these outcomes benefit the public health.

## 1. The Concept of Risk Management

Risk management as a concept can mean different things to different people. Some definitions have included only minimising risks; others focus only on the postmarketing period of a drug. We view risk management as a strategic endeavour across a continuum, encompassing many activities. The definition that we propose for the purposes of this article is 'the comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate and minimise risk throughout the life cycle of a drug so as to establish and maintain a favourable benefit-risk balance in patients'. This concept of risk management implies that there is an inter-related process involved, that there will never be 'zero risk' and that judgement and communication will be a necessary part of the plan. The Centers for Education and Research on Therapeutics has defined risk management as "a coordinated effort applied to the use of therapeutic agents that seeks to assure benefits to patients outweigh risks".[3] Although the language of the definitions may differ, all recognise that there are both risks and benefits inherent in therapeutic interventions and express the common goal of maximising the benefit while minimising risk. The focus of RMPs would usually be on those risks that are avoidable and serious; in essence, those that would tip the benefit-risk balance or have public health implications.

We see risk management as inclusive of risk assessment, continued data gathering, risk communication and other interventions, as well as plan evaluation. A key factor in the success of any risk management approach or strategy is to begin risk management as early as possible in the product's development. The FDA noted, in its recent concept paper on risk management programmes, that "FDA approval of a product means FDA believes that it is safe and effective for its labeled indications under its labeled conditions of use".[4] However, the FDA's determination that a product is safe does not suggest an absence of risk. Therefore, when developing any risk management strategies, we assume that after understanding the information available on a product, a certain level of risk is accepted in view of the potential benefit of the drug. Available tools are then employed as we seek to extend the knowledge base of the safety of the product or to minimise potential risk for a patient. In the future, it will be important to seek new scientific tools as well as to continue to achieve a better balance of benefit and risk.

Tools in an RMP will depend on a number of factors: the nature and magnitude of the inherent risk of the drug, disease state being treated, availability of other therapeutic options and willingness of patients and providers to tolerate risk, among others. Tools utilised will need to be individualised for each drug.

This article reviews current risk management practices and tools, as well as some new approaches that have been proposed.

## 2. Risk Management Practices

### 2.1 Risk Management During Drug Development

Although some have described risk management as commencing around the time of drug approval, risk management activities begin at the earliest stage of new drug/biological development.

#### 2.1.1 Drug Development Programme Inception

Before deciding to initiate a drug development programme, pharmaceutical industry sponsors require a good understanding of the natural history of the target disease, the demographics of patients affected by the disease, the risks and benefits of currently available and evolving therapies, and a vision for what advantages a new therapy might offer future patients. Currently, basic scientists, clinical personnel and market research departments conduct this initial assessment. Although it has been uncommon for drug safety departments to actively participate at this stage of drug development, the more involvement there is by those with human safety expertise, the more successful the overall programme is likely to be. The experience, expertise and analytical skills of drug safety departments may provide additional perspectives even at this early stage of drug development. Examples might include conducting demographic studies, determining the background incidence and prevalence of medical events (e.g. hepatic enzyme abnormalities) in the anticipated patient population, assessment of safety profiles of drugs currently available for the anticipated indication and input into which events may require special attention during clinical trials.

#### 2.1.2 Non-Clinical Activities

Molecules identified as potential drug candidates undergo toxicology screening using a variety of tools, including toxicology databases and *in vitro* or *ex vivo* screening toxicology studies. Promising drug candidates are evaluated in nonclinical studies to define their basic pharmacological activity, which forms the basis for predicting potential clinical efficacy. In addition, pharmacokinetic and more extensive toxicology studies are conducted to further narrow the field of candidate drugs for phase I studies. The final candidate is generally selected to provide the best combination of predicted efficacy, pharmacokinetics, pharmacodynamics and potential safety. Results of animal studies and mutagenicity studies that reveal potentially unacceptable toxicities lead to many drug candidates being discontinued from development before the drug is ever introduced into human studies.

For drugs deemed appropriate to progress to human trials, preclinical data are used to identify potential safety concerns that might be expected in phase I studies, as well as to minimise any potential risk to patients or subjects. Many sponsors develop a target product label early in phase I, outlining anticipated indications, doses and preliminary safety information.[5] The initial target product label contains little definitive information; however, it serves to focus development on important issues and may help regulators more easily understand the development plan. The development of this plan requires multidisciplinary input to optimise the safety aspects of planned phase I studies. Newer techniques are evolving to improve our ability to predict the potential for drug interactions and metabolism,[6,7] hepatotoxicity,[8] idiopathic adverse events[9] and hypersensitivity reactions[10] earlier in development. For example, both industry and regulators are considering whether there are reliable, predictive markers to detect liver toxicity and how to use those markers appropriately in the approval process. The extent to which data from animal trials or other preclinical studies can be used for such predictions is an active area of research.

