Understanding Risk Management Plans and Translating the Development Program Results

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Introduction

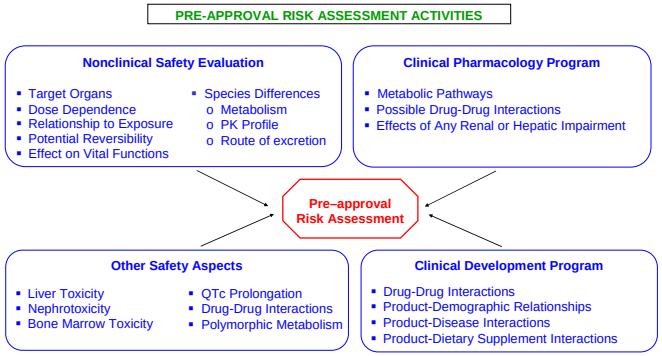
Monitoring drug safety is routinely performed during nonclinical and clinical development. However, the pre-marketing safety database is usually limited in the number of patients exposed, length of exposure, and types of safety assessments performed during the clinical trials. Despite proper diligence, some safety signals will not be discerned until after marketing of a new therapeutic agent. These post-marketing safety signals have resulted in market withdrawal in some cases.

Objective

The goal is to develop risk management and pharmacovigilance plans based on the integration and assessment of the data from both the nonclinical and clinical development program.

Methods

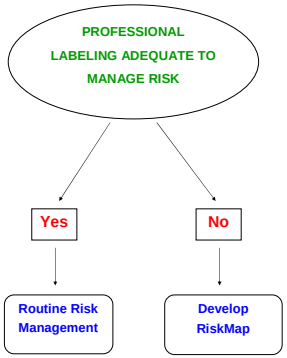
A process for the review, assessment, and integration of data from the nonclinical and clinical development programs needs to be in place in order that potential and real pre-marketing safety signals are assessed and appropriate risk management and pharmacovigilance plans are developed and implemented prior to marketing new drugs.



Risk information generated during clinical trials is limited by the following:

- Size of the safety database;
- Considerations given to developing the pre-marketing safety database when studies were planned (populations, indications, etc.);
- Whether comparative safety data have been obtained (active comparator data);
- Accuracy of coding and descriptions of adverse events to identify safety signals; and
- Proper attribution of an adverse event to the drug.

Integration of all preclinical and clinical data to synthesize the risk assessment will determine whether a formal RiskMap needs to be developed and submitted with the marketing application or if routine risk management is sufficient. The risk assessment is based on the safety data and a determination of whether the professional labeling is adequate to manage the risks associated with the use of the drug.



Results

Nonclinical testing strategies currently recommended by ICH guidance documents may detect safety signals that have resulted in market withdrawal of some drugs in the past. One example is QTc prolongation associated with terfenadine, but not its acid metabolite, fexofenadine, that is readily demonstrated in animal models.

The subsequent development of Torsades de Pointe in some patients associated with terfenadine and concomitant administration of drugs, such as ketoconazole that competitively inhibit the CYP_{3A4} isozyme system, only became apparent during post-marketing surveillance of terfenadine when reports of these serious cardiac arrhythmias were attributed to the drug.

Even though not yet approved by FDA, Tazoral is an example where teratogenic effects seen in animal reproductive toxicology studies resulted in the sponsor proposing a RiskMap to FDA.

However, nonclinical testing is not always predictive of toxicity in humans nor will it detect rare or idiosyncratic events.

Well-thought-out nonclinical and clinical pharmacology testing strategies can reveal potential target organs or systems for adverse drug effects and if the adverse effects are dose dependent and/or reversible. The determination of the metabolic pathway(s) provides information for potential drug-drug and drug-disease interactions that should be further investigated either during Phase 3 or post-marketing. The effect or lack of effect of hepatic or renal impairment on pharmacokinetic parameters provides important information for product labeling.

The pre-marketing risk assessment should be based on the integration of all available nonclinical and clinical safety data. This pre-marketing risk assessment is used to determine whether routine risk management post-marketing is adequate or if safety signals require the implementation of a risk minimization plan to manage the risks associated with the drug. When safety signals and case series indicate the need for further study, pharmacoepidemiologic studies should be considered in addition to other active surveillance mechanisms.

Conclusions

Developing risk assessment during the clinical development program is optimized by integration of nonclinical and clinical safety data. The pre-marketing risk assessment is essential to developing appropriate post-approval risk management and pharmacovigilance plans.