Roadmap to risk evaluation and mitigation strategies (REMS) success

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Abstract: Medical safety-related risk management is a rapidly evolving and increasingly important aspect of drug approval and market longevity. To effectively meet the challenges of this new era, we describe a risk management roadmap that proactively yet practically anticipates risk-management requirements, provides the foundation for enduring yet appropriately flexible risk-management practices, and leverages these techniques to efficiently and effectively utilize risk evaluation and mitigation strategies (REMS)/risk minimization programs as market access enablers. This fully integrated risk-management paradigm creates exciting opportunities for newer tools, techniques, and approaches to more successfully optimize product development, approval, and commercialization, with patients as the ultimate beneficiaries.

Keywords: benefit/risk assessment, drug toxicity, risk management

Introduction

The drug approval process is increasingly dependent upon the development of risk-management plans that ensure appropriate prescription behaviors and balanced risk levels. Although these requirements place new responsibilities on pharmaceutical companies, innovative and effective designs of regulatory applications and commercialization plans that ensure optimal usage can help mitigate the associated burdens and even help secure benefits for affected products and patients.

With the pressure of these new expectations, the medical safety-related risk-management paradigm is evolving rapidly. Patients, physicians, and regulators are moving towards a more holistic, contextual benefit/risk equation. The pharmaceutical industry is in the midst of exploring new scientific tools, procedures, relationships and the development of different skillsets to operate effectively in this new era. Successful pharmaceutical leaders will be able to construct and communicate a dynamic yet enduring and meaningful benefit/risk message throughout the drug development and commercialization lifecycle that is not undermined by individual variations or evolving global regulatory requirements.

Risk evaluation and mitigation strategies (REMS) replace voluntary risk-management programs

with legally binding commitments defined by specific requirements, assessment timelines, and civil penalties for noncompliance. Implementation of REMS/risk minimization programs is an exercise in managing complexity, since commitments for an evolving portfolio of products vary considerably. While for the majority of products REMS are still limited to MedGuides [US Food and Drug Administration, 2010a] that can be relatively easily assembled and distributed, obligations to deliver communication plans and various parts of ‘elements to assure safe use’ require consistent coordination across many parties and processes that sometimes last indefinitely. Furthermore, failure to adequately execute REMS elements can lead to the often-impossible task of retroactive compliance. Thus, effective implementation early in the process is essential to remaining compliant and enabling more sustained drug lifecycle management.

In this article, we present a roadmap for proactively shaping the risk-management strategies for products, anticipating risk management requirements, and creating and implementing well-formulated risk-management plans. For companies that have had the foresight to successfully implement organizational and medical/safety governance models that fully anticipate the new world of risk-management requirements, these tactics will not require major operating

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model changes, but can be achieved through incremental processes or checkpoints laid on existing infrastructure, while for others it could mean a complete transformation [Wherry and Balian, 2010].

Overview of risk-management roadmap

This article proposes five major stages in creating a holistic risk-management framework as illustrated in Figure 1: (1) shaping the benefit/risk profile and drug development decisions; (2) articulating risk-management plans, as appropriate, in regulatory submissions; (3) implementing risk-management plans and strategies; (4) risk-management monitoring, assessment, and refinement/revision; and (5) conducting portfolio assessments.

Stage 1: shaping the benefit/risk profile and drug development decisions

Safety and efficacy are longstanding concepts in drug development. Historically, however, safety has tended to have the more static definition, typically implying a bar to be met. Similarly, public interpretation of regulatory drug approval is seen

as a stamp that the drug will be efficacious and safe. In reality, of course, safety and efficacy are evaluated in patient populations, in aggregate, so that the individual who experiences a safety risk is not necessarily the same person who experiences the benefit. In an effort to better capture and communicate this nuance, especially as increasing product complexity makes the implicit tradeoffs more important, the concept of maintaining a positive 'benefit/risk' profile is more appropriate. Implicit in this terminology is the concept that risk is always present in some form and safety becomes a question of proving that the benefits outweigh the potential incidence and type of safety risks in the target population [Goldmann, 2008].

Recent regulatory activity, and specifically the institution of REMS (and previously EU-RMP and RiskMAP) requirements, has been undertaken to more systematically evaluate this benefit/risk balance and implement plans to ensure this balance remains positive [US Food and Drug Administration, 2009a; European Medicines Agency, 2008]. While it is tempting to develop a specific REMS or EU-RMP to

The risk management process within drug development can be broken down into four distinct stages

Figure 1. Risk-management roadmap stages.

respond to an individual regulatory requirement, tying a holistic risk mindset into development and marketing efficacy discussions and product decisions helps to meet higher expectations about patient safety and potentially market success as safety increasingly becomes a vital product differentiator. Thus, a thorough understanding of risk that takes regulatory and market context into consideration ensures that product sponsors can prepare for regulatory activities and create post-market confidence that patients are benefiting from use of the drug.

Figure 2 illustrates key steps within the product lifecycle that can be used in proactive, iterative development of the overall risk-management plan. While specific steps and exact milestones for each step may vary from organization to organization and product to product, this process map provides a starting point from which to develop a roadmap for efficient risk management and informed decision making.

Traditional pharmacovigilance (PV) tools and more recent approaches to data sources and techniques should be pursued throughout drug development to inform on product planning and decision making. Although such emphasis

on early evaluation of benefit/risk may initially require additional resources, these upfront costs are well balanced by cost savings in realizing better trial design, contingency planning, preparedness for regulatory documentation, potentially earlier drug approvals, and more sustained postmarketing lifecycle.

The following tactical areas provide recommendations on how to develop a true company-wide management of the benefit/risk profile throughout a drug's lifecycle.

Use broad sources of safety information and tools early to build a fact base of safety evidence that informs product decisions. While safety signal surveillance is an established function within PV organizations, safety is increasingly becoming the key differentiator in product and regulatory strategy decisions. Thus organizations should embed and further the safety surveillance capabilities earlier in the drug development process to inform product decisions. Expanding the sources and tools to access safety data earlier and more consistently throughout the drug's lifecycle, will result in more efficient compliance, less late stage attrition, postmarketing advantages, and cost savings.

Figure 2. Process map of risk management in drug development and postmarketing.

The following tools provide opportunities to systematically integrate safety information beyond data from controlled trials, and create visibility and increased clarity into lower frequency or ambiguous safety risks. Several of these sources of data have not been widely adopted but have the potential to improve understanding of benefit/risk and guide asset program strategy, planning, and decision making.

