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Risk Management – Translating the Results of the Development Program in Today's Regulatory Environment

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The October 2004 issue of *Regulatory Affairs Focus* introduced three draft guidance documents on risk management in the article, "Creating a Risk Management Framework." Risk assessment and risk minimization together form what FDA has termed risk management. The concept of risk management took on new meaning for regulatory affairs professionals with FDA's issuance of the final guidance documents[1] in March 2005. Other factors have also influenced how regulatory affairs professionals view risk management: the market withdrawal and restrictions of some COX-2 drugs; increased focus on drug safety by FDA and consumer groups; and lawsuits related to adverse effects of drugs such as Vioxx, Accutane and others.

Despite proper diligence, some safety signals will not be discerned until after a new therapeutic agent is marketed. These postmarketing signals have, in some cases, resulted in withdrawal from the market.

This article discusses the development of risk management and pharmacovigilance plans based upon the integration and assessment of data from both the nonclinical and clinical development programs.

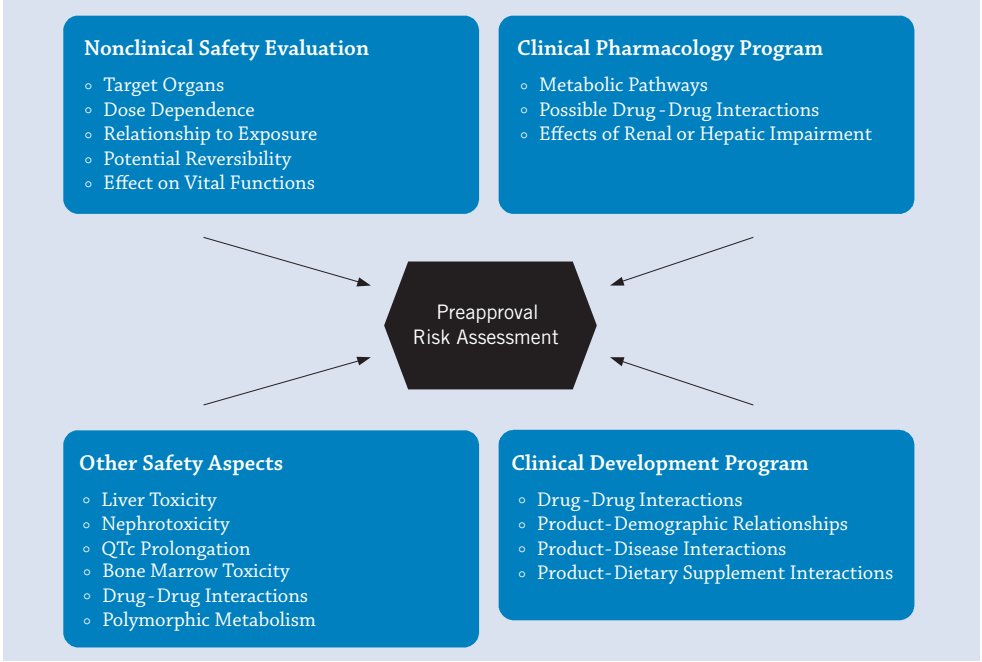
Premarketing Risk Assessment

Drug safety is routinely monitored during nonclinical and clinical development programs. Preapproval risk management activities are shown in **Figure 1**.

Nonclinical Data

Nonclinical pharmacology and toxicology studies are performed prior to initiating human studies and continue during the new drug or biologic clinical development program. The nonclinical testing program's goals are, first, to demonstrate that it is safe to proceed with human testing and, second, to provide information on the drug's toxicological profile, including adverse effects that should be monitored during the clinical trials. Well-designed nonclinical testing programs employ animal species that are sensitive to the therapeutic agent's potential toxicity and respond in a manner most like that of humans. Animal toxicoki-

Figure 1: Pre-approval Risk Management Activities



netic data allow the correlation of observed toxicities with blood drug levels, comparison to human blood levels and calculation of the safety margin for particular toxicological findings. However, nonclinical testing is not always predictive of toxicity in humans and will not detect rare or idiosyncratic events.

Clinical Data

The clinical development program will detect the investigational therapeutic agent's more common adverse events and those with a relatively short latency period. Rare adverse events and those with long latency periods are detected after exposure of a large number of patients and with long-term follow-up. In addition, clinical trials do not always incorporate the safety assessments necessary to detect some of these adverse effects. For example, before QTc prolongation was associated with some nonsedating antihistamines, ECGs or Holter monitoring typically was not performed on patients participating in clinical trials for seasonal allergies.

