Preventing for safety issues following drug approval: pre-approval risk management considerations

Gretchen S. Dieck and Robert G. Sharrar

Abstract: Risk management plans and risk minimization plans as well as postapproval commitment studies are based on risks identified pre-approval that need to be further characterized or minimized in the postmarketing environment. Although the implementation of these activities are conducted in the postapproval arena, the design of the plans and studies as well as the development of effective postapproval tools and mitigation strategies should be carried out pre-approval. The pre-approval period also provides the opportunity to fully understand the treatment population that is included in the clinical trial program and to determine how the target population for the drug after approval may differ from the clinical trial patient population. When regulators or sponsors have expressed concerns about safety issues identified during clinical development, the result may be a postapproval commitment in the form of a registry or an observational safety study or, in the US, a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval. Specific examples are given for risk mitigation activities that can be conducted pre-approval.

Keywords: pre-approval, postapproval, risk management, risk mitigation, safety

Introduction

In order for a biopharmaceutical company to obtain approval to market a product, it must prove to the satisfaction of regulatory agencies that the benefit–risk balance of the product is positive. Clinical trials, which are powered on efficacy, are designed to answer this question from the regulatory perspective. From the patient perspective, all risks about a medicine should be identified and fully understood before the drug is approved; however, the process for developing medicinal compounds for clinical use and the science of identifying risks are such that only the most commonly occurring risks are identified before the drug is approved for general use. Clinical trials are typically carried out with too few individuals to identify rare, serious risks and are not conducted for a long enough period of time to identify risks with long latency periods or risks associated with long-term use. Furthermore, clinical trials are conducted on a relatively homogeneous population under ideal circumstances. In the postmarketing environment a drug may be given for many years to a large number of individuals, many of whom have multiple medical problems and are on multiple concurrent medications. Unanticipated and unknown safety issues may become apparent in the postapproval period [Dieck et al. 2009].

This paper discusses what a biopharmaceutical company can do during drug development to pro-actively prepare to monitor and assess patient safety in the postapproval period. It is targeted toward smaller companies that may not have extensive experience in the area of risk management or personnel dedicated to these issues. The paper may also be pertinent to larger companies where development teams may have competing priorities around the peri-approval period where a reminder of some straightforward and relatively inexpensive preparatory activities may be useful. For instance, it is less costly to examine automated databases to determine the underlying occurrence rate of an event of interest in the target population pre-approval,
than to quickly set up a comparative *de novo* study to evaluate comparative risk postapproval. Although these activities may not be inexpensive themselves, they are less expensive than the alternative.

The paper also focuses on activities that are carried out in the US, Canada, Europe and other areas where there are regulations for risk management, although some of these activities can be carried out in other regions where there is sufficient infrastructure and adequate exposed population. A companion paper will discuss how a sponsor can monitor safety and assess risk post-approval [Sharrar and Dieck, 2013].

Globally, regulatory agencies are concerned about risk management, which includes risk assessment and risk mitigation. Guidance documents and regulations have been issued that have addressed these issues through pharmacovigilance, signal detection, observational studies and registries [Committee for Medicinal Products for Human Use, 2005, 2008; European Union, 2010; Food and Drug Administration, 2005a, 2005b, 2005c; International Conference on Harmonisation, 2005].

One guidance or regulation that applies to risk management is in reference to the development of a risk management plan (RMP), which is required by the European Medicines Agency (EMA) for all new submissions. The new EMA template [European Medicines Agency, 2013], which was released in April 2013, contains seven parts. The details of the different sections are explained within the template. Essentially, the RMP is a summary of what is known about the product and the target population at the time of the application. It contains a summary of all of the important data collected during clinical development and a description of the epidemiology and natural history of the target population. It also includes missing information or data on populations that were not studied in clinical development, but who might receive the drug postauthorization. This information is important because it is needed to properly assess adverse events that are reported in the postauthorization period. The new EMA template also has a new section, Part IV, which discusses the need for postauthorization long-term and real world efficacy studies for certain medicinal products. This reflects the Agency’s agencies desires to shift from a risk assessment to a benefit–risk assessment. These data are used to determine the important identified and potential risks and missing information that are discussed, evaluated and minimized in the rest of the RMP. It is not possible or necessary to address all of the identified and potential risks, so regulatory agencies want biopharmaceutical companies to focus on important risks. The most difficult part of developing an RMP is to determine which risks may potentially impact the benefit–risk balance and requires input from many different components of the company including input from clinical pharmacology, clinical development, epidemiology and pharmacovigilance as well as from regulatory agencies. This should be done as early in the drug development process as possible. The EMA definitions [European Medicines Agency, 2012] in Table 1 should be used as guiding principles; however, these definitions are not precise and allow room for individual interpretation. Questions that should be considered include: how is an adverse reaction seen in nonclinical studies confirmed or not confirmed in clinical trials, and what is the magnitude of difference between a treated and control group that should be used to distinguish between an indentified or potential risk and no risk at all? What constitutes an important risk will depend on several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health (absolute number of events). Normally, any risk that is likely to be included in the contraindications or warnings and precautions sections of the product information should be considered important.

While the EMA requires a RMP for all product applications, the FDA may require a Risk Evaluation and Mitigation Strategy (REMS) for some products to ensure that the benefits of the product outweigh its risk [Food and Drug Administration, 2007]. A REMS focuses on some of the strategies that may be described in Part V of the RMP. Among the strategies that may comprise a REMS include: a Medication Guide to educate the patients about the safety risks associated with the product and about how to properly take the product, a Communication Plan to educate healthcare providers about the risks associated with the product; and Elements To Assure Safe Use (ETASU), which restrict the distribution of the product in some fashion by requiring certification of prescribers and pharmacists, by restricting use to inpatient settings, by monitoring patients, by only dispensing to patients with...
RMPs and risk minimization plans as well as postapproval commitment studies are based on the identified risks that need to be further characterized or minimized in the postmarketing environment. Although the implementation of these activities are conducted in the postapproval arena, the design of the plans and studies as well as the development of effective postapproval tools and mitigation strategies should be carried out pre-approval.

Pre-approval planning for proactive risk management

Ideally, proactive risk management begins early in product development, well before the dossier or new drug application is submitted to regulators for approval. The pre-approval period provides opportunities to develop risk management strategies and risk minimization scenarios while beginning to compile the safety profile of the product and put together the RMP. The clinical development period also provides the opportunity for identifying and quantifying potential unique benefits of the compound. Identifying a unique benefit is useful, particularly as it may be instrumental in keeping a drug on the market if the compound is later found to have a unique and serious risk. The pre-approval period also provides the opportunity to fully understand the treatment population that is included in the clinical trial program and to determine how the target population for the drug after approval may differ from the clinical trial patient population. These differences may be related to exclusion in the clinical trials of patients who are at the severe end of the spectrum of a disease, patients who are on multiple concomitant medications and patients who are in special demographic groups such as the elderly or women of

**Table 1.** EMA definition of important regulatory terms [European Medicines Agency, 2012].

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Adverse event/experience</td>
<td>Any unfavorable and unintended sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medical product.</td>
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<tr>
<td>Adverse reaction/drug reaction</td>
<td>A response to a medicinal product which is noxious and unintended and in which a causal association between the medicinal product and the adverse event is at least a reasonable possibility.</td>
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<td>Identified risk</td>
<td>An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include: (1) an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data, (2) an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest suggests a causal association, or (3) an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.</td>
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<tr>
<td>Important identified and potential risk</td>
<td>Any risk that could have an impact on the risk–benefit balance of the product or have implications for public health.</td>
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<td>Missing information</td>
<td>Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the market place.</td>
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<tr>
<td>Potential risk</td>
<td>An untoward occurrence for which there is some basis for suspicion of an association with the product of interest but where this association has not been confirmed. Examples include: (1) nonclinical safety concerns that have not been observed or resolved in clinical studies, (2) adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal association, (3) a signal arising from a spontaneous adverse reaction reporting system, or (4) an event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.</td>
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<tr>
<td>Risk–benefit balance</td>
<td>An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks.</td>
</tr>
<tr>
<td>Risks related to the use of a medicinal product</td>
<td>Any risk relating to the quality, safety, or efficacy of the medicinal product as regards patients’ health or public health and any risk of undesirable effects on the environment.</td>
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documentation of safe-use conditions or by requiring a patient registry.
reproductive potential. It is important to understand as much as possible how the clinical trial experience a drug will differ from post-market use. Many of these activities are listed in Table 2.

It is no longer sufficient to say that a particular risk is associated with a product. Regulators now expect sponsors to further characterize the risk in terms of quantifying the risk in different segments or subgroups of the population and to determine if there are risk factors that could explain why some individuals taking the drug experience the adverse event while others do not. For example, if the clinical trials show an increase in risk of certain adverse events among those taking the study compound (e.g., increase in risk of gall bladder disease in an overactive bladder compound or significant weight gain in patients treated with a compound for neuropathic pain) a nested case–control study can be carried out within the active study arm of the clinical trial, comparing those that exhibited the adverse event to those that did not. By carrying out these types of analyses, it may be possible to identify factors that may predict why some individuals may develop the adverse event of interest while others do not. Such information can be used in the product label or may result in hypotheses that lead to further study.

Further characterization of the target population being treated can also be conducted pre-approval, particularly in reference to particular real or hypothetical risks of interest through the use of

<table>
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<th>Focus of activities in pre-approval period</th>
<th>Activities</th>
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| Activities related to compilation of RMP and/or REMS | • Design of materials such as:
  • Medication Guide
  • Invitation letters
  • Forms
  • Educational materials
  • Prescriber Communication Plan
  • Special instructions to prescribers
  • Physician–patient agreement
  • Patient reminders
  • IRB approvals
  • Design of postmarketing study or registry
  • Testing of product packaging as mitigation tool
  • Determine need and options for pharmacist and prescriber certification
| Activities carried out using clinical trial data or using clinical trial patients and investigators | • Nested case–control study in clinical trial exposed population on issue of interest
• Consenting clinical trial patients for direct patient interviews for future studies
• Testing understandability of materials such as:
  • Medication Guide
  • Invitation letters
  • Forms
  • Educational materials
  • Special instructions for prescribers
  • Physician–patient agreement
  • Patient reminders
  • Test monitoring for abnormal laboratory values
  • Test recognition of important signs and symptoms that may be part of RMP or REMS
| Activities focused on information derived from automated databases | • Design and conduct of studies to determine occurrence rate of events of interest in target population
• Identification of subgroups with additional risk that may need special mitigation activities (elderly, pregnant women)
automated databases including administrative databases such as claims data or medical records databases. Depending on the outcomes of interest, claims databases and electronic medical records (EMRs) can be used to determine the incidence of certain conditions or outcomes in the treatment population or the occurrence rate of certain adverse events in patients on similar drugs. Claims data are most useful for outcomes where there are hard endpoints such as death or hospitalization and for circumstances where important confounding information such as body mass index or smoking status and alcohol use are not necessary as they are often missing [Hennessy, 2006]. The use of multiple data sources to confirm study findings provides stronger support [Food and Drug Administration, 2013] and should be considered when a drug or biologic will be used globally as regional differences in the treatment population may be important. The information provided by studies using automated databases can be used in RMPs to estimate the occurrence of identified or potential risks, and can be used to inform regulators on what to expect when the study drug is approved and available for use. Although not as large as automated claims data, databases comprised of EMRs can be used to better characterize the treatment population under ‘real life’ circumstances and provide data from a provider rather than a reimbursement perspective [Hall et al. 2012; Hennessy, 2006; Strom, 2012].

An example of using automated data resources to characterize risk pre-approval is found with work carried out for the drug Geodon® (ziprasidone). Geodon was found in the clinical development program to have evidence of QT prolongation with the potential to lead to torsades de pointes and sudden death. Several studies were conducted pre-approval on automated databases to help characterize the risk of sudden death or cardiac morbidity and mortality. The first was a study of cardiac arrest and ventricular arrhythmia in patients with schizophrenia taking the antipsychotic drugs clozapine, haloperidol, risperidone or thioridazine compared with nonpsychotic controls [Hennessy et al. 2002]. This study was carried out using Medicaid data and showed that patients with treated schizophrenia had higher rates of cardiac arrest and ventricular arrhythmia than the comparison group of patients with glaucoma or psoriasis. A second study examined similar cardiovascular morbidity and mortality outcomes in the Saskatchewan, Canada, data resource among patients diagnosed with schizophrenia compared with those with no diagnosis of schizophrenia or other mental disorders and who had no prescriptions for antipsychotic medicines. Similar findings were noted in that those with schizophrenia had significantly increased risks of a number of cardiovascular outcomes compared with those without [Curkendall et al. 2005]. This information is useful in showing that the underlying disease of schizophrenia (regardless of treatment) may be related to the event of interest as opposed to the treatment. It is advantageous to conduct these types of analyses in multiple data sources as demonstrating similar finding in multiple sources lends strength to the findings.

In addition to carrying out studies to see whether the treatment population of schizophrenics were at higher risk of serious cardiac outcomes, the sponsor also examined whether antipsychotic drugs with greater QT prolongation (>25 ms) that were already on the market were found to have increased cardiac risk compared with those with less QT prolongation (<10 ms) although it is important to keep in mind that the extent to which a compound affects QT may not be indicative of its affect on risk. In the previously mentioned study using Medicaid data [Hennessy et al. 2002], thioridazine (greater QT prolongation) was not associated with a higher rate of cardiac arrest and ventricular arrhythmia than haloperidol (lower QT prolongation) (rate ratio 0.9, 95% CI 0.7–1.2) although a significantly higher rate ratio was found for high-dose thioridazine compared with haloperidol. In a second study, patient experience from the (then called) General Practice Research Database (GPRD) were analyzed to determine serious cardiac risk in users of haloperidol compared with users of thioridazine [Hennessy et al. 2004]. The study had similar findings in that there was no evidence of an association between the use of thioridazine and the rate of ventricular arrhythmia, sudden death or unattended death compared with users of haloperidol. These studies helped the sponsor to estimate the potential risk of cardiac events with ziprasidone which had QT-prolonging properties in between those of haloperidol and thioridazine.

Pre-approval consideration of registries or observational studies

When regulators or sponsors have expressed concerns about safety issues identified during clinical development, the result may be a postapproval commitment in the form of a registry or an observational safety study as a condition of approval. A
registry is a postapproval tool that is composed of a cohort of individuals with a particular disease in a defined population or in individuals exposed to a specific medication. Observational registries can be used to characterize important identified risks, to determine the significance of important potential risks or to understand the relationships between treatment and outcomes with respect to unknown risks. When little is known about the course of the underlying disease, registries containing patients with the specific disease are useful for learning more about the target population, the disease itself and potentially for identifying important subgroups of patients who may experience differences in the course of the disease. Before approval, disease registries can provide information on current treatment patterns and may identify factors that drive treatment. Collecting observational information on cohorts of individuals with specific exposures or on diseases under ‘real-life’ circumstances provides for flexibility in identifying and responding to postapproval safety issues quickly. The information collected facilitates identifying and characterizing risks in real time and also serves as a framework or contributes to the design of future studies. The design of a registry may be included in the RMP to the EMA, or may be part of a postapproval commitment to the FDA.

Both disease registries and exposure registries document actual clinical practice and as such, may be useful for understanding facilitators or barriers to treatments. Registries can also be used to calculate rates as the total registry population serves as a defined denominator. This is particularly important in determining if an important potential risk is occurring at a higher rate than expected. The need for a pregnancy registry (a type of exposure registry) may be identified pre-approval based on preclinical or clinical evidence of reproductive risks or teratogenicity and again, may be an important component of the RMP or may be a key element of a postapproval commitment.

Much of the design of a registry can be carried out pre-approval. Registry protocols can be written and potentially sent to regulators for input and comments, the countries and sites where the registry will be implemented can be determined and IRB-equivalent approvals obtained, and many of the forms, invitation letters and communication or educational tools can all be designed and evaluated pre-approval. Sponsors can set up their own exposure registry or may join an already existing registry for a particular treatment population and then follow their own compound once it is approved. In order for this to be effective, sponsors must identify and evaluate the suitability of existing exposure registries pre-approval.

Although a powerful postapproval surveillance tool, registries are not usually used for comparative hypothesis testing as they typically lack a control group. Global registries are also challenging in that a product is often approved at different times in various countries making implementation of the registry difficult. In these circumstances, it may be advisable to carry out an observational study to overcome some of these limitations.

When regulators or sponsors have identified a risk pre-approval to be evaluated in a formal study as a postapproval commitment, the sponsor and regulators agree to a study design and a timetable for the study to be carried out in a timely fashion. Often these studies are a condition of approval and, as with many registries, much of the design on operational aspects of the study can be performed pre-approval. An example of an observational safety study that was carried out as a condition of approval was the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) which was an international, multicenter study comparing the relative incidence of nonsuicide mortality in users of Geodon compared with Zyprexa® (olanzapine) [Strom et al. 2011]. The pre-approval identified risk was QT prolongation and regulatory agencies were concerned about an increased risk of cardiovascular mortality in schizophrenic patients taking ziprasidone. The study was completed in 2007 with no finding of an increased risk of nonsuicide mortality in users of ziprasidone. The design of the study was developed as well as many of the operational features of the study before drug approval.

**Proactive risk mitigation strategies pre-approval**

The product development period can also be used to design and evaluate postapproval risk mitigation strategies and interventions. Planning risk management strategies, including the need for a REMS, earlier in the development program provides more flexibility for developing a comprehensive plan. The focus of the planning should be on those important risks, both identified and potential, that may tip the benefit–risk balance of the drug. There may be sufficient knowledge...
about the compound or its class that suggests a priori postapproval risk minimization actions. For example, some compounds may have an interaction with other drugs or with certain foods or are associated with significant changes in laboratory values. These circumstances may suggest obvious postapproval mitigation strategies such as informing the patient through a Medication Guide, putting stickers on the medication for potential interactions, or requiring monitoring for abnormal laboratory values. In some instances, using these types of strategies may sufficiently mitigate the postapproval risk, particularly if the sponsor is able to develop and test the effectiveness of the mitigation activity before approval.

Postapproval risk mitigation strategies to be considered in the planning phase of clinical development include risks associated with the drug class. For instance, if class labeling exists for similar drugs that are already on the market and those marketed drugs have postapproval commitments or REMS, then the sponsor of the development compound may need to consider similar postapproval activities. For example, the REMS commitments for the long-acting beta agonists initially applied to products that had been on the market for some time such as Symbicort® (budesonide/formoterol) as well as for newly approved drugs such as Arcapta® (indacaterol). Although the entire class was subsequently released from its REMS requirements, this example is still pertinent in instances where sponsors have a class REMS. Similarly, class-wide REMS requirements are applied to new manufacturers or new supplemental New Drug Applications (sNDAs) approved for extended release and long-acting opiates where the details of the REMS have already been worked out and are being implemented by a single shared system. Other issues requiring postapproval mitigation strategies are preclinical findings of reproductive risks or teratogenicity. If reproductive or teratogenic risk signals are seen in development, then educational materials, a REMS, a pregnancy registry, or a postapproval safety study may be needed once the drug is marketed. For example, the Vibativ® (telavancin hydrochloride) Pregnancy Registry [Food and Drug Administration, 2000] was set up in response to preclinical evidence of limb malformations. Elements of these postapproval mitigation strategies can be developed and tested pre-approval such as the Medication Guide, the prescriber Communication Plan, the Patient–Prescriber Agreement, educational materials and certain other elements of the REMS. Educational materials can be tested using the clinical trial patient population and certain types of patient reminders can be evaluated such as whether patients adhere to using birth control measures for teratogenic drugs or whether reminder notices for blood monitoring are understood and followed. Options for restricted distribution can be evaluated if it appears that restricted distribution is the optimal form of risk mitigation for the drug. The need for prescriber and/or pharmacist certification can be determined and the respective attestation points can be developed.

Other risks that can and should be proactively considered include those obtained from clinical pharmacology studies that may suggest potential postapproval risks related to how the drug works intrinsically or to how it is metabolized. Risk mitigation strategies may include determining whether monitoring for abnormal laboratory values should be recommended for risks such as potential liver or renal injury or whether concomitant medications that use the same metabolic pathways should be avoided. Information on the mechanism of action of the drug may also suggest potential patient risks with the subsequent need for the development of appropriate risk mitigation strategies. Examples of potential risks due to mechanism of action include potential first-dose hypotensive effect such as may occur with alpha blockers that may require postapproval mitigation strategies if the drug is to be used in the elderly and centrally acting psychotherapeutic medications that may have risks of suicidality. For the first-dose hypotensive effect, the sponsor could explore options such as having the patient take the dose directly before going to bed, or taking the dose in the doctor’s office and being observed for an hour. These mitigation activities can be tested while the product is still in development. Risks of suicidality such as reported with the selective serotonin reuptake inhibitors (SSRIs), certain atypical antipsychotic medications and anti-epileptics can be addressed by developing and testing education materials to inform patients and caregivers to recognize the signs of suicidality. As with other risks or potential risks identified before approval, these strategies can be developed and tested in the pre-approval period.

Additional risk mitigation strategies for consideration and testing are whether there is a need for specific instructions directed to the prescriber. An example of a prescriber-directed instruction is in
the instance of a complex treatment regimen where multiple treatments are used in sequence or when the medication has to be carefully titrated. Postapproval mitigation strategies that can be evaluated pre-approval include special office monitoring for first-dose hypotension, determining the effectiveness of infusion checklists and identifying how best to implement special laboratory monitoring. Special patient and caregiver instructions can be developed and evaluated pre-approval as well, particularly in instances where there are special instructions for safe use.

Other postapproval strategies that can and should be considered and assessed include consenting clinical study participants for direct patient interviews for evaluating aspects of a potential future studies. Clinical study participants can be queried about the understandability of certain tools as well as potential barriers to study participation. Patterns of care can be proactively evaluated such as whether certain tests are being carried out on schedule or the number of days between the onset of the adverse experience and its diagnosis. These factors could be critical to a postapproval mitigation program that depends on early recognition and diagnosis of a precursor to a serious adverse event (e.g. serious skin conditions where early recognition and discontinuation of the drug may result in a less severe outcome). Adherence to treatment may be another factor that is important to risk mitigation postapproval. Before approval, clinical trial patients can be asked about problems with adherence to treatment regimens and studies can be carried out examining adherence for similar drugs that may already be on the market.

It is possible to assess pre-approval whether impediments to implementation or process breakdowns occur within a proposed postapproval mitigation strategy. Using strategies such as root-cause analysis, investigators or other healthcare providers as well as patients can be interviewed as to what caused the impediment and potential solutions to the impediments can be identified. These include determining potential causes of low patient recruitment and lack of interest by prescribers to participate in certification programs. Finally, the sponsor can evaluate whether there are potential postapproval barriers to correct use of the drug. These are indirect risk mitigation activities that can play an important role in the future success of a postapproval study. Product packaging should be considered as a potential postapproval mitigation tool as it presents a unique opportunity for the sponsor to communicate directly with the patient to ensure safe use. Mitigation steps carried out through packaging include the use of starter packs or blister packs for drugs with complicated dosing and titration instructions, and devices for self-administered injections. In some instances, biopharmaceutical products with special patient-related packaging may also have educational programs to inform patients and caregivers about safe use. As with other mitigation activities previously discussed, many of these tools can be tested and evaluated pre-approval.

Conclusions
The evaluation of safety of a pharmaceutical or biological product is carried out throughout the lifecycle of the compound. In order for a biopharmaceutical company to be prepared for postapproval safety monitoring, evaluation and mitigation, it must know what is required in terms of a RMP and a REMS and development of these tools must be started during drug development. Postapproval safety is not just a postapproval consideration. The earlier in clinical development that important identified and potential risks are determined, the greater the opportunity there is to develop, evaluate and start implementing a flexible and effective risk management strategy which may consist of epidemiologic studies to further characterize the risk and risk mitigation strategies to minimize risks while maintaining the benefits. A wide range of mitigation activities can be carried out ranging from activities as simple as designing packaging to minimize risks and developing and testing educational materials, to more complex activities such as implementing a postapproval registry, or designing an observational safety study. These pre-approval activities will not be sufficient to prevent an unknown, serious risk being identified postapproval, but proactive preparation can put a sponsor in a better position to be able to respond quickly and efficiently to unexpected safety issues as well as to actively manage identified risks.

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