#### 2.1.3 Phase I Studies

Phase I studies are designed to provide initial estimates of human safety and tolerability, define pharmacokinetics, assess pharmacodynamics and provide an early measure of drug activity. Phase I studies may also be used to characterise metabolites, identify potential drug-drug interactions and determine safety and pharmacokinetics in special populations. Pharmacokinetic studies in various patient subpopulations (e.g. elderly, paediatrics, renal insufficiency, hepatic impairment) often occur concurrently with phase II and phase III studies.

Clearly, it would be desirable to be able to identify differences in the way drug candidates behave in different subpopulations. Pharmacogenomics, a field aimed at understanding the genetic contribution to variability in drug efficacy and toxicity, may permit identification of patient subgroups most likely to benefit or less likely to experience adverse events with a particular drug.[11] However, as promising as this field may be, it is still in an early stage of maturity with regard to widespread application and use during general drug development.

#### 2.1.4 Phase II Studies

Phase II studies represent initial therapeutic exploratory studies. Patients are generally selected to represent a narrow spectrum of disease and demographic makeup. Phase II studies are typically well controlled, closely monitored and conducted in a relatively small number of patients, usually involving no more than several hundred subjects. In addition to providing the first meaningful assessment of the effects of a drug on key clinical endpoints, generally phase II objectives also include the determination of an appropriate dose. Pharmacokinetic and pharmacodynamic studies may provide information about the effects of dose on different subpopulations. Phase II studies may also include experiments to look at drug-drug interactions as well as interactions of the study drug with pertinent concomitant illnesses.[12] Although the number of patients exposed to a drug in phase II studies is higher than in phase I studies and may be able to reveal certain adverse reactions, phase II studies are generally unable to provide the evidence of efficacy and safety necessary to support approval of the drug, except under the FDA's expedited drug development programmes.[13] For the most part, phase II studies are critical for identifying agents with a high probability of proving efficacy in phase III clinical trials at a dose that affords efficacy with reasonable safety.[14]

Traditionally, sponsors meet with the FDA to discuss the data collected and analysed through phase II. FDA regulations state that the purpose of end-of-phase-II meetings is to determine the safety of proceeding to phase III, as well as to evaluate the clinical plan and identify any additional information necessary to support the proposed New Drug Application (NDA). This meeting is an ideal time for the sponsor to discuss any potential safety risks of the compound with the Reviewing Division and with the Office of Drug Safety. Ideally, there would be a consistent approach across reviewing divisions as to how particular safety issues should be approached and how risk management techniques will be employed. The sponsor and the FDA should agree on the phase III protocols during the meeting.

#### 2.1.5 Phase III Studies

In addition to documenting efficacy and safety of the dosage and administration regimen studied, phase III studies more precisely define the safety profile of the compound. These studies may also explore the use of the drug in broader populations or in a broader spectrum of disease. These studies are much larger than those in phase II, typically enrolling over 1000 patients. Specifically, for products intended to treat chronic, non-life-threatening conditions that occur in large populations, the International Conference on Harmonisation (ICH) recommends a baseline safety database that involves at least 1500 patients treated over 6 months, usually achieved over multiple large trials;[15] some product databases include information on up to 10 000 patients. However, the pre-marketing safety database does have limitations.[16] Unfortunately, even the absence of a particular event in a relatively large safety database of 10 000 patients cannot exclude the occurrence of that event in fewer than 1 : 3500 patients with 95% probability. Also, most trials are not of sufficient duration for potential long-term risks to be identified. Finally, those patients who will be treated post-approval may differ in certain respects from those in

the clinical trial population, and although efforts are made in designing clinical trials to match demographic variables with those of the intended patient population, there are also aspects of the clinical trial environment that are different from using the drug in real life. As a result, further understanding of the safety profile of a drug will depend on data obtained in the post-approval timeframes; this will include postmarketing experience (spontaneous reporting) and may include data that can be gathered via epidemiological means or through additional clinical trials.

#### 2.1.6 Data Monitoring Committees in Clinical Trials

Data Safety Monitoring Boards (DSMBs), also referred to as Data Monitoring Committees, allow ongoing review of clinical study safety during the conduct of clinical trials. National Institutes of Health (NIH) policy calls for the establishment of a DSMB for multisite clinical trials involving interventions that entail potential risk to participants.[17] Further NIH guidance[18] has extended the use of DSMBs to include some phase I and II trials. The ICH Guidance on Statistical Principles for Clinical Trials (ICH E9) states that "for many clinical trials of investigational products, especially those that have major public health significance, the responsibility for monitoring comparisons of efficacy and/or safety outcomes should be assigned to an external independent group".[19] These committees are usually composed of experts who are independent of the company as well as one or two experts from the sponsor who are there to help evaluate data from their areas of expertise. Since sponsors are usually the most knowledgeable about a given study and can devote resources to finding information quickly, this approach has been found to be an effective way to add extra safety oversight to particular ongoing trials.