The risk information generated during clinical trials is limited by the following:

- safety database size
- consideration during the planning stage for developing the premarketing safety database (populations, indications, etc.)
- whether comparative safety data have been obtained (active comparator data)
- accuracy of coding and adverse event descriptions to identify safety signals
- proper attribution of adverse drug events

Integration of Nonclinical and Clinical Data

A process for reviewing, integrating and assessing nonclinical and clinical development program data needs to be in place to enable potential and real premarketing safety-signal evaluation and the development and implementation of appropriate risk-management and pharmacovigilance plans prior to new-drug marketing.

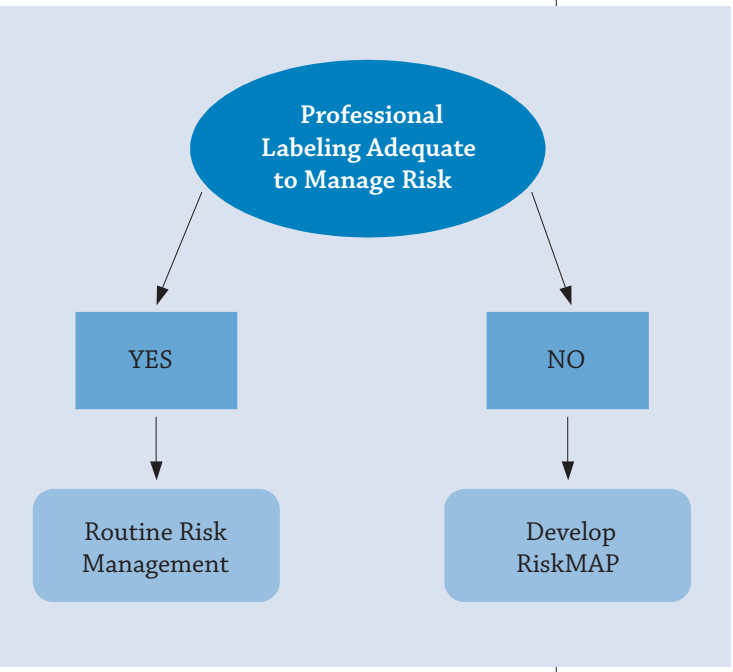
Nonclinical testing strategies currently recommended by ICH may detect safety signals that have resulted in previous drug market withdrawals. One example is QTc prolongation associated with terfenadine but not its acid metabolite, fexofenadine; this adverse effect is readily demonstrated in animal models. The development in some patients of Torsades de Pointe, associated with terfenadine and concomitant administration of such drugs as ketoconazole that competitively inhibit the CYP3A4 isozyme system, only became apparent during terfenadine postmarketing surveillance when reports of these serious cardiac arrhythmias were attributed to the drug.

Integration of nonclinical and clinical safety data is used to synthesize the risk assessment. The risk assessment can determine if safety signals observed in the nonclinical testing program also were observed in the clinical program and, thus, need to be addressed in the product's labeling. In addition, the risk assessment is used to ascertain whether routine risk management is sufficient and professional labeling is adequate to manage the risks associated with the drug's use, or if a formal risk minimization action plan (RiskMAP) needs to be developed and submitted with the marketing application (**Figure 2**).

RiskMaps

Not every drug requires a RiskMAP; according to the guidance, FDA envisions that few products a year will do so. The package insert, updated periodically with postmarketing surveillance or study information demonstrating new benefits or risk concerns, is still considered the cornerstone for minimizing risk. A RiskMAP should be developed when an appropriately implemented plan will prevent predictable events or significantly reduce or eliminate the hazard to patients. Examples of appropriate use of RiskMAPs include drugs with known teratogenic or carcinogenic potential. RiskMAPs may be developed and submitted prior to marketing a new therapeutic agent or

Figure 2 : Risk Management Decision Process



may be initiated in response to a safety signal detected during routine postmarketing surveillance.

Discussion

Well-designed nonclinical and clinical pharmacology testing programs can reveal potential adverse drug effect target organs or systems and whether the adverse effects are dose-dependent and/or reversible. Determining the metabolic pathway(s) provides information on potential drug-drug and drug-disease interactions that should be further investigated either during phase 3 or postmarketing. The effect or lack thereof of hepatic or renal impairment on pharmacokinetic parameters provides important product labeling information.

The premarketing risk assessment should be based upon the integration of all available nonclinical and clinical safety data. This risk assessment is used to determine whether routine postmarketing risk management is adequate or if safety signals require implementing a plan to manage and minimize the drug's associated risks. When safety signals and case series indicate the need for further study, pharmacoepidemiologic studies and other active surveillance mechanisms should be considered.

Conclusions

Given today's regulatory environment, risk management is becoming an important facet of drug development. Risk assessment during the clinical development program is optimized by integrating nonclinical and clinical safety data. Premarketing risk assessment is essential to developing appropriate postapproval risk-minimization and pharmacovigilance plans. ■

REFERENCES

1. Guidance for Industry: *Premarketing Risk Assessment; Development and Use of Risk Minimization Action Plans;* and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*

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