Predictive modeling. The application of predictive modeling techniques, such as Bayesian methods, can lead to earlier anticipation of high-risk areas for thorough exploration in drug development, anticipate results leading to a fewer number of subjects needed in clinical development or increase confidence in the outcomes of clinical trials or a drug's postmarketing performance with respect to new subpopulations [Berry, 2001].

Academia. Academic research can provide access to information collected outside of an organization's own trial data to support safety evidence, provide insight into likely safety issues, and suggest other efficient ways of providing confidence in drug safety. For example, academic work at Georgetown University led to the discovery that CYP2C19 drug metabolic diversity was linked to distinct genotypes, this lead to screening methods for drugs that undergo metabolism by CYP2C19 to identify potential for adverse drug reactions [Balian *et al.* 1995]. Similarly, other academic discoveries, such as the development of a mathematical model that simulates QTc elongation in the heart, can be successfully used to enhance data analysis and reduce risk-management costs [Clifford, 2006].

Nontraditional data sources. Rich sources of 'nontraditional' data can also be used to provide better safety evidence through 'real-world clinical trials'. These nontraditional data sources include online physician communities, consumer-generated media, and use of aggregated patient electronic health records (EHRs), e.g. accessing de-identified data including clinical, insurance claims, patient outcomes data, pharmacy, and laboratory records. By accessing this data, pharmaceutical companies may be able to buttress their understanding of potential safety risks or support benefit/risk profile development by reducing investing in new trial activity that would be needed to support new risk-management assertions. For example, evaluation of

aggregated health records could lead to identification of subpopulations with variations in either efficacy or safety, thus indicating off-label benefits of the product, or suggest latent safety issues that were not identified in small patient numbers associated with controlled trials. Data collaborations could expand the data that is available for safety signal assessment and interpretation leading to the identification of rarer events not apparent in smaller datasets.

Industry collaboration. As with the use of non-traditional data sources, industry–industry or industry–health authority collaborations expand the sample size and capabilities and aid in safety evaluations not possible with smaller datasets. For example, the Predictive Safety Testing Consortium (PSTC) is a public–private partnership of pharmaceutical companies who share and validate each other's safety testing methods as part of a US Food and Drug Administration (FDA) and European Medicines Agency (EMA) critical path initiative in five working groups: carcinogenicity, kidney, liver, muscle and vascular injury. The PSTC has been successful in identifying biomarkers of renal injury leading to submission of the first biomarker qualification package to the FDA and EMA [Predictive Safety Testing Consortium, 2010]. Similarly, the International Serious Adverse Event Consortium (iSAEC) is a nonprofit industry–FDA–academic consortium initiated in 2007 to identify DNA variants useful in predicting the risk of drug-related serious adverse events (SAEs). The iSAEC has been successful in identifying MHC chromosome 6 in the pathogenicity of drug-induced liver injury [International Serious Adverse Event Consortium, 2010].

Evaluate product safety information through various lenses to create a more accurate, contextual understanding of potential issues and advantages in order to guide product decision making. Both regulatory approval and postmarketing success depend on a range of contextual factors including the profile of available alternatives. External information can provide important cues about the drug's benefit/risk profile relative to other products and standard of care. Therefore, early consideration of, and continuous updates to, the benefit/risk profile using multiple perspectives will direct rational development and portfolio decisions.

Therapeutic landscape. Collection and assessment of safety data provided by preclinical, clinical, and postmarketing ‘real-world’ trials is enhanced by understanding alternative therapies and competing trial results. Thus, formulation of the benefit/risk profile should consider implications of safety events in context of current standard of care, alternate treatment options, specific populations and subpopulations for which there are benefit/risk advantages of one therapy versus another.

Regulatory landscape. Given the varying bar for drug approval, it is contingencies. Health authority guidance, published articles, public forums and other information gleaned from health authority releases can instruct on particular issues of concern and likely scenarios in health authority approaches to various benefits or risks.

Build closer collaboration between product teams and epidemiology to help maximize value from population and disease insights throughout

the product lifecycle. Epidemiological tools can be used to enhance understanding and assessment of the benefit/risk of drugs in development and postmarketing [Eichler *et al.* 2006]. Epidemiological insights can be especially important in postmarketing monitoring and compliance with formal risk management requirements, e.g., REMS/EU-RMPs. Organizations should consider three areas in unlocking more of the function’s value potential (Box 1).

Make organizational changes to hardwire internal communication of holistic benefit/risk profile into all product decisions and deliverables. Optimization of internal communications is key in a holistic risk-management approach. Breakdowns in communication can result in serious development failures at any stage of development in the absence of consistent and timely communication of emerging benefit/risk information. Many companies can improve systematic development of appropriate

Box 1. Areas for consideration by organizations to unlock more of the function’s value potential.

Build closer collaboration between product teams and epidemiology throughout the product development process to create enhanced safety signal interpretation and ‘smarter’ hypothesis testing:

- *Subpopulations.* Pharmaceutical companies typically employ epidemiologic evaluations to characterize key subpopulations. However, the potential of epidemiologic evaluations extends to additional areas relevant to risk-management assessment such as to provide further critical insights on ‘real-world’ situations such as cultural treatment habits and goals, provider culture, reimbursement, likely patient flow (e.g., channels, treatment flow, initiation *versus* switch), and relative value of subpopulations (e.g. price premiums for certain subpopulations, payor realities).
- *Background incidence rates.* Background incidence is typically developed to inform on an initial list of potential safety risks. However, assessment of background rates is important throughout development to fully understand the context of the emerging adverse event profile.
- *Disease progression and modifiers.* Epidemiologic assessments drive more precise definitions of the risk profile, avoiding more general and less useful approximate/inappropriate definitions of the target patient groups. Similarly, appropriate epidemiologic modifiers can enhance interpretation of trends and risks. Disease modifiers may also provide insights on best ways to design drug delivery systems to align with existing behavior and, thus, increase compliance and safety.

Build new ways of understanding individual patient diversity by incorporation of advances in pharmacogenomics and personalized medicine

- Understanding individual variation in both disease nuance and implications for benefit/risks of drug interaction allow companies to create more precise markets and explicit risk-management strategies [Becquemont, 2009]. Applications of genetic profiling to interindividual genetic characterizations may aid in the selection of optimal patient subgroups for treatment. Genetic profiling may identify patient subgroups with unique toxicities, leading to a specifically targeted risk-management programs, potentially allowing drugs to remain on the market despite obvious toxicities.

Re-engage epidemiological tools and capabilities in analyzing ‘real-world trials’ of postmarketing data to shore up safety evidence and refine market/commercialization strategy:

- Conduct observational studies to give insights into ‘real-world’ populations, enhance understanding of the natural history of disease, and identify appropriate populations for further clinical study. Drug utilization studies are important in assessment of the effectiveness of implemented risk minimization strategies at predetermined milestones for formalized risk-management assessment updates. Observational/longitudinal trials can be used to inform on potential effects of actual dosing in ‘what-if’ situations (e.g. taking drug a day late, forgetting a dose), identify risk profiles of various subpopulations, and further define which subpopulations (e.g. demographic, incidence of comorbidities) might derive the best benefit from the drug.
- Drive partnerships to enhance epidemiologic capabilities. Epidemiologic partnerships, as with other collaborative efforts, are rapidly progressing both across industry and industry–health authority (e.g. Observational Medical Outcomes Partnership (OMOP) of pharmaceutical industry, academic institutions, nonprofit organizations and FDA and other federal agencies [Observational Medical Outcomes Partnership, 2010]).

communication channels in their organizations. A comprehensive and cohesive benefit/risk profile will be difficult to achieve as long as the components of the profile are exclusively owned by separate parts of the organization. Pharmaceutical companies therefore should make appropriate organizational changes that drive close partnerships to ensure consistent communication of benefit/risk between safety teams and those responsible for development and commercialization to bring about more informed decision making. Examples of potential internal benefit/risk-related communication failures may include the following:

- *Siloing between functions and development phases.* To bring about more informed decision making, pharmaceutical companies may need to make organizational or procedural changes to build consistent communication of benefit/risk between safety teams and those responsible for development, commercialization and lifecycle management.
- *Large numbers of phase III attritions or rework in late drug development to meet regulatory requirements.* In a survey of attrition rates of over 3000 different compounds, the average rate of phase III failures is >35% of which 30% are due to safety issues [Singh *et al.* 2010]. This rate has remained relatively stable, however, the number of failures in phase III resulting from previously identified safety concerns is rising. Clearly, reworking late in drug development is not optimal especially if earlier characterization of unacceptable concerns could have informed decision making.
- *Inadequate preparedness for REMS/risk minimization requirements.* In a coordinated risk-management effort, ongoing alignment of PV evaluations, characteristics of the intended target population, warnings, and precautions in labeling all result in implementation of the appropriate level of REMS/risk minimization. An apparent mismatch between the known safety profile and level of proposed REMS/risk minimization program can lead to significant, and generally highly public and costly, health authority actions with a potential for resulting in protracted negotiations and an overly restrictive REMS or other postmarketing commitments. For example, Roche's Accutane (isotretinoin) faced escalating safety requirements (1982: original warning; 1988: patient consent forms and required pregnancy tests; 2001: 'SMART' program requiring additional pregnancy testing) and finally a REMS requirement for iPLEDGE which took 2 years

from FDA request to implementation, but reduced the pregnancy rate by 63% (from >3/1000 to >1/1000) [Brinker *et al.* 2005].

In addition to maintaining solid PV systems, the principles and tools of risk assessment and minimization must become part of systematic planning throughout drug development and postmarketing, including early and iterative alignment of the safety risk profile, proposed labeling, dossier preparation, launch planning, and REMS/EU-RMP implementation and assessments as described in Figure 3.

To optimize information sharing and consensus among critical internal stakeholders and strategic leadership for risk-management strategies, changes to a company's organization, governance or processes may be needed. Examples of such structural changes are as follows:

- *Safety governance board.* Decisions regarding significant changes to benefit/risk require senior leadership input. A clear medical/safety governance process should be developed for detection, immediate notification, and actions regarding urgent safety signals and the endorsement of safety and risk-management strategies. These bodies must retain independence from development and business teams and their line management to engender complete confidence and avoid impressions of conflict of interest [DAMOCLES Study Group, 2005].
- *Communication platforms.* It is critical to establish clear guidelines and tools to increase transparency and safety considerations. For example, a sponsor designed a process tool (e.g. the Medical Differentiation Index [MDI]) [Christel, 2010] for products in development that highlights safety as one of the core considerations (along with criteria such as efficacy, dosing, tolerance, and convenience) that define how the product compares with existing standard of care and the competitive landscape. The MDI creates a simple visual representation that enables constituents to recognize the characteristics that will drive optimal value. The MDI is self-perpetuating by facilitating feedback from a broad group of internal constituents, payors, healthcare groups, and other external stakeholders.
- *Targeted expertise.* Within-company subject matter experts (SMEs) should be identified early on for consultation on potential drug-induced disease situations (renal toxicity, liver toxicity, etc.). The contact information

Figure 3. Integrated risk management. Reprinted with permission from *DIA Global Forum* [Wherry and Balian, 2010].

on these SMEs should be accessible to product teams and such experts should have the resource flexibility to provide in-depth *ad hoc* support to teams. Internal expertise can be supplemented by external experts to assure SME support for drug-induced disease etiologies and also to pressure test product assumptions and decisions based on real-world expertise on competitive environment, disease, or health system issues.

Engage in scenario planning for alternative safety, market, and regulatory outcomes to avoid disruption, delay, and suboptimal product decisions. Effective scenario planning should account for changes on a range of different contexts and from a diverse set of perspectives. Rather than focusing on whether the product will or will not likely ‘have a REMS’, more attention should be directed to assuming a REMS and focusing on scenario planning around a broad range of elements and types of tools to implement such elements.

Scenario planning for less likely safety outcomes. Pharmaceutical companies should consider the implication of potential developments from safety trials and postmarketing safety reports on a product’s profile and should understand the range of corresponding changes. For example, Vimpat (lacosamide) was initially required to enact a REMS consisting of a MedGuide, but FDA later revised the

requirements to follow the same REMS guidelines for another UCB drug, Cimza (certolizumab). However, UCB was not prepared to formally address these aspects and in adjusting to the requirements ended up delaying approval for 7 months [McCaughan, 2009a].

Scenario planning for less likely environmental (e.g. market, regulatory) shifts. There are also elements to consider beyond the drug itself. Rapid shifts in regulatory or advocacy landscape have become the norm and thus companies are well advised to consider both the obvious trends in risk-management perceptions and regulatory actions (e.g. REMS, class REMS, increased scrutiny and requirements for implementation and assessment of risk-management programs, etc.) as well as less immediate scenarios (such as ‘what-if’ possibilities that REMS status will be extended to all products with preexisting MedGuides [US Food and Drug Administration, 2010b] or that REMS will be extended to include all marketed compounds).

While the concept of REMS being extended to all marketed compounds or to all products with currently in use MedGuides is a possibility but not an immediate certainty, what is a current reality are class-wide REMS (for example, for fluoroquinolones, tumor necrosis factor-alpha antagonists) and the list is expanding. Given this reality, companies are advised to review each of their mature products, regardless of whether such

compounds have a MedGuide to identify key risks and formulate a contingency plan in the event these drugs are included in future class-wide REMS actions. Likely next candidates (aside from the opioids) are groups of drugs with pre-existing class labeling.

Internal preparedness. Pharmaceutical companies are not necessarily poised to respond quickly and strategically to implications of risk management strategy changes. Such ability requires close collaborations across internal functions and fully developing, at risk, alternatives to the lead risk-management strategy. Aside from the time and cost implications of proactive ‘readiness’, such contingency planning has additional secondary gains in strengthening the cross-functional lines of internal communication and consensus building, to more thorough pressure testing of choice scenarios, and to re-evaluation of the risk plan with internal and external SMEs. Thus, developing scenario planning provides clear next steps across the organization and thereby reduces the disruption, delay, and suboptimal execution that such shifts can cause.

Stage 2: articulating risk-management plans

This stage focuses on how best to approach and design a REMS/risk minimization submission from both an organizational and tactical perspective. Risk-management strategies are complex, requiring input from multiple stakeholders and dedicated risk-management functions that can further develop internal expertise with regulatory policy. We review different cost savings that can be achieved by specific tactical approaches, e.g. expanded statistical capabilities, leveraging risk-management plans to follow on indications to help defray market delays, unanticipated implementation costs and rework in subsequent submissions.

If a product requires a REMS/risk minimization plan, the design of the plan and submission can have very important implications for the product’s success. Risk-management requirements will frequently last the lifetime of a product; they are not temporary obstacles but long-term investments.

While the steps described herein focus primarily on US and EU requirements, given the current formalized risk requirements (REMS, EU-RMP, respectively), organizations should plan for a global risk strategy that encompasses a product’s

global approvability. In particular, other company risk-management policies, also undergoing rapid evolution, will need to be met and maintained. While the EU-RMP is generally recognized in other ex-EU countries, it is likely in the future that these other countries will also at some point have unique risk-management requirements. Thus, successful pharmaceutical leaders consider design implications of risk strategy as a global evaluation and strategy affecting approvability in each applicable country.

Assemble an internal risk-management center of excellence to guide development of risk-management plans alongside product teams. Some pharmaceutical companies localize much of the development risk strategy preparation process within each product teams. Product teams provide therapeutic area leadership and expertise regarding the specific drug profile, may be sufficient for delivery of REMS without complex elements to assure safe use, and may be the simplest and most direct approach for smaller companies, for larger pharmaceutical companies or those administering complex REMS. Given the complexities of risk-management documents and alignments, and the formalization of REMS implementation and assessment requirements, a dedicated risk-management center of excellence (COE) can leverage SME advice and provide a much needed dimension of ‘how-to’ practical experience and focused document preparations.

In addition, by establishing a formalized COE, companies may be better positioned to partner with the product team in rapidly designing effective and successful risk-mitigation programs as well as overseeing handoff between benefit/risk teams in product development and risk-management submission/implementation teams for the regulatory and postmarketing processes. There are pros and cons to developing a COE.

Create the COE without necessarily encumbering a significant resource investment. The creation of an internal risk-management or REMS COE does not necessarily involve a significant investment in resources or personnel; it does require, however, an internal orientation towards a strong well-informed function that can have a clear impact on governance, strategic, implementation, or assessment decisions. ‘The whole process requires a significant effort by a company and should have its own discipline and methodology behind it [...] A REMS program is not

a little roadblock on the way to launch that is jumped over before going back to business.' [Silverman, 2009].

Hand tailor the specific team structure to meet the company's risk-management needs. The internal implementation team to support articulation of REMS/risk minimization plans varies depending on a company's product pipeline and portfolio needs, internal organizational capabilities, decision-making authority of a REMS/risk minimization group, and beliefs about the incidence and likelihood of REMS/risk minimization for the company's portfolio of products (refer to Figure 4). Regardless of model, REMS/risk implementation groups should facilitate preparation of the implementation plan by working closely with product teams and regulatory affairs, to facilitate development and handoffs. In Figure 4, three scenarios for REMS/risk minimization development and preparation are considered, depending upon frequency and severity of potential elements.

Pharmaceutical companies should assemble a risk-management COE to assist product teams in preparing risk strategy and documentation to successfully navigate the evolving external

regulatory climate in preparing global submissions. This COE, comprising a cross-functional team of experienced individuals, can assist at a variety of levels for risk-management planning, from a strategic role (e.g. compiling and synthesizing internal and external expertise, SME advice, regulatory feedback and recommendations from guidance/directives) or a more tactical role in facilitating articulation of the risk safety profile and plans, employing best practice processes.

Leverage internal statistical and analytical capabilities to create compelling assessment plans. The need for a REMS/risk minimization plan has, in some cases, raised the need for new capabilities in the teams that are typically responsible for regulatory activities. Specifically, in designing program and implementation plans for assessment activities that are part of some REMS requirements, regulatory or risk-management groups will need to define success metrics. This means internally resolving questions such as: What is the right sample and sample size to be surveyed? What kind of results from patient surveys are acceptable? How do we demonstrate that physician education/certification programs have informed and influenced physician

Degree of investment in specialized REMS expertise	Option	What you have to believe to choose this option
	Products teams own REMS preparation <ul style="list-style-type: none"> Product teams develop benefit/ risk profiles that feed risk mgmt requirements Teams hand off information to regulatory/ medical writing that are responsible for writing REMS late in drug development 	<ul style="list-style-type: none"> Limited products in pipeline and portfolio, including in-market and new indication drugs, requiring REMS Products requiring REMS will only need simple elements such as MedGuides Product teams have the capabilities to collect benefit/ risk data and anticipate/ plan for REMS requirements REMS will not provide opportunities for strategic differentiation among products/competitors
	Product teams prepare for REMS with earlier regulatory/ PV engagement <ul style="list-style-type: none"> Product teams develop benefit/ risk Teams involve PV/regulatory functions earlier in product development to inform design strategy Encourage collaboration and discussion around REMS within PV/regulatory functions and across teams 	<ul style="list-style-type: none"> REMS will rarely include ETASU (e.g. registries) Few in-market drugs in portfolio will require REMS Regulatory/ PV leads on projects will be able to share and leverage internal experience informally or formally REMS requires a basic compilation of data that the organization effectively captures and communicates The product is the most important consideration in REMS design and requirements and there is little applicable information that must be institutionalized
	Distinct REMS center of excellence (CoE) guides risk mgmt development and REMS design <ul style="list-style-type: none"> CoE collects and synthesizes RA and competitive information about REMS CoE works with product teams at pre-determined milestones to develop key risk mgmt deliverables CoE maintains strong, continuous collaboration with product teams to understand nuances of product 	<ul style="list-style-type: none"> Many/ most products, including in-market and pipeline drugs, requiring REMS REMS requirements will include varying, complex, and/ or ongoing submission and implementation elements Product teams lack capabilities/ decision-making authority needed to drive systematic risk mgmt planning Organization can benefit from synthesizing experience/ best practices from submissions, institutional learning needs to be centralized to capture efficiency gains Effective REMS design is a key differentiator in a product's risk management plan and market impact

Figure 4. Organizational approaches to risk evaluation and mitigation strategies (REMS)/risk minimization development.

prescription behavior? To this end, creating a formal link between internal analytical teams (e.g. epidemiology, biostatistics) and regulatory or risk-management functions to support analytical and statistical capabilities needed for new formalized assessment processes of REMS will limit the need for investment in new capabilities. Rather, the latter group can benefit from more sophisticated design considerations if the company can create effective internal processes, such as training and/or communication channels, to support the link.

Gather input from knowledgeable stakeholders to design most appropriate elements for the risk-management plan. Teams should gather early and ongoing input from knowledgeable internal and external stakeholders to design and continue to evaluate the most appropriate elements for REMS/risk minimization programs. This is accomplished by proactively engaging key stakeholders to generate a well-supported recommendation of how best to address safety concerns through a REMS/risk minimization program. Engagement with these stakeholders, which includes regulatory authorities, prescribers, pharmacies, advocacy/patient groups, insurance companies and others, can bring additional insights and new perspectives leading to formulation of a robust position in defending a REMS/risk minimization plan. Furthermore, understanding perspectives from each part of the health system is critical to creating a holistic understanding of how the REMS/risk minimization program will fare once implemented and will provide additional dividends later on by opening up communication channels from which to quickly and efficiently evaluate future challenges in the product benefit/risk profile.

Capture the advantages of risk-management plans by considering REMS/risk minimization programs as strategic enablers. All pharmaceutical companies are familiar with anecdotes about REMS causing long project delays, limiting patient access, and creating onerous and/or expensive implementation challenges. Unfortunately, there are multiple very highly publicized examples, particularly with the older REMS. For example, Entereg (alvimopan) has a very restrictive REMS, significantly limiting sales by restricting it to short-term inpatient use. Thus, if a product requires a specific REMS program the design of the plan and submission can have very important implications. Rather than

considering a REMS/risk minimization implementation program to be a hindrance to marketing success, in some cases pharmaceutical companies find significant advantages in the complexity and processes required in the product's REMS [PR Newswire, 2005]. So rather than 'checking off regulatory boxes', these companies are thinking 'strategically in order to make it a success' [Silverman, 2009]. Examples of using REMS/risk minimization as an enabler are listed in the following.

Use REMS/risk minimization to enhance physician interactions. REMS/risk minimization can help reinforce the value and re-establish the bond between prescribers and sponsors as well as increase 'physician and patient familiarity with the drug profile. This can only ultimately improve perceptions of sponsors and reinforce the value proposition of the products.' [Marre and Berry, 2008]. REMS requirements often increase physician information and therefore comfort level, increasing the likelihood that the drug will be prescribed and the patients remain on the much needed medicine. The increased comfort with a drug on the part of prescribers helps to provide 'a market position that helps the sponsor far more than the added regulatory burden hurts.' [Singer, 2009].

NPlate (romiplostim), a drug developed to increase blood platelet levels, has a restrictive REMS (with patient and physician registries) requiring significant physician time and effort resulting in some physicians prescribing (off-label) Rituxan (rituximab). NPlate developers are using a variety of methods to conduct market research with physicians to forecast their reactions in preparation for the REMS submission, resulting in streamlined electronic delivery that has helped defray the added REMS burdens. This ability to streamline electronic delivery, while potentially saving prescriber time, could also improve the drug's attributes [McCaughan, 2009b; Silverman, 2009]. Similarly, even though Tysabri (natalizumab), a drug with potentially fatal side effects has a very restrictive REMS (including patient, physician, and pharmacy registries along with patient treatment monitoring and other requirements), the drug has still achieved significant market success. Thus, a well-developed REMS may not dissuade use, but rather inform and enable use.

Use REMS/risk minimization to extend a product's lifecycle. By accurately defining a drug's target population or by requiring postmarketing assessments, the FDA can approve drugs with carefully monitored postmarketing programs rather than withholding drugs with otherwise unacceptable risk profiles from the market. The implementation of a REMS program for Tysabri with restricted use in a patient population for which it had a stronger benefit/risk profile allowed the compound to be reintroduced to the market [Taulbee, 2009]. Tysabri has since become almost a blockbuster drug despite the reduced specialty market that it serves. REMS may protect products from generic competition and thereby extend their lifecycle in instances where generic pharmaceutical companies lack the sales forces and other infrastructural elements that are integral to an effective REMS. For example, for many generic companies, REMS that require elements such as educational programs may act as a significant barrier to entry [McCaughan, 2009c].

Use REMS/risk minimization to optimize market impact. In some instances, sponsors of niche or orphan therapies have begun to see benefits from REMS/risk minimization in increasing products' market impact [McCaughan, 2009b]. Also, REMS can enhance the approval of a drug by increasing the FDA's acceptance of the inevitable unknowns associated with drugs and reducing pre-launch requirements for clinical trials. For example, Xenazine (tetraabenazine) had attained a 'fast-track' designation, but there was still a delay in approval until the REMS concept was available [Hughes, 2009].

Strategic flexibility for follow-on indications. Given the new regulatory environment of additional REMS/risk minimization requirements, the ability of follow-on indications to extend the product lifecycle may frequently require new or additional REMS/risk minimization planning. When developing a drug with known or likely follow-on indications, there are several opportunities for a flexible presentation and design of the primary REMS/risk minimization plan to benefit the follow-on indications. These synergistic opportunities include a presentation of the drug's impact in a holistic mechanism-focused format that increases the approvability of similar drugs, the collection of real-world data, and the potential to combine elements of the REMS/risk minimization

implementation to share costs [McCaughan, 2008]. Other potential efficiencies are listed in the following.

Use tools/frameworks to anticipate changes to benefit/risk with follow-on indications. By focusing on common pathway tools in the REMS, there is a higher likelihood of multi-purposing across indications. For example, in Cimzia's REMS application, rather than emphasizing the basic reduction in symptoms seen among patients with Crohn's disease, the application for approval might focus on the pharmacokinetics of the drug and therefore benefit both the rheumatoid arthritis and Crohn's disease indications for the drug.

Incorporate real-world trial data. Data collection from the postmarketing experience of the lead indication can enhance the development and approval speed of follow-on indications. Depending on the characteristics of the two indications, the applicability of such postmarketing data can be used to bolster follow-on submissions; specifically proposals to collect data that supports the efficacy or benefit/risk profile of a follow-on indication may require only minor additional cost to the original process, avoiding preparation of new surveys or deep data mining and statistical analysis efforts.

Stage 3: implementing risk-management plans and strategies

Pharmaceutical companies can reduce compliance challenges around finalizing and implementing complicated REMS/risk minimization plans by leveraging independent medical/safety governance bodies and procedures and instituting small, agile and focused PV and medical affairs teams that ensure accountability and enhance decision making throughout implementation. In addition to ongoing implementation activities, these teams can provide feedback as to the true costs of implementation activities based on a postmortem analysis that can be used to inform the risk-management plan development process.

Leverage new expertise and tools strategically to increase operational efficiencies. Pharmaceutical companies may leverage operational efficiencies by maximizing operational efficiencies in standard operating procedures and by enhancing implementation toolkit and sourcing noncore competencies.

Ensure strategic and informed vendor selection and partnership. Although pharmaceutical companies have always used vendors for certain functions such as clinical operations, some of the more recent REMS/risk minimization requirements oblige these organizations to perform new activities or perform older activities in a new way. The use of vendors and strategic partnerships can provide leverage to sponsors in accessing valuable implementation expertise, and providing flexibility for regulatory requirement variation across products.

In-house versus outsourcing decisions. As with all vendor/outsourcing decisions, companies must assess the frequency and type of expertise necessary to perform implementation tasks. Companies should evaluate their research and development pipeline and look to the market for clues about REMS/risk minimization requirements for similar products, delivery systems, and mechanisms of action to understand what may be the demand for registries, dispensation restrictions, and other elements to assure safe use. Companies should understand the technical capabilities of existing vendors, the quality and comprehensiveness of their offerings, and the level of direct control over a task that is needed to mitigate liability.

Types of vendors and partnerships. Many existing players that already provide services to pharmaceutical companies have developed capabilities in REMS. In addition, niche and peripheral players have begun to specialize in REMS implementation activities and fill in support gaps for activities newer to the pharmaceutical industry such as point-of-service pharmacy data transfer. Contract Research Organizations (CROs) tend to provide the most comprehensive offerings, supporting anything from design to full implementation and postmarketing surveillance. For example, Covance has provided comprehensive services for iPLEDGE, including mandatory registration of prescribers, patients, wholesalers, and pharmacies; laboratory-certified monthly pregnancy tests for female patients; authorization management to ensure all criteria for prescriber, patient, and pharmacy have been met prior to dispensing [Covance, 2005]. Niche players are increasingly expanding their services to include REMS-oriented offerings. For example, Apogenics, ParagonRX, United BioSource Corporation, BioTrak, and Gigamoto Technology Partners provide specific components of REMS.

Use technology to implement coordination and handoff solutions. As programs become more complex, technology can also play an important role in implementation solutions by coordinating the data and exchanges needed for many program components in elements to assure safe use; increasingly system-wide opportunities exist to combine risk management programs with reimbursement support systems and avoid unnecessary costs [Congressional Budget Office, 2008]. For example, for REMS elements that require verification of patient and physician registry, clinical verification and exception handling, there are systems, such as Relay Health's registration verification system, which have the capability of verifying insurance at point of sale and connecting to patient, physician and pharmacy registries [Relay Health, 2010].

Ensure currency of team knowledge of latest risk-management activities. The product teams and specialized PV teams should frequently monitor the external landscape to identify approaches to REMS/risk minimization and uncover innovative FDA/EMA-accepted solutions to regulatory challenges [McCaughan, 2009b]. In addition, the teams should continually remain up to date on newly published literature interpreting regulatory climate and requirements, and should drive ongoing active dialog with the FDA/EMA to obtain further clarity on implementation requirements or specific aspects of the product application.

Ensure coordination with every stakeholder throughout the REMS process. Implementation of elements of risk management could break down at any stage of the process, and in a variety of ways. For each REMS there are different concerns, but successful implementation requires exquisite coordination with virtually every stakeholder. For example, patients still need continuing access to the drug despite a variety of potential REMS challenges, such as inability of the patient to pass online risk-awareness comprehension tests, delays in pharmacy or physician access to instructional materials or test results (e.g. pregnancy tests for iPLEDGE).

REMS programs can be exceedingly complex, involving coordination and documentation of a number of physician, pharmacist, and patient interfaces. Class-wide REMS introduces further complexities, with potential of cross-company coordination or information sharing.

Distribution to restricted wholesalers and pharmacies, assurance of appropriate training requirements for distribution centers, wholesalers and end users involves exquisite coordination and ongoing management. More in-depth REMS also requires ongoing customer service, such as sponsor-appointed case managers to provide regular contact with patients, pharmacies and other end users of the programs. Appropriate, coordinated and timely responses to issues are critical to assure the quality and documentation of ongoing REMS programs.

Stage 4: risk-management monitoring, assessment, and refinement/revision

Maintenance, monitoring, and assessment of REMS activity can represent a significant long-term cost [Kirschenbaum, 2009] with any drug and/or impact on company reputation. However, a comprehensive risk-management approach to the development, implementation, and maintenance of REMS can help mitigate these costs, avoid unnecessary fines associated with regulatory compliance, extend postmarketing longevity, enhance prestige, and provide valuable market insights for new product/indications. As REMS programs are binding legal commitments, pharmaceutical companies are also obligated to demonstrate successful impact and compliance with those measures.

Monitoring, assessment, and interpretation of AEs and safety data is at the core of compliance but each drug with a REMS will have, to a certain extent, a unique profile with its own safety concerns, and the implementation plan/operational approach will vary accordingly. Nevertheless, in each case, there are several principles that are important to consider in determining the best monitoring strategy. The collection and monitoring of this postmarket data also provides information to update a product's benefit/risk profile and reposition it more effectively in the market. Finally, collaboration opportunities can create industry-wide improvements in REMS maintenance and postmarketing monitoring by providing new sources of information and mechanisms for assessing it.

Develop appropriate and effective post-marketing drug safety and compliance strategies. Pharmaceutical companies already conduct post-market monitoring and assessments to assure continued information gathering on drug safety in patients. The introduction of

REMS (and to some extent, the EU-RMP assessment requirements), legally binds sponsors to specific required monitoring activities. As a result, companies should think strategically about their monitoring and compliance end-goals for each product. These strategies should clarify the safety signals that the company is looking for, define the best sources of data for that information, and provide clear triage guidance and communication responses to trigger the gathering of the appropriate data.

Oftentimes, companies will be able to use existing surveillance infrastructure, but where needed, companies may need to leverage new tools that capture this information with appropriate levels of signal-to-noise detection.

The Sentinel Initiative is an effort launched by the FDA in May 2008 in conjunction with several major industry players (e.g. Harvard, Mayo, GE, the VA) with the goal of actively querying 'diverse automated healthcare data holders, such as EHR systems, administrative and insurance claims databases, and registries, to evaluate possible medical product safety issues quickly and reliably.' [Medical News Today, 2009]. A variety of organizations are involved in the Sentinel pilot including insurance groups, academic institutions, and government agencies. As another example, researchers have piloted compiling safety analyses of sequential detailed cumulative data culled from publicly available clinical trial results to monitor for drug safety signals.

Whereas interactions with regulatory authorities have historically involved formal and informed discussions about data uncovered and disclosed either through clinical trials designed and managed by pharmaceutical companies or spontaneous reporting to drug sponsors, efforts like the Sentinel Initiative could create informational asymmetry. Thus, REMS/risk minimization requirements, coupled with regulatory efforts to promote and facilitate more proactive risk management, make ongoing surveillance and monitoring capabilities particularly important.

Identify key safety signals affecting benefit/risk balance. In addition to tracking traditional safety signals in patients, the product profile may require unique or nontraditional safety monitoring challenges [Webster and Fine, 2010]. For example, in addition to standard evaluation of the safety profile of opioids, sponsors face the

difficult challenge of collecting and monitoring data related to incidence of abuse. Sponsors must answer questions such as where are opioids being distributed illegally? What are the system breakdowns that enable this? How common are these risks? Thus, it is critical to effective monitoring of REMS/risk minimization programs that the company accurately identifies all types of safety signals that are important to assessing safety and benefit/risk balance.

Efficiently and effectively triage information internally so that it can be reported to regulatory authorities and inform decisions across the organization. Companies should establish trigger systems along with triage processes that provide standardized guidelines for addressing potential issues by the PV and product teams, evaluation by governance committees and escalation to appropriate seniority levels. It is critical for companies to triage information internally for timely and informed decision making across the organization on changes to the benefit/risk profile of medicines and for rapid communication to the regulatory authority and other external stakeholders.

Leverage or create new tools for monitoring, assessment and reporting. In many cases, compliance with REMS/risk minimization monitoring and assessment rules will leverage existing IT tools and surveillance infrastructure. However, certain types of data collection may also require use or development of more specific or sophisticated analytical mechanisms. Companies will need to consider the extent to which new technology and infrastructure tools may be required. Some examples are discussed below.

Many pharmaceutical companies are already mining payor claims data. EHR reviews are also becoming an increasingly foundational source of data. For example, Humedica provides clients access to clinical data to monitor specific patient subpopulations as to their treatments, therapy time course, sequence of care, and associated outcomes. Humedica further leverages this data in a partnership with Anceta (itself a partnership of AMA, Sanofi-Aventis, and Accenture), to leverage the latter's collaborative data warehouse of participating AMGA multi-specialty medical group members [Anceta, 2010].

As pharmaceutical companies increasingly leverage nontraditional data sources, industry-wide terms for use and interpretation of data should be standardized to facilitate cross-industry collaborations and alignment. For example, while companies are already using EHR data to some extent, there is no clear agreed-upon standard about how to evaluate and report such information in NDA/BLA applications. Pfizer, through the ASTER program ('ADE Spontaneous Triggered Event Reporting') and in partnership with Partners Healthcare in Boston, has piloted a system to automatically extract postmarketing adverse drug reports from the EHR, process the data in a registry-like setting, and report it directly to the FDA [ASTER, 2010]. If expanded, this type of system could end up being one part of an Elements to Assure Safety Use (ETASU) program associated with a REMS. REMS conversations must also be covered in this dialog so that emerging standards alleviate some of the implementation and other burdens that programs may entail.

Pharmaceutical companies will need to assess how they think their surveillance and monitoring needs will progress. In addition, they should evaluate different models for engagement based on desired levels of risk and investment (e.g. participation in round tables, being a vendor's lead customer, JV/acquisition of investment in new technologies).

Share and triage postmarketing safety information with commercial groups to inform market strategy and positioning. While concepts like speaker's bureaus, scripted medical science liaisons, and call center support programs have historically been viewed negatively as inappropriate ways in which pharmaceutical companies have overstepped their bounds in selling drugs, these activities have actually been formalized and legitimized as elements of some REMS programs. As one article suggests, 'It is just possible that the new rules of REMS will mean that marketing practices currently perceived as fraught with abuses are redefined as what they were originally intended to be: the best way to educate prescribers about advances in medicine.' [McCaughan, 2009a].

For postmarketing assets, linkages between clinical research, safety, and marketing are increasingly required. Recognizing the synergies between the collection of data on a drug's

benefit/risk profile and the impact that information has on a product's strategic market positioning is key to maximizing benefits from regulatory compliance. For example, Amgen's postmarketing commitment for Nplate, to continuously track safety-related data (e.g. daily number of treated patients), has been used to the advantage of marketers at Amgen to 'see baseline information about what treatments patients have been on and understand a little more about what's happening with the treatment paradigm faster... [marketing doesn't] have to wait for IMS to report something or do market research.' [Silverman, 2009].

Commercialization/marketing: pharmacovigilance/risk management collaborative data sharing. The new risk-management environment requires companies to move beyond traditional roles of commercialization/marketing (communicating drug benefits) *versus* PV/risk management groups (managing safety risk). As REMS/risk minimization formalizes the communication of benefit/risk to patients and physicians, it is important for these two groups to monitor the drug's performance postmarketing through collaborative data sharing and messaging.

Better understanding of benefits. Enhancing communication between the regulatory compliance functions and commercialization functions within an organization is essential for capitalizing on the information synergies. Assessment processes that provide information on patient responses to REMS/risk minimization communication, compile data on the diagnoses for which a product is prescribed, or provide feedback on the prescriber perception of a product's benefit/risk profile, each provide valuable information that can be used to adjust how a product is presented in the market. Furthermore, feedback that commercial functions, such as sales, receive in the field about a product's real-world performance can provide valuable insights for REMS/risk minimization monitoring activity.

Better understanding of risks. Companies can also learn about safety risks by institutionalizing learning from market-facing parts of their organizations. Gathering information from sales teams, capturing data from medical science liaisons and medical affairs groups, and checking logs of call center support programs can all contribute to a more robust understanding of safety risks. The incidence of safety signals and effects

in real world environments may also yield different results from randomized, controlled studies. Understanding the risks associated with a product can serve to enhance its value as much as understanding its benefits.

Promote industry-wide improvements in risk-management maintenance and postmarketing monitoring. Develop coalitions of industry stakeholders to help reduce inefficiencies that burden the healthcare system. Potential avenues for action by coalitions of industry stakeholders are listed in the following.

Pursue noncompetitive process improvement opportunities to reduce risk management costs. Co-invest in technology projects that would further automate management of implementation and REMS/risk minimization compliance activities (e.g. switch vendors that manage registration and prerequisite validation, IT solutions to manage compliance timelines and deliverables).

Build coalitions of key stakeholders to develop recommendations for improving regulatory standards, evaluation activities, and requirements. Build coalitions that draw upon input from stakeholders such as professional societies, hospitals, and other pharmaceutical companies to develop recommendations for improving regulatory standards, evaluation activities, and requirements.

Nontraditional data sources. Engage in dialog on use of nontraditional data sources in clinical trial design and data monitoring. For example, the FDA data outputs from the 'Safe Use Initiative', a collaboration with healthcare professionals and other stakeholders to 'identify drugs and drug classes that are linked to preventable harm' [US Food and Drug Administration, 2009b] might yield important information on medical misuse or preventable toxicities.

Standardizing tools. Pool postmarketing safety data and assessment conclusions to identify ineffective or even harmful regulatory requirements (e.g. that overly impede patient access) and codevelop alternatives that may more effectively enhance patient welfare.

Advantages to class-wide risk management. Initiate conversations for discussions about class-wide REMS in areas where it would decrease burden on all companies.

For example, class-wide REMS may reduce the complexity of building and implementing REMS, and collaboration could reduce the required components that are legally binding relative to sponsor-specific voluntary submission.

Assemble cross-industry groups to devise approaches on improving dialog with the public and media. Many people currently expect a drug to work for everyone with minimal, if any, side effects. Clear communication with the public, in a more meaningful way than current probabilistic terms, could enhance understanding of what a drug's benefit/risk profile means and improve relations between pharmaceutical companies, the media, and, ultimately, the general public.

Benefit/risk is generally a poorly understood concept in the public and media. As benefit/risk becomes the primary vehicle for communication, pharmaceutical companies should aim to fill the vacuum for interpreting safety information and present frameworks to guide dialog. This becomes especially important when looking at emerging trends where risk-management elements disintermediate traditional pharmaceutical company's relationships with prescribers, and patients take greater ownership of self-education on drugs through user forums and internet research.

Stage 5: overall portfolio risk management

In light of the push towards proactive risk management for drug safety (evidenced by passage of the FDAAA and initiatives such as Sentinel), developing a benefit/risk posture is increasingly becoming a key success factor for all drugs, regardless of stage of development or lifecycle management. This process can also help the industry take ownership of the challenging question of how to enhance drug, and ultimately, patient safety. In practice, however, a company will have to make tradeoffs across its portfolio on which products require greater or more immediate risk management efforts.

Steps 1–4 take a product perspective and describe, in detail, the tactical and operational activities, along with capabilities and governance, required to effectively, plan, implement and monitor risk management approaches for an individual product. However, from time to time, a portfolio-level risk assessment is required to ensure that a pharmaceutical company is

properly allocating its resources. The implementation of annual portfolio reviews is an effective preliminary approach to identifying gaps in current risk management preparations and avoid being forced to retroactively attempt to gather data and development REMS/risk minimization plans.

Annual reviews. Pharmaceutical companies should conduct annual reviews of their entire product portfolio to identify potential emerging risks associated with a product.

A complete annual review of the whole portfolio (especially of established and mature products) from the perspective of benefit/risk is essential for public health and company and product protection. The first review will likely be most time consuming, but subsequent reviews will be able to build on the information and formal processes from previous assessments and thus will be increasingly more efficient in making prioritization and tradeoff decisions about which products need further attention label revisions or risk communication. The next step is to prioritize development of risk-management plans for portfolio products. Companies should develop initial hypotheses of which products may require formal risk management plans.

Establish ownership of postmarketing safety profiles. For mature postmarketing products, internal knowledge of the risk/benefit profile may be limited. For mature products that do not have a dedicated product team, it is vital that pharmaceutical organizations establish an 'on-call' group (PV team and safety physicians, medical affairs, epidemiology, and regulatory affairs) to articulate clear benefit/risk profiles. By constructing such upfront organizational ownership and accountability for all products pharmaceutical companies can reduce the likelihood of being caught unawares by new regulatory requirements or surprises of new findings from external sources and avoid the much larger long-term costs of retroactive risk-management planning.

Conclusions

Pharmaceutical companies are investing in ways to successfully develop and enhance their product portfolio with patient safety foremost in that process. The fast pace of changes in the REMS/risk minimization regulatory climate, with multiple stakeholders each with unique perspectives

and assumptions, and a shrinking operating budget, while ensuring patient access to the medicines discovered makes for a very challenging environment. By using a proactive, holistic approach to integrate risk-management strategy as a prerequisite in every phase of drug development, REMS/risk minimization programs become access enablers. The success of an integrated risk-management strategy is measured not only by traditional measures (approval date, time to launch, market share, etc) but more importantly, in developing an enduring framework of communication and collaboration that opens up exciting and challenging opportunities for newer tools, techniques, approaches, and abilities for the benefit of patient care.

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