### 2.2 Risk Management Planning Around the Time of Approval

Under PDUFA, the US FDA can apply user fee revenue to fund activities that meet the PDUFA definition of the "process for the review of human drug applications". In PDUFA III certain FDA risk management activities were added to this definition. A call for sponsors to voluntarily develop and submit RMPs was incorporated into the PDUFA III goals. Thus, a key risk management activity in the pre-approval time period will be consideration of the development of a formal RMP for certain products to be submitted with the NDA. The RMP will outline procedures proposed by the sponsor to assess and manage potential risks in the time around approval and beyond. In many instances, the RMP will be straightforward and, for some, may not require more than the collection and assessment of spontaneous reports and the submission of cumulative periodic reports that current regulations mandate. With other drugs, the RMPs may undergo change and refinement as the NDA is reviewed. In some circumstances, the focus may be on educational activities or on specific intervention programmes, while in others it may also involve commitments for formal, post-approval studies.

Risk management planning relies upon preclinical and clinical data to identify potential safety signals, but the ultimate focus of these plans is on the methods and strategies for managing known or theoretical risks of a product in the post-approval environment. These strategies can include postmarketing surveillance activities, formal studies (e.g. post-approval observational studies) and managed distribution systems, or a combination of these elements, including drug-utilisation studies.

Epidemiology is an important tool in the development of product RMPs. A goal of risk management activities around the time of approval is to understand drug risks through studies of the natural history of the disease, incidence and prevalence

studies, mortality patterns, patient populations and disease progression/treatment pathways. When possible, studies can be planned to quantify unanticipated benefits that became evident during the clinical development programme beyond the obvious benefits of drug efficacy. Quantitation of such potential benefits may aid in the overall benefit-risk discussions during the drug approval process and also lend support during regulatory product defence. In addition, identifying safety signals, assisting in clinical programme planning, designing epidemiology and post-approval safety studies, and working with safety and product teams to develop comprehensive postmarketing surveillance plans, are critical risk management activities.

For risks that have been identified as needing a risk minimisation plan, some aspects of the plan may be developed and tested in the pre-approval time period. Such work carried out before approval will help ensure that the intervention plan can commence as soon after approval as possible.

## 2.3 Risk Management During the Post-Approval Period

### *2.3.1 Risk Ascertainment/Assessment*

Pre-approval clinical trials routinely identify the most commonly occurring adverse events (from 1 in 100 to 1 in 1000) among patients who participate in these studies.[20] One factor that is critical in risk management is the integrated use of tools to ascertain and evaluate the benefits and risks of pharmaceuticals in a real-world setting, rather than under the controlled conditions imposed by clinical trials. Available tools that may be used in the peri-approval and post-approval period to evaluate benefits and risks include: spontaneous reports, intensive postmarketing surveillance, active surveillance, comparative observational studies and targeted clinical investigations.

In order to use risk management tools in an integrated approach, an RMP should be thought out prior to marketing. The spontaneous reporting system is a tool that is capable of identifying rare events or potential signals, although epidemiology studies may be better suited to monitor the profile of a drug in actual clinical practice or in testing hypotheses. Epidemiological studies examine the risks (and benefits) of a drug in a quantitative fashion and include a comparison group, usually another drug of interest. From these studies, incidence rates (the rate at which new events occur in a population) and relative risks (the risk associated with one drug relative to another, for example) can be calculated and compared. Once a safety issue is identified, a risk management strategy may be planned, incorporating various methods as outlined in the following sections. The more sources of information that can be compiled, the stronger the risk management message. This is most critical in the case of very serious rare events when information regarding the frequency of events is needed.

#### Spontaneous Reports

Spontaneous reports are an important risk management tool for identifying safety signals, particularly for ADRs that occur rarely. Unfortunately, there is a tendency to interpret comparative safety signals generated through the spontaneous reporting systems as if the signal had been tested and determined to be real. Spontaneous reports are often incomplete in nature, and the rate at which cases are reported is exquisitely sensitive to many external factors such as time since launch, regulatory activity, media attention and the nature of the indication for use or the event reported.[21-24] Interpretation of information generated from spontaneous reports should be exercised with extreme caution, although spontaneous reports still play a part in RMPs. Attempts have been made to develop methods that would scientifically assess the causality of events identified in individual spontaneous reports. It has been shown, though, that the results are too inconsistent to be a useful tool.[25,26] In one study, dis-

agreements regarding causality occurred in 50% of events – a rate similar to chance.[27] Even the use of standardised rule-based systems for causality assessment do not appreciably improve agreement.[28-30] The spontaneous reporting system in the majority of cases should not be used to compare reporting rates between different drugs because of differential reporting rates among products.

