what to learn from US FDA Warning Letters and their impact on pharmacovigilance operations

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Drug safety and pharmacovigilance (PV) are paramount to the development of new drugs and the continued use of approved medications. PV remains a complex series of activities that must be well planned and coordinated as well as operational in all countries where the drug is used. Continual monitoring initiated by companies with both internal and external audits becomes essential to ensure appropriate PV. In addition to company-directed audits, regulatory agencies also inspect PV activities to ensure compliance with regulations. In this review, US Food and Drug Administration (FDA) Warning Letters (WLs) to pharmaceutical companies regarding post-marketing PV are discussed in an attempt to understand and learn from the failures identified, and, thus, continually improve the quality of PV globally.

The inspections carried out by the FDA can result in the FDA issuing WLs to persons or organisations for violations of regulatory significance, and these WLs may lead to serious consequences. FDA WLs are characteristically informal and advisory, the ultimate aim of a WL is to establish voluntary compliance with the law and provide prior notice. WLs are issued for violations of regulatory significance and can lead to enforcement actions if not adequately corrected; however, a WL does not commit the FDA to take action. On the other hand, the FDA can take action without prior issuance of WLs. Corrective, preventive or promised actions by the company do not preclude the FDA from issuing a WL. Thus, receiving a WL is a cause for real concern to companies, as the identified violations can lead to significant enforcement actions by the government negatively affecting public relations and future regulatory interactions[1,2].

Methods

For this review, WLs were identified on the FDA web page http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm, and searched by employing various PV terms. Out of approximately 6500 WLs from 2005 to 2015, 17 WLs were identified with post-marketing PV violations from pharmaceutical companies[3].

Results

PV observations in FDA WLs

FDA WLs are available in the public domain, while the findings from inspections (FDA Form 483 reports) are generally not in the public domain. The WL library on the FDA website covers a wide range of violations related to foods, tobacco products, and promotions of pharmaceutical products; only a small fraction are related to PV issues. As described in the methods section, from 2005 to 2015, 17 FDA WLs related to post-marketing PV violations were issued to pharmaceutical companies. All of these WLs followed FDA inspection with Form 483 issued to the company; most WLs also contained comments regarding inadequate response to Form 483 as well as some WLs with comments regarding repeat findings.

Three of the 17 WLs were to large pharmaceutical companies, while the other 14 were issued to small pharmaceutical companies and generic manufacturers. Thirteen WLs were written as primary PV

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violations, three WLs were focused on good manufacturing practices, but also had comments about PV, while one WL was focused on a new drug definition. The WLs were generally evenly distributed over the time period 2005 to 2015, with most years having none, one or two WLs issued; whereas 2010 had four WLs, while 2008 and 2011 had three WLs each year.

The two most common findings by FDA inspectors identified in the WLs were review of adverse drug experience (ADE) and reporting requirements. The review of ADEs were mostly focused on failures in written procedures regarding ADEs, while the violations in reporting requirements most often related to violations in post-marketing 15-day 'Alert reports' and subsequent follow-ups, as well as oversights in periodic adverse drug experience reports (PADERs). Other common findings included failures in record keeping and reporting ADEs on marketed drugs without approved new drug applications, reporting of ADEs from a product complaint, and reporting requirements for Annual Reports[3,4].

Consequences of FDA WLs and failure to correct violations

Consequences of FDA WLs fall into two general categories: 1) regulatory actions, and 2) outcomes related to public disclosure of the WL. The regulatory actions are usually associated with failure to correct the violations and can include recall, seizure of products, injunction, administrative detention, civil penalties and/or prosecution. Additionally, a WL may negatively impact future regulatory activities, e.g. approvals. Public disclosure of the FDA WL can negatively impact company public relations leading to a loss of trust from patients and healthcare professionals, a decline in the stock price, and a negative perception of the PV group within the company[1,2].

Response to Form 483 following an inspection

At the close of an FDA inspection, the violations observed by the FDA are presented in Form 483 and discussed with the senior management of the company. Form 483 is not an all-inclusive list, but it identifies the FDA inspector's observations regarding regulations that have been violated. Unless agreements have been made between the company and the FDA, the company has 15 days to respond to the findings in Form 483; however, ongoing or promised actions in the company's response to Form 483 do not preclude the FDA from issuing a WL.

Good responses to Form 483 following an inspection are crucial. In most of the 17 WLs discussed in this review, the FDA has made a comment that responses to Form 483 were inadequate. Successful responses most often include the following: 1) acknowledge the problem, 2) address each problem separately, 3) demonstrate an understanding of the problem, 4) evaluate the impact and determine the cause, and 5) describe corrective and preventive actions. If an activity is likely to take months, this activity can be split into milestones; thus, providing the FDA with the company's road map for corrective and preventive actions. This road map will offer additional assurance to the FDA that the company has a realistic plan with intent to complete the corrective and preventive actions. Additionally, if possible, correct the problem(s) in the 15 days following the issuance of Form 483 and notify the FDA in the 483 response. Add any evidence of your actions in the response to the FDA, such as a new or corrected standard operating procedure, missing protocol, updated software, etc[2,5].

Methods to ensure PV compliance and good practices

The optimal approach to avoid an FDA WL is to clearly understand the effectiveness of your PV organisation, especially the operational aspects; set acceptable targets which meet regulatory standards; and ensure appropriate monitoring is in place. Monitoring of the PV process can be done with metrics that evaluate key PV activities and audits, both internal and external; however, the monitoring data must be reviewed optimally by a standing committee, and the results used to initiate corrective and preventive actions to correct any deviations from the acceptable targets.

It is vital that the mind-set of organisations become more open and accepting of the importance of effective PV. Safety is not just a PV activity, and everyone in the company should be involved – including those outside of the company, such as vendors and distributors. Leaders of organisations have to

understand the importance of PV and lead by example. By increasing employees' awareness of safety, and creating an organised, transparent, predictable process, companies can enable the FDA to clearly see how safety is being handled.

Summary

The best way to avoid FDA WLs is to ensure a highly effective PV organisation with a monitoring system, acceptable targets, a review committee, and the ability to enact corrective and preventive actions to address any deviations from target levels.

Repeat findings and poor responses to Form 483 increase the risk of WLs drastically and serious consequences exist for failure to correct the issues identified in the WL. Companies can partner with service providers to mitigate violations identified in both Form 483 and WLs, implementing different solutions such as improving the structure and setup of a PV organisation, developing appropriate standard operating procedures and processes, tracking important PV functions, and ensuring inspection readiness.

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