Predictors of Post-market FDA Safety Actions between 1992 and 2014

Brendan Heiden

2018

UMMS Capstone for Impact
Branch: Procedures Based Care

Project Summary

What is the impact of FDA policies, namely the Prescription Drug User Fee Act (PDUFA) of 1992, on the incidence of post-market FDA safety actions, including black-box warnings and drug withdrawals? Do drugs that received adverse FDA safety actions have inferior clinical trial design?"

Action Items/Outcome

All drugs between 1992 and 2014 were identified. Drug characteristics and clinical trial designs were catalogued using publicly available FDA review documents. Occurrence of safety action and time to safety action were collected, along with year of approval, drug class, priority review designation, orphan designation, and accelerated approval status. Pivotal efficacy trials for drugs requiring safety actions were then identified and catalogued according to randomization, blinding, comparator, clinical outcomes, trial size, and duration.

Conclusion/Reflection

Of the 529 drugs approved between 1992 and 2014, 83 (15.7%) had a safety action following approval. Drugs approved for oncologic, hematologic, neurologic, and anti-infective conditions were more likely to receive safety actions over time ($p=0.018$). Among cardiovascular, respiratory, endocrine, and gastrointestinal drugs, FDA priority review designation significantly increased the likelihood of safety actions whereas standard review was associated with lower occurrences (OR 0.16, 95% CI 0.04-0.52, $p<0.001$). The quality of clinical trials supporting the approval of drugs that eventually required safety actions appeared to be excellent. These data suggest that all drugs, except cardiovascular, respiratory, gastrointestinal, and endocrine agents undergoing standard FDA review, require aggressive post-approval pharmacovigilance for safety concerns not recognized during clinical testing. Surprisingly, pivotal clinical trial design does not appear to be inferior for drugs that required FDA safety actions.

Overall, nearly 1 out of 6 drugs in the last 25 years had a serious safety problem that was realized by the FDA only after approval. These findings are alarming and may be relevant to policy makers and those tasked with the challenge of ongoing

pharmacovigilance. After all, faster review times – while important to those patients who are currently suffering from diseases with ineffective treatments – may come with significant safety costs. Our study suggests that for some drug classes, this may be true, and in those classes, priority review may merit stricter scrutiny after approval. However, for other classes, even drugs approved via standard review have substantial rates of post-approval safety concerns, such that drugs in those classes cannot be afforded any laxity of vigilance. The paradox of speed versus safety will continue to challenge the field of medicine. We hope that these results enlighten physicians and policy makers to the potential perils of this dichotomy.