A review of a series of case reports that include all reports of medically similar events may provide more information than isolated spontaneous reports; however, a case series is also primarily an hypothesis-generating tool rather than a method of confirming an association. In one review of 18 adverse reactions published in the medical literature, 14 (77.8%) were identified through case reports or case series.[31] Certain adverse events are particularly associated with drug therapy, including agranulocytosis, anaphylaxis, aplastic anaemia, Stevens-Johnson syndrome and toxic epidermal necrolysis.[32] Well documented case reports concerning these events may be helpful in identifying important potential risks.

Spontaneous event reporting rates cannot be used to estimate the incidence of adverse events because only an unknown proportion of adverse events are ever reported.[33-36] Periodic reminders may increase the frequency of adverse event reporting.[37] Mandatory reporting by healthcare providers has been suggested as one method for improving the utility of the adverse event reporting system.[38,39] Although mandatory reporting would likely increase the quantity of adverse event reports, there is no assurance that (i) such a measure would improve the quality of reports; (ii) regulators or pharmacovigilance departments would have sufficient staff to manage a large influx of additional reports; or (iii) the signal-noise ratio would improve. In addition, development of a mandatory reporting system would require a large investment in infrastructure, personnel, enforcement and maintenance, which could detract from other more valuable interventions. The difficulties associated with mandatory reporting need to be weighed against the benefits of such a system, but it is likely that mandatory reporting would create more problems than benefits.[40]

To enhance the reporting of adverse events, some have suggested that pharmaceutical companies include a toll-free adverse event hotline in direct-to-consumer advertising.[41] Internet sites have also been suggested as an avenue for increased adverse event reporting. In fact, Internet reporting is currently available for healthcare providers to report directly to the FDA. As with mandatory reporting, simply increasing the volume of adverse event reports would provide no assurance that risk ascertainment will be improved. In fact, simply increasing the number of reports is likely to obscure potential safety signals. Because the most common adverse events are usually those that are non-serious and expected, it is highly likely that these reports would be significantly large in number and dominate the system, making it more difficult to detect potential serious and unexpected safety signals.

Until a few years ago, little attention had been given to how adverse event data should be systematically evaluated to identify potential safety signals. Much effort is now dedicated to the development of signal detection techniques. A variety of techniques have been proposed for automating the detection of potential safety signals, including calculation of proportional reporting ratios and use of Bayesian techniques.[42-44] Drug-drug interactions may also be explored using data-mining techniques.[45] Although these methods may identify potential signals, they should be viewed as a starting point for further case review and evaluation. The sensitivity and specificity of detecting new and significant safety signals need to be defined and compared among various data-mining techniques. When these techniques are validated, they may then become a component of RMPs.

### Intensive Postmarketing Surveillance

As noted previously, the major role for the spontaneous reporting system is the identification of truly rare events. However, the spontaneous reporting system can be used as a good information source depending on the success of efforts to collect details of the individual reported cases. Getting complete information when the case is initially reported, as well as through follow-up, helps both the regulators and the manufacturer have a better understanding of the circumstances surrounding the reported event during general use of the product.

Several measures may be undertaken to ensure that information from spontaneously reported cases is as complete as possible. In addition to the routine requests for follow-up information, a script of standard questions tailored for the specific events of interest may be asked of anyone reporting deaths or other events that are of key importance to the product. The more detailed information obtained from the scripted questions will enable more precise interpretation of the events reported.

Requests for follow-up of individual cases should be coordinated worldwide to include activities carried out by local country offices. An algorithm may be created to outline what specific information is needed from the individual sites where selected postmarketing serious adverse events have occurred. The individual cases, as well as aggregated cases, should be reviewed in a timely fashion periodically by qualified medical staff to detect potential signals. In addition, an outside panel of experts in the fields of interest may be convened on an as-needed basis to review individual or aggregate cases. Furthermore, thorough review of aggregate spontaneous reporting experience may occur at periodic interdisciplinary team meetings.

### Active Surveillance

In contrast to the spontaneous reporting system, which collects adverse events through a passive system, an active surveillance system, such as sentinel surveillance and prescription event monitoring (PEM),[46-48] actively seeks to ensure the complete detection and ascertainment of adverse events within a predefined subpopulation.

In conducting sentinel surveillance, all adverse events that occur with a given product are actively sought, either by reviewing medical records or by interviewing patients/medical staff in a representative sample of sentinel sites to ensure the full and accurate capture of adverse events. Sentinel sites may provide information not otherwise available from spontaneous reports, such as incidence rates, information on specific patient subgroups and efficacy information. The US FDA Task Force on Risk Management has suggested the creation of a network of sentinel sites.[49] On the other hand, sentinel sites may suffer from several deficiencies, including bias (a tertiary referral centre, geographic effects), limited numbers of patients and high cost. This type of postmarketing surveillance may be useful for drugs that are used mostly in a hospital or other institutional setting or for drugs that present specific concerns.

PEM is a form of active surveillance performed in some countries, including the UK and New Zealand.[46-48] A drug-specific cohort of patients is identified from electronic prescription data. A questionnaire (green forms in the UK) is sent to each prescribing physician 6 months following the first prescription for each patient. The questionnaires collect patient demographics, indication for treatment, start and stop dates, dosage, clinical events and reasons for discontinuation. The mean size of the drug-specific cohort studied is approximately 11 000 patients.[48] Unfortunately, the response rates from physicians are variable (in general, 40–75%)[48] and, therefore, PEM is subject to some of the same limitations associated with the spontaneous reporting system that may affect interpretability of findings.

The FDA has proposed a type of surveillance similar to PEM through the establishment of an independent drug registry centre. In this system, manufacturers would be able to contract with the centre to develop product registries when needed.[49] By prospectively following patients, these registries would be able to collect information using standardised questionnaires. However, the use of mandatory registries of all patients taking new drugs raises certain ethical issues regarding coercion and confidentiality of medical information;[50] in addition, registries of a single drug cohort without a comparison group make the study findings difficult to interpret.

### Comparative Observational Studies

Comparative observational studies are an epidemiological tool that has been used as a key component of successful risk management strategies.[51-53] Comparative observational studies include such methods as cohort and case-control study designs. Implementation of such epidemiological methods should be considered early in the development programme as potential issues are identified. These methods have been used to learn more about the patient population being treated, including identifying the prevalence of the disease being treated in different countries as well as estimating the incidence of potential outcomes of interest in the underlying population. These studies can help identify key subsets of patients who may be at risk for potential adverse events. This type of information can be used to help put spontaneous reporting rates in perspective. Other observational studies can be designed to identify the potential benefits of a drug.

Traditional epidemiological methods, especially cohort and case-control study designs, have been widely applied to examine both the benefits and the risks of medications. Observational studies may be conducted using an existing automated database, using an existing case-control surveillance database or patient cohort (such as the Nurses Health Study cohort),[20,54] or using data collected *ad hoc* specifically for the research topic. In order to address adverse events that are too rare to be detected in pre-approval clinical trials, large population-based existing databases are especially useful in providing sufficiently large drug exposure and medical outcome data in a relatively short period of time.[20] A concurrent comparison group can be easily identified in the same database to make a comparative observational study. These data are extremely helpful in promoting sound and prompt regulatory decisions that may have a significant public health impact.

Data that are collected in a case-control surveillance setting are designed for specific targeted events. Boston University's Slone Epidemiology Unit has such existing databases for birth defects, cancer and myocardial infarction.[55] Cases and controls of these events have been collected continuously for over a decade. All drug exposures prior to the occurrence of such events have been ascertained through interviews. The data may be used to study the association of these events with multiple drugs.

Several types of automated databases are currently available for pharmacoepidemiological research. They include databases of automated medical records (e.g. the UK General Practice Research Database, the Harvard Pilgrim database) and automated accounting/billing systems (e.g. United Healthcare Research Database, Medicaid database).[20,56,57] The database of an automated accounting/billing system is a linkage of pharmacy claims and medical claims. These are huge databases, which usually include information on more than 1 million, and sometimes more than 10 million, patients. Since they are created for administrative or billing purposes, they may not have the detailed and accurate information needed for some research.[20] For example, these databases usually do not contain data on over-the-counter medications, dietary supplements or hospital in-patient drug use or human

behaviour information, such as compliance with drug therapy. These data elements may be very important confounding factors that should be considered in the study design. In addition, with the implementation of the Health Insurance Portability and Accountability Act (HIPAA) rules to protect patients' confidentiality, patient medical records are more difficult to access to validate the information recorded in the databases. Even so, these data are much better in quality than spontaneous reports. Concurrent comparison groups can be more easily identified in the databases than in an active surveillance system.

The automated databases may be queried for signals of any problem occurring in excess frequency in association with drug exposure. In this sense, they may serve as a data source for data mining for signal detection, similar to the way spontaneous reports are used. The methodology and best practices for such recurring queries have not been thoroughly explored. How one can address the problems associated with multiple simultaneous queries to minimise the possibility of generating a false signal will need to be further explored.

#### Targeted Clinical Investigations

During the pre-approval investigation phase, potential significant risk or unexpected benefit may be identified. Each of these areas may require a targeted clinical trial, pharmacology study or toxicology study to further evaluate the mechanism or the long-term consequences of these events during the post-approval phase.

In addition, studies, such as a 'large simple trial', may be necessary in some instances to help ensure a positive benefit-risk balance in the usual care setting, especially when multiple effective alternative therapies are available in practice. Patients enrolled in a large simple trial are usually randomised to a treatment group to reduce the selection bias or to avoid a 'channelling' effect.[20] The study outcome is focused and simplified to ensure a manageable and practical study. These types of studies are especially useful when there is the possibility that certain patients will be prescribed one drug over another because of the patient's medical history. Such selection of a drug therapy could lead to different rates of events if the patient population selected is at a higher or lower risk of an event.[20] However, these studies are extremely expensive and may not be cost efficient for research questions that may be answered by existing databases or other tools.

It is essential to keep in mind that a signal or a suspected risk does not mean that a real risk exists. Although in rare cases exceptional risks can be identified through the reporting of individual cases, such as with thalidomide and limb reduction defects, most risks need to be evaluated through more scientific means. Information from clinical trials, epidemiological studies and spontaneous reports should be continually reviewed. Epidemiology is a useful tool that can provide valuable information for comparing benefits and risks between drugs during the post-approval phase, particularly as the drugs are used in a real-life setting.

### 2.4 Risk Intervention Tools

Just as tools are employed to seek to extend our knowledge base about products, tools are also used to attempt to increase the understanding of others about risk and to minimise risk by affecting behaviour. Risk communication is one of the major approaches used today to minimise risk. It is also an area of much research and discussion. We are learning techniques and increasing skills in order to be as clear as possible with the message. There are also other interventions that have been used or contemplated. RMPs for drugs with a complicated risk profile may need to have redundancy in order to achieve effectiveness. However, any risk intervention that is chosen should be as simple as possible in order to avoid confusing patients, pharmacists and healthcare providers and to avoid overly burdening

the healthcare resources available. Finally, any risk management technique should not result in a decrease in benefit to the patient as attempts are made to decrease potential risk.

#### 2.4.1 Risk Communication

Effective risk communication requires scientific knowledge of the product(s) and an understanding of the roles and responsibilities of all stakeholders (including industry, regulators, healthcare providers and patients). In an ideal world, communication of the benefit and risk of marketed products is predicated on trust in the integrity of all parties. To be effective, the message must reach the target audience, influence the behaviour of the target audience and generate an appropriate response by the target audience.[58]

Industry plays a key role in communicating the benefit-risk balance of pharmaceuticals to healthcare providers and patients.

##### Healthcare Providers

Healthcare providers obtain benefit-risk information from a variety of sources, including the product label, the Internet, Dear Healthcare Professional letters, the medical literature and pharmaceutical sales representatives. The product label remains a key component of risk communication; however, its length, text size, complexity and lack of standardisation may diminish the utility of the label as a method of risk communication. A variety of proposals have been described to improve the effectiveness of the label in communicating risk to healthcare providers. The FDA has proposed a rule revising the format of professional labelling to improve understanding.[59] This proposed format provides for a 'highlights' section containing bullet point information. Some proponents have suggested that the most recent label changes need to be highlighted to focus the prescriber. Although improved formatting of the product label may, upon further research, improve the communication of benefit-risk to the prescriber, concerns regarding the legal liability implications (failure to warn) of emphasising some risks versus other revisions remain.

Use of the Internet by the industry and regulatory agencies to communicate label changes and important safety messages to prescribers has become a powerful tool of communication in our daily activities. The Internet provides a means for rapid, concise and consistent up-to-date messages to be communicated. With the continuous updating of product labels, a website repository of current FDA-approved labels could provide the latest product information in a central location. In May 2002, the FDA issued a proposed rule that would require industry to provide electronic labelling submissions that could then be housed in a centralised library of current labels.[60] This type of centralised system would allow providers and patients the opportunity to search drug information by keywords. It would also permit vendors to develop information systems that deliver up-to-date electronic labelling to healthcare providers in a variety of ways.

The Pharmaceutical Research and Manufacturers of America (PhRMA) is leading an initiative to make electronic package inserts for non-emergency prescription medicines available to dispensing pharmacists. One of the key goals of the initiative is to ensure that the dispensing sites have electronic access to the most current prescribing information.

With advancing computer technologies, there are many opportunities, such as the one just described, to strengthen the role of the pharmacist in risk communication. In the future, pharmacies could provide online access to patients/consumers concerning product-specific information such as regimens, precautions, warnings and contraindications. Since patients often bring prescriptions from different healthcare providers to a single pharmacy, the pharmacist has the opportunity to integrate information and to use existing computer decision support

systems to identify potential drug interactions or to reinforce messages regarding other risks.

In addition to providing information to healthcare providers via the product label, important safety messages have been communicated via Dear Healthcare Professional letters. Research on the effectiveness of the Dear Healthcare Professional letter in changing prescribing behaviour has resulted in the advancement of proposals to increase the value of these letters as communication tools by using them as part of a coordinated multiphasic campaign (e.g. e-mail, fax, US FDA MedWatch programme, medical society website postings).[61]

Use of the professional sales representatives to communicate the benefit-risk profile of a product to healthcare providers should also be considered as an important part of a multiphasic campaign on risk communication. Promotional materials used by sales representatives are an important source of benefit-risk information for the healthcare provider. These materials are monitored by regulators and are required to have an appropriate balance between benefits and risk. In addition to sales representatives, many pharmaceutical companies also use medical service liaisons to provide further scientific data on the benefit and risk of pharmaceutical products to the healthcare community.

#### Patients

Several avenues are available for communication of risk to patients including communications from healthcare professionals, medication guides and direct-to-consumer advertising. As patients assume more responsibility for their own healthcare, it may be difficult for the patient to absorb information coming from so many diverse sources. It may also become difficult for the patient to discern the validity of many of the information sources.

Industry provides information to the healthcare provider to help in determining the benefit-risk for individual patients through the various resources previously described. Clinicians need to communicate to patients to assist them in making informed choices about their illnesses. Healthcare providers communicate this information to patients, both orally and in writing, via patient information leaflets and medication guides.

An FDA-commissioned study mandated by law in the US noted that 89% of prescriptions were accompanied by patient information leaflets; however, the quality and legibility of the information in the patient information leaflets were insufficient.[62] The authority to mandate medication guides and patient information leaflets, as well as the impact of innovative formats to enhance comprehension, is being further explored. Additional research is necessary to assess the effectiveness of these instruments.

Finally, industry also provides the patient and the public with information about potential risks and benefits of its pharmaceutical products via direct-to-consumer advertising. Although some have suggested otherwise,[63] direct-to-consumer advertising may benefit public health[64,65] in providing patients with important safety information that may otherwise become confused with inaccurate and inconsistent information available on the Internet.

Effective communication of the benefit-risk profile of pharmaceutical products to the patient and the public depends on accurate, relevant and consistent messages.

### *2.4.2 Other Risk Intervention Tools*

Physician certification, which requires mandatory training and assessment before authorising the prescription of certain drugs, has generally not been accepted as a useful tool since it infringes on the doctor's right to practise medicine[66,67] and would also be a burden to the US healthcare system. If certification were to be used, then stickers on prescriptions might be used to indicate certification, but this would have resource implications for pharmacists[67] and alternatives would have to be found for prescriptions submitted electronically. In addition, unless a national system is going to be developed to

coordinate the use of stickers for various medications, the stickers could be confusing to healthcare professionals when more than two or three medications are involved. Once again, there might be large resource implications if certification is used often.

One promising option to help reduce medication errors is the use of computers for medication ordering;[68,69] this is easiest to implement in inpatient settings, but as those in outpatient settings gain more access to electronic means, use there could increase.

Greater use of pharmacists to decrease prescribing errors and, therefore, potential adverse drug reactions has been suggested.[70] Roles that pharmacists might play include serving as consultants to prescribers, particularly in hospitals as participants in hospital rounds or in reviewing certain test results before filling a prescription. To provide the required coverage, however, the number of pharmacists needed would increase greatly. There is currently a shortage of pharmacists[71] and, more importantly, no agreement on how they would be paid in the current system. Restricted distribution of certain drugs by limiting their availability to pre-certified pharmacies has also been suggested as a risk-intervention tool. There are a number of issues with this option, including its potential to limit access to beneficial products by patients in need who are not near a certified pharmacy. Such plans may also conflict with or require changes in individual state laws. Use of restricted distribution as a risk minimisation tool should also be applied cautiously so that safe and effective drugs are not unfairly subject to restriction compared with other similar (perhaps older) drugs in the therapeutic class.

Other approaches, such as the bar coding of medicines and unit-of-use packaging (e.g. individual blister packs), have been used with some medications. It is anticipated that this would reduce medication errors. The FDA recently issued a final rule that requires the inclusion of bar coding on the product labels of most prescription drugs, certain over-the-counter drugs and biological products.[72]

It is also important to mention education as a risk management tool. Because healthcare professionals must stay abreast of an ever-increasing amount of information and data, new techniques will be needed to assist them in assimilating all these data. Medical school curricula will need to be enhanced to include information and training about thoughtful prescribing of drugs, as well as more information about drug interactions. Also, patients will need to take more accountability for understanding more about their own illnesses and disease and become more knowledgeable about the drugs that they take so that they can better participate in decision making regarding benefits and risk. Both the public and healthcare professionals would benefit from education about what risk actually means and how to put the benefit-risk evaluations of drugs in the context of more familiar activities such as occupational hazards, risks of injury in sporting events and general life events.

## 3. Measuring Effectiveness of Risk Management Plans and Tools

Certainly an integral part of any RMP must be an assessment of the effectiveness of the plan. Indeed, it will be necessary to assess the individual components making up the whole RMP as well as the overall effectiveness. The questions remain about how these evaluations are to be done, the timing of the assessments, the identity and qualifications of the evaluators, what metrics should be proposed and what the consequences would be for unexpected results. For instance, an RMP focusing on physician education programmes may result in an increase in reporting rate for a particular adverse event. This may become a problem if the measure of success for that plan is an apparent decrease in reporting. None of these questions are easy to answer, especially

in a proactive plan for a drug that has never been marketed.

Evaluation of individual components of RMPs has not proven to be quite so difficult as measuring the overall effectiveness of the plans, based on industry experience to date. It can be done by such approaches as testing comprehension of methods of communication, surveying healthcare databases for appropriateness of prescribing patterns and ongoing pharmacovigilance. However, the choice of metrics to be used for any drug will be determined by how much interaction and intervention is called for in the RMP.

Although individual outcomes of components of an RMP may be easier to measure, the true effectiveness of an RMP should ultimately rest on documentation of overall safety outcomes. As has been stated, there is risk inherent in all drugs. RMPs are attempts to increase the benefit-risk balance for all patients, but how will success be measured? A zero level of serious adverse reactions cannot be achieved, but how much risk is tolerable? It seems that each drug and patient population will have different responses, both negative and positive, based on a number of factors specific to the drug, the alternatives available and the acceptance of risk/uncertainty by the patients themselves. It is also important for RMPs to focus on scientifically established risk, while theoretical risks need further evaluation before risk minimisation plans are applied.

The assessment and measurement of the effectiveness of RMP outcomes are areas that need much more discussion by stakeholders and this is clearly an evolving field.

## 4. Conclusions

Regulators and the public have been placing greater importance on managing the benefit-risk balance of pharmaceuticals. In response, pharmaceutical sponsors are focusing on the area of risk management to ensure that their products are used safely for the purposes for which they are intended. The goal of the industry is to work in concert with the global health authorities to ensure safe medicines for the public and also that evaluations and decisions concerning individual drugs are made on a scientific basis.

No matter what the drug or how extensive a plan may be, there will never be ‘zero risk’. As we drive towards safer products, we must ensure that our risk management activities do not become simply those of risk aversion. It is important to assess the potential risks of drugs and then take steps to minimise the probability of adverse outcomes for those risks that are real. Over the past few years, as the spotlight has intensified on concerns about risk, the pendulum has swung in the direction of being averse to even theoretical risks. However, regulators and industry alike must withstand pressures to base detailed RMPs on data that are subjective or vague. We must direct our efforts to using objective data that have been carefully assessed as the basis for our RMPs.

The activities involved in risk management need to be proactive and integrated and must begin at the time of first development. The area of risk management is evolving as we develop more tools, understand better the ones we have and learn how best to use them. Clearly, collaboration between regulators and industry will be key as we begin to develop and implement these important plans.

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## Appendix: Glossary

**Benefit:**[1] Benefit usually refers to gain (positive result) for an individual or a population. Expected benefit can be expressed quantitatively and this

would ordinarily incorporate an estimate of the probability of achieving the gain.

**Large simple trial:** A large simple trial is a simple observational study of a large population of patients who are randomised to receive treatment and are followed for a single outcome or, at most, a few outcomes.

**Pharmacovigilance:** Pharmacovigilance may be thought of as the collection and evaluation of reports of adverse events in patients who are or have been undergoing treatment.

**Risk:**[1] The simple, standard, epidemiological definition of risk is the probability that something will happen. In the context of medical interventions (e.g. drugs), the 'something' is almost always associated with a negative event. In defining or describing a specific risk, it is always important to include information on intensity (e.g. severity), time of the event (onset or duration) and time period over which the probability applies. Some definitions attempt to include concepts of rate, intensity and time:

"The probability of the occurrence of an adverse or untoward outcome and the severity of the resultant harm to the health of individuals in a defined population, associated with the use of a medical technology for a specified medical problem under specified conditions of use."

**Risk management:** Risk management is the comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate and minimise risk throughout the life cycle of a drug so as to establish and maintain a favourable benefit-risk balance in patients.

**Risk management plan:** An RMP is a strategic approach that encompasses all planned efforts to increase knowledge about a drug, including additional data on risks and benefits, as well as all efforts to minimise or mitigate the risk from the use of the drug. The plan may be quite extensive and include epidemiological studies, clinical trials and a number of interventions to minimise risk, or it may be as simple as professional product labelling and good routine postmarketing surveillance. The detail needed in the actual plan is driven by the specific risks of the particular drug.

**Risk management tool:** A risk management tool is a specific approach, process, study or system that is designed to add to the knowledge base of the drug concerning risks and benefits, to enhance safety in patients by reducing risk or to communicate risks and benefits to healthcare providers and patients.

**Sentinel surveillance:**[73] Surveillance based on selected population samples chosen to represent the relevant experience of particular groups.

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