

A Science-Based Approach to Responsible Risk Management for a Novel Long-Acting Opioid Analgesic

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Purpose

The use of long-acting and extended-release opioid analgesics has inherent potential patient risks such as overdose, abuse, misuse, and addiction. The US Food and Drug Administration (FDA) continues to explore and employ regulations to minimize these risks and is considering a class-wide Risk Evaluation and Mitigation Strategy (REMS) for long-acting and extended-release opioids to reduce these risks. Opioid diversion, although not addressed in the proposed REMS, nonetheless is also a class-wide concern and risk. Mallinckrodt Inc., a Covidien company (Hazelwood, MO), received approval March 1, 2010, to market EXALGO® (hydromorphone HCl) extended-release tablets CII, a novel and unique extended-release tablet formulation of hydromorphone, indicated for once-daily administration. To help ensure appropriate prescribing, the manufacturer used failure mode and effects analysis (FMEA), a science-based methodology, to assist in the specification and design of tools to assure safe use.

Method

FMEA has been used in aviation, healthcare, manufacturing, and the military to assess and reduce risk in high-risk environments. RxFMEA® uses proprietary software that evaluates both the process and human factor failures for pharmaceutical products. The goal of the RxFMEA was to develop an overall risk mitigation program that results in best possible outcomes for patients by supporting safe-use performance goals that are consistent with the manufacturer's priorities and values of safe use for all medications. The 3-month process consisted of topic definition, multidisciplinary team formation, medication-use process graphing, failure analysis/hazard index scoring (frequency x severity of failure), and actions taken to prevent failure. Causes of failure were defined as behavioral and leading to unsafe actions. Interventions were selected to mitigate negative behavior and consisted of educational programs/materials and enabling tools. Metrics were employed as the measurement of how each intervention is accepted, understood, and utilized. Project briefs were created to aid in intervention tool development, specifically targeting a behavior(s).

Results

The five individual steps of the medication-use process, each with five sub-processes, were analyzed. A total of 79 failure modes and 290 potential causes of failure were detected, which led to 929 interventions; 37 preliminary interventions were specified, including product labeling, REMS tools, and distribution through three stakeholder programs. The REMS tools identified and implemented consisted of a Medication Guide, Dear Healthcare Professional letter, Prescribing Brochure, dedicated REMS Web site, and full Prescribing Information (use not limited to REMS). Importantly, the analysis revealed that the REMS tools identified were found necessary, but not completely sufficient, to mitigate important patient safety risks. Therefore, additional tools were voluntarily developed to mitigate risks as prioritized by the RxFMEA hazard index. Eight tools were developed to mitigate the highest risk and were implemented at launch; 12 additional tools have been identified and will be implemented in phases based on REMS assessment and need.

Conclusions

REMS tools were identified and specifically designed; however, RxFMEA identified additional tools to mitigate patient safety risks that were not mandated by the REMS. These additional tools have been voluntarily employed to help assure patient safety with additional tools to be implemented in a phased approach following the 6-month assessment of REMS performance. This approach will help guide and direct the most appropriate tools to be deployed. The use of a science-based approach to analyze the patient care process led to deployment of tools beyond those mandated by the regulatory agency to protect patient safety.