Warning Letters & Close-out Letters

Why does it take so long to get a close-out letter?

One of the enforcement tools that FDA has in its toolbox is the Warning Letter. Most people in the pharmaceutical industry are quite familiar with Warning Letters. For all Warning Letters issued on or after September 1, 2009, FDA will issue a close-out letter for Warning Letters when all observations have been appropriately resolved, which basically states that the FDA is satisfied with a company's response, corrective actions, and subsequent actions. This was intended to give industry clarity about the status of their sites, and to provide consumers, buyers, and potential partners insight into the state of compliance of manufacturers. In theory, it is possible to aggressively manage remediation and to satisfy FDA to get the Warning Letter lifted in an expeditious manner; however, a quick review of available data shows that this isn't always the case.

I've reviewed Warning Letters and close-out letters for the last several years, and find that the length of time to achieve close-out can be two plus years. For example, in 2014, there were 16 Warning Letters issued for drug facilities, but only 11 have subsequently received close-out letters. For Warning Letters issued in 2014, which have been closed-out, the average time for API facilities from issuance of a Warning Letter to close-out was 795 days, and the average time for finished dosage form facilities was 555 days. Add to those numbers the fact that there are 5 Warning Letters from 2014 that still haven't been closed-out. If these Warning Letters are lifted, those statistics will climb. Similarly, in 2015 there were 20 Warning Letters issued, with only 3 closed-out to date. In 2016, there were 44 Warning Letters issued, with only 3 closed-out to date. Average time to closure with respect to Warning Letters issued in both 2015 and 2016 is currently much lower than those issued in 2014, but there is also a much lower percentage of close-outs relative to the total amount of Warning Letters issued, so average close-out time for Warning Letters issued in 2015 and 2016 is likely to rise if and when more close-outs occur.

The time from receipt of a 483 to issuance of a Warning Letter has also risen over the last several years, with many Warning Letters being issued over a year after the 483 was issued. This adds to the overall time that companies are in limbo, without a clear direction as to their compliance status in the eyes of FDA.

What are some of the possible reasons that it is taking so long for companies to resolve Warning Letters to FDA's satisfaction? We believe it is attributable to any one (or a combination) of the following factors:

Inadequate initial response to the Warning Letter

When FDA issues a Warning Letter, generally it is because they have some concerns over the firm's response to

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one or more 483s. However, at times, companies make the mistake of just re-iterating the responses they gave in the initial 483 response when responding to a Warning Letter. Just restating the same thing isn't going to change FDA's mind. It's very unlikely that FDA missed something in your initial response that would change its mind. Companies need to break down the Warning Letter citations to determine where they went wrong with the initial response, and try to rectify it.

Another issue that makes companies' responses inadequate in FDA's eyes is when they are very narrow. If the FDA cited something in one system, or for one product, the firm needs to assess similar situations for other products or systems. Good responses look at overall systems, across the entire product line, site, and even across sites. This lets FDA know that you are serious about examining your entire systems and operations.

Another pitfall that companies make is not implementing interim controls. If you have determined that an effective corrective action is going to take a year to implement, and you haven't implemented an interim control in that year, you are still manufacturing product under the same objectionable conditions that FDA observed and cited, and that will erode FDA's confidence in your company. Closely related to this failure is not assessing the impact of the Warning Letter citations on product currently on the market. Remember that FDA's mission is to protect public health, and a response that doesn't take this into consideration will be seen by FDA as inadequate.

Not providing periodic updates

Unless everything that you have committed to do has been completed prior to sending in your Warning Letter response, it's important to keep FDA updated regularly. We've seen examples of companies that have committed to periodic updates and haven't submitted them, haven't had any dialogue with FDA, and then are surprised when FDA hasn't scheduled a re-inspection because of this uncertainty. In a similar vein, letting FDA know when you have completed all the corrective actions is crucial, particularly with foreign sites. This lets FDA know that you are ready for a re-inspection.

Thinking that the Warning Letter citations are all inclusive

FDA states that the violations listed in a Warning Letter are not all inclusive; however, we frequently hear companies state that, because a certain system wasn't listed on the Warning Letter or 483 with any observations, it must be acