Integrating Risk Management Across the Product Lifecycle

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Risk management has become critical to successful drug development. Over the past decade, regulatory authorities have issued various guidelines emphasizing the importance of risk management in supporting marketing authorization and in the support of marketed products throughout their lifecycle. US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance documents and regulations on risk management principles and expectations serve as the framework for risk assessment and risk management. In this evolving environment, the goal of incorporating risk management into drug development should be to minimize risks to patients while ensuring appropriate access to novel therapies. Within this context, there are opportunities to change the paradigm of drug development to better define benefit:risk and, more appropriately, inform risk management strategy to support products throughout their lifecycle. To achieve these opportunities the biopharmaceutical industry must ensure that robust pharmacovigilance systems designed to assess safety signals and processes to support risk management are in place. The industry should also recognize that continuous assessment of benefit:risk and risk management adds value for external stakeholders. To effectively impact public health, regulators will need to transparently partner with sponsors, healthcare providers, and academia to support robust assessment of risk and ensure that appropriate mitigation measures are implemented.

In drug development, risk is viewed disproportionately from benefit, in part because clinical trials are often not assigned to assess risk. In addition, in the current environment there is an expectation that risks of drugs are transparently communicated. As a consequence there is the opportunity to enhance the value of new drugs by continuous assessment of benefit:risk throughout the innovation cycle. While global regulations regarding implementation of risk management programs vary, there are common themes. These are the identification, assessment, communication, and management of risk to maximize benefit and minimize risk to patients.

The pharmaceutical industry needs little rationale to introduce more-focused risk management strategies to accommodate the evolving trends in globalization, demands on research and development (R&D) productivity, and regulatory requirements. In practice, the challenge is to create a framework that encourages innovation, provides access to important new therapies, encourages continuous benefit:risk assessment, and addresses regulatory and public concerns regarding safety.

Continuous assessment of benefit:risk plays an important role in a system that is inherently inefficient because the critical factors to the overall success of drug innovation as you go further down the development pipeline are often safety issues. At every stage of drug development,there is a degree of uncertainty (see *Figure 1*). To maximize success, the current paradigm emphasizes early no-go decisions, when there is very little information around the overall benefit:risk for the candidate molecule. Unfortunately, this paradigm may lack a thorough understanding of the ultimate value of a new therapeutic agent. By introducing benefit:risk assessment methodologies earlier in the process, with effective knowledge management and other novel tools such as predictive toxicology, greater understanding of the safety and benefits of a molecule can be achieved, which has the potential to improve the success of drug development.

Regulatory Framework for Risk Management

The increased focus on risk management has been implemented in the EU through the regulatory requirement for risk management plans (EU-RMPs). The EU-RMP is a mandatory aspect of the EU drug application process that comprises an outline of the product risks (safety specification), the post-marketing surveillance plan, and risk minimization activities. In the EU companies must submit an EU-RMP in accordance with a detailed template and guideline at the time of marketing authorization application. Risk management plans also must be submitted if new safety concerns are identified for a marketed product and must be updated as circumstances change. Thus, companies are required to specify safety issues about which there is uncertainty and how they will address potential concerns after the drug is on the market at the point of first marketing.[1] A company must also indicate, when appropriate, what

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additional studies will be conducted after marketing to fill important knowledge gaps. The final component of the EU-RMP details how a company proposes to reduce the severity or frequency of known adverse reactions (i.e. risk minimization). This may involve special communication programs, educational exercises, or registration programs for patients, doctors, and/or pharmacists, as well as other measures.

Preparing for an EU-RMP may require a costly and intensive use of resources, primarily with respect to medical and regulatory staff. The combination of planning, study design of modifications to reduce risks, and close or increased safety monitoring is required to produce a well-substantiated RMP, as well as appropriate patient and healthcare provider educational materials. When well designed and executed, an RMP should allow for optimization of appropriate use of drugs to improve public health.

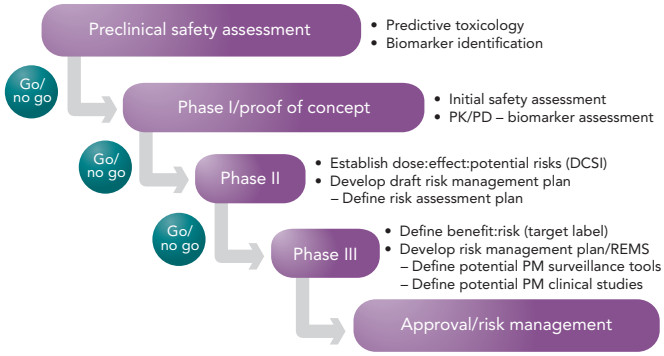
The FDA, while following a similar approach conceptually, is required to implement risk minimization programs under a statutory framework, as defined in the FDA Amendments Act (FDAAA) of 2007, called the Risk Evaluation and Mitigation Strategy (REMS). Sponsors must develop risk management programs in a framework that satisfies the requirements for high-quality, closely managed processes designed to assure risk communication and appropriate use of the drug (i.e. Elements to Assure Safe Use). To do so, sponsors should incorporate a methodology for identifying and evaluating risks; and a process for generating intervention plans to reduce the risks to an acceptable level. While implementing REMS when necessary to manage known or potentially serious risks may be of value, the concern now is of its potential to impose new challenges during the drug development process. In addition, the effectiveness of these programs in mitigating risk needs to be established. The FDAAA legislation envisions assessments to determine both effectiveness and continued need for a REMS based on data acquired with real-world use of a product.

To be prepared for design and implementation of RMPs, clinical researchers at all stages of drug development should adopt a proactive approach to continuous assessment of benefit:risk. If necessary, there should be awareness at an early stage regarding the potential need to formulate a REMS when there are safety issues that may require post-approval risk minimization. Therefore, it can be argued that the impact of REMS may be to increase costs during drug development, especially if more safety measures are implemented than would have been previously envisioned (e.g. initiation of additional trials, an increase in site budgets, increased data capture, and/or increased frequency of on-site monitoring). This should be justified by the need to ensure appropriate use of new drugs to optimize benefit:risk and improve public health.[2,3]

Considerations in Processes to Assess Benefit:Risk

Proactive and continuous benefit:risk management requires pharmacovigilance systems that are designed to deliver key elements. These are: risk identification and evaluation, development of risk minimization and mitigation strategies, and communication of the strategies to all relevant parties.

Figure 1: Continuous Assessment of Benefit:Risk—The Changing Paradigm of Drug Development



DCSI = Development Core Safety Information; PK/PD = Pharmacokinetics/ pharmacodynamics; REMS = Risk Evaluation and Mitigation Strategy.

In clinical development, there is considerable investment into trying to identify molecules suitable for 'early kills'. Often, this will be based on assessment of safety. However, it is important to recognize that this can lead to ending the development of a molecule very early in development rather than considering means to mitigate potential risks and take the molecule forward (see *Figure 1*). That said, care needs to be taken to balance benefit:risk assessment at each stage of clinical development. From an innovation perspective, there is a risk that go/no-go decisions will be made with incomplete data. Without full understanding of the potential value of a candidate molecule there is a risk of reducing the benefits of novel therapeutics to a point where it will impact public health.

The challenge is to create a framework that encourages innovation, provides access to important new therapies, encourages continuous benefit:risk assessment, and addresses regulatory and public concerns regarding safety.

An effective, reactive capability to manage risk is the minimum requirement, but this alone will not encourage confidence in medical innovation. Active steps must be taken to transparently communicate uncertainties in benefit:risk and how they will be assessed and managed after a new product enters clinical use. Without these measures, public attention will continue to focus on risk rather than benefit:risk and useful innovations could be lost as a result. Proactive pharmacovigilance is only possible if robust processes exist to respond to the new information as it evolves. The requirements of a comprehensive pharmacovigilance program are shown in *Figure 2*.

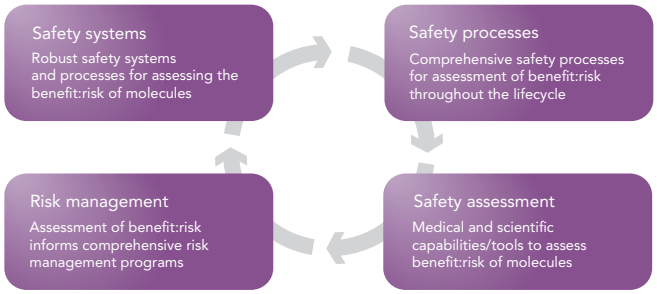
Risk Assessment in Drug Development

In developing methodologies to achieve robust risk assessment, companies need to build awareness early in the drug development process to address key questions, such as:

- what study enhancements should be pursued to acquire the necessary data for potential risk management strategies?; and
- at what point will it be possible to identify whether a product's risks outweigh its benefits?

1. Banerjee S, Barr B, Risk rationale. Pharma needs a culture of proactive pharmacovigilance and risk minimisation, Opinion, *Pharmaceutical Marketing Europe*, July/August 2007.
2. *Improving Clinical Trials by Implementing Information Technology (IT): Where will you be in five years?*, April 2005. Available at: www.saic.com/health/life-sciences/pdfs/mcv.pdf
3 Honig PK, Drug Safety and the Role of Clinical Pharmacology in the Safe Use of Therapeutics, *Clin Pharmacol Ther*, 2009; 85;225–8

Figure 2: The Pharmacovigilance System—Required Capabilities



It is important to communicate issues in a way that supports cross-functional risk management. Often there are areas where enhancement to existing processes should be considered. Examples include: effective serious adverse event (SAE) reporting and internal review processes, increased use of medical monitors and/or pharmacovigilance staff, improvements in display of data and other communication tools, and increased frequency of on-site monitoring of adverse events (AEs). Study design components that warrant examination include the frequency of visits and adverse event assessments, inclusion and exclusion criteria, the frequency and type of laboratory testing, the frequency and type of assessments (including electrocardiogram [ECG] radiology studies, ultrasound, and biopsies), and timing or addition of one or more follow-up visits.[4]

The best methods to address specific situations may vary depending on the product, the indication, the population being treated, and the issue to be addressed. The methods chosen will also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective. When choosing methods to address a safety concern, sponsors should carefully consider whether future studies are designed appropriately to assess the issues.

In the post-marketing setting, systematic methods for the detection of safety signals from spontaneous reports have been employed. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection. Data mining techniques have also been used to examine drug–drug interactions. These techniques facilitate the evaluation of spontaneous adverse event reports by using statistical methods to identify potential signals for further evaluation. However, there are many limitations to these techniques that need to be considered and particular caution should be exercised when comparing safety signals between drugs.

Sources of Safety Data

Historically, safety data have been captured from clinical trials, and in the post-marketing phase from spontaneous reporting of adverse events. However, there are opportunities to use other sources of safety data as part of risk assessment throughout a drug's development. In addition, with safety data being received from numerous sources and held in different clinical and safety databases, effective data flow and reconciliation is essential. Reconciliation and analysis of safety data will often be cross-functional and may involve external groups such as contract research organizations (CROs).

In addition to clinical safety data, toxicology studies and other non-clinical data are of value in a comprehensive risk assessment program. However, it is important to consider how these data are put in context in risk assessment. Epidemiologic data can also provide important information on the disease and disease population, while post-marketing data from other indications and published data from other compounds in the same class also have the potential to be data sources in risk assessment. Consistent collection of data and overall integration of these data should be an important component of a comprehensive risk management program.

The adoption of advanced data management tools is crucial as the regulatory scrutiny of drug safety issues increase. Specifically, adverse event reporting, signal detection, and data management and mining tools are important to handling the vast amounts of safety data. The ability to perform realtime, ad hoc analysis in clinical trials is often more challenging because of issues such as blinding of treatment, but methods for signal detection and data mining tools are available. In post-approval safety surveillance data mining is frequently used. The use of data mining in the clinical trial process is less common, but should be considered (e.g. analysis across trials or other clinical databases).

The statistical analysis plan (SAP) for efficacy is the critical component of defining the level of evidence based on data from clinical trials. Regulatory bodies in Canada, Europe, Japan, and the US expect that the SAP will meet requirements in pre-specifying inferential analyses and other important statistical techniques, such as meta-analyses and modelling. The SAP defines the analyses that support the level of evidence provided by clinical trial data that are pivotal to determining the approval and label claims for new drugs.

Safety analyses have tended to be based only on qualitative assessment of adverse events, but more recently there has been interest in developing more-explicit safety statistical assessment plans for drug development programs. When properly implemented, the safety statistical analysis plan may also evolve to support the assessment by regulators of the strength of the level of evidence with respect to presence or absence of safety signals.

New data sources for safety signals may provide further insight, but inclusion of these data into risk assessment may be challenging. For example, toxicogenomics is now recognized as a major tool in early preclinical drug safety assessment. There are a number of advantages. Gene expression can be predictive and be more sensitive than traditional approaches. Many criteria are measured at the same time and, in particular, biomarkers from multiple endpoints can be measured in a single experiment. To be effective, toxicogenomics requires the collection and analysis of large amounts of data. These data are diverse, not only in terms of the types of drugs and compounds that are represented in the database but also with respect to the types of data collected. For example, gene expression data should be collected in addition to traditional

4. Myshko D, A New Era of Drug Safety, *PharmaVOICE*, September 2008.

toxicology endpoints, such as clinical chemistry and histopathology. The data should be organized in a well-curated database, and their interpretation requires novel methods of analyzing patterns and predicting outcomes. The hope is these capabilities will lead to better decision-making, removal of candidate compounds from the development pipeline earlier in development, and increased confidence in moving compounds forward. However, traditional toxicology studies are still an important component of most drug development programs.

Biomarkers are also being widely recognized as important in the future success of drug discovery and development and clinical use. The FDA has recently provided guidance on the processes that need to be undertaken by sponsors to validate biomarkers that are relevant to their submissions. It goes without saying that regulatory agencies will need to collaborate with sponsors and academia to support validation processes to allow incorporation of biomarkers into drug approvals. In addition, regulatory processes to support approval of diagnostic tests for biomarkers are an emerging issue.

Process maps for the validation of preclinical and clinical biomarkers are likely to share some steps and to have steps that are specific for each area. Scientific consensus over the validity of biomarkers requires an open and active dialog between sponsors and regulators. The Critical Path initiative and the enabling policies and regulatory documents emerging from this effort have set the stage for the dialog that can lead to this consensus in the US. In Europe the Innovative Medicines Initiative seeks to support similar goals.

Detecting Safety Signals Using Enriched Populations

It is difficult to design a clinical study to provide reliable inferences about safety effects of drugs in addition to providing robust evidence for efficacy. Patient eligibility criteria and experimental design are appropriately targeted at demonstrating primary efficacy endpoints. Specification of safety endpoints is often a problem, either because there are too many potential endpoints to be able to control statistical errors or the endpoints are too infrequent in the study to assess with appropriate statistical power.

Randomized clinical trial (RCT) populations ideally aim to reflect the patients who will ultimately receive the study treatment in practice. Therefore, applicability of the results to real-world use is a major issue for RCTs. For example, patients treated in clinical practice often differ from trial participants, who tend to be younger and healthier. However, the results of RCTs performed in these highly selected groups are extrapolated to higher-risk populations despite the fact that the efficacy and safety of new therapies likely differ across such populations. In addition, clinical research is frequently performed in academic environments, which differ from most common patient care settings, although this trend may be changing. Finally, large global studies may not fully reflect regional differences in clinical presentation, patterns of care, and outcomes. The scientific and ethical challenges of data from RCTs conducted mainly in developing countries owing to the globalization of clinical research is an issue that has recently been of regulatory concern.

RCTs can be 'enriched' by including higher-risk populations during the early (Phase Ib/II and/or adaptive designed trials) and late phases of development. The real-world applicability of RCTs can also be improved by encouraging recruitment in typical patient clinical care settings in a broad geographic outreach to achieve consistency and geographic validity. Attempts should also be made to reduce regional variations in processes of care and background therapies.

The New and Evolving Paradigm of Integrated Lifecycle Safety and Risk Management

Risk management programs should be based on high-quality assessment of safety signals during drug development. When implemented appropriately, risk management contributes to establishing a continuum between assessment of benefit:risk pre-approval and optimizing benefit:risk post-approval. By assessing and defining safety parameters, the evaluation of benefit:risk can support appropriate use of a product throughout its lifecycle .

The lifecycle approach requires safety and efficacy to be evaluated continuously before and after market approval of a product. Before approval, clinical trials will demonstrate drug safety and efficacy in small, controlled populations. After approval, drug risks and benefits will continue to be assessed under rigorous requirements for safety surveillance and risk minimization in real-world medical practice. The lifecycle approach has been endorsed in the US by the FDAAA of 2007 and in the EU by the EMA's Road Map initiative.[5]

Involvement of pharmacovigilance experts throughout the product lifecycle is critical and is occurring at a much earlier stage than in the past, and long before license application. Often the pharmacovigilance plan will need to be discussed with regulators as part of the clinical development plan. A safety specification and pharmacovigilance plan can also be developed for products already on the market (e.g. for a new indication or regarding a major new safety concern). Such a plan should be used as the basis for discussion of pharmacovigilance activities with regulators.[6]

The new and evolving paradigm of integrated lifecycle safety and risk management creates exciting opportunities for newer tools, techniques, and approaches to more successfully optimize product development, approval, and commercialization—with patients as the ultimate beneficiaries. Many risk management interventions were designed and implemented in reaction to new safety information, mainly in an attempt to avoid product withdrawal. There is now a desire for a continuous improvement culture with proactive pharmacovigilance and risk minimization methods. Given its nature, risk management is a constantly evolving process and biopharmaceutical companies should look for ways to improve their approach to, and execution of, risk management plans.[7]

Risk Communication

While recent initiatives—such as the FDA's work to make important information more prominent on labels—have addressed some of the issues relating to clarity of communication, there is still room for improvement in terms of refining communication methods to physicians as well as patients to raise awareness of the full extent of

5. Bates DW, Gawande AA, Improving Safety with Information Technology, *N Engl J Med*, 2003;348;2526–34.
6. *New European pharmacovigilance legislation: getting it right*, 2008. Available at: www.isdbweb.org/documents/uploads/neweuropeanpharmacovigilance.pdf
7. Honig P, Lalonde R, The economics of drug development: a grim reality and a role for clinical pharmacology, *Clin Pharmacol Ther*, 2010;87:247–51.

the benefits and risks of medications. The labeling of prescription drugs is intended to ensure the safe use of medicines and effect changes in use when required by new safety information. However, withdrawal of drugs from the market despite label changes and medication errors demonstrates the limitations of labeling as a tool for risk management. As a means for risk communication, labeling continues to be bound to conventional processes for communication and is often restricted in its ability to meet the heterogeneous needs of its intended audience. Technological developments such as electronic prescribing and the availability of electronic decision support systems can effectively implement compliance with labeled conditions of use and safety precautions in the prescription process. It will be one of the major challenges to make labeling readily available and suitable for use in such systems. These types of technologies, as well as bar-coding of medicines and preventive evaluation of labeling and packaging (to improve clarity and readability and to alleviate potential confusion), may also help reduce medication errors.

Concluding Remarks

Implementation of risk management strategies can be more complex than is often appreciated. The overall public health implications are often not considered and there is the danger of reducing the benefits of novel therapeutics to a point where there may be an impact on public health in a negative manner. It is important to get the balance right. There are unprecedented opportunities to improve public health through innovative diagnostics, therapeutics, and expanded access to healthcare. There is also an expectation that the scientific advances that are leading to innovative therapies recognize and minimize risk.

As companies begin to embrace more-formalized risk management plans they will also need to bear in mind the increasing number of stakeholders, which calls for a more comprehensive communication of risk management. Stakeholder involvement is expected to increase, especially as patients are more active in their participation in earlier stages of the process.[8]

Pharmacovigilance is becoming integrated throughout the product lifecycle, involving input from stakeholders from within and external to the pharmaceutical company. Benefit:risk assessment throughout drug development drives successful risk management. Sponsors and regulators are endeavouring to meet the challenges posed by ongoing management and evaluation of safety data, consolidating and integrating data from different sources, and carrying out systematic signal detection and evaluation. With the increasing demand for transparency, communication of potential safety issues, risk minimization strategies, and the correct prescribing and use of medicines are important goals.

The challenges are great and there are no quick solutions but, by focusing on these key aspects, pharmacovigilance systems can be improved to allow more-effective management of the benefit:risk profile of medicinal products. Developing robust processes to assess benefit:risk and implement risk management throughout a molecule's lifecycle will enable us to move closer to the ultimate shared goal of the delivery of the safest and most effective medicines possible in order to maximize their contribution to public health. A key component of this goal is to strive toward a regulatory environment that encourages innovation and appropriate risk management. ■

8. Burnstead B, Streamlining Safety, Data Management and IT Solutions, *European Pharmaceutical Contractor*, 2006;80–2. Available at: www.samedanltd.com/magazine/11/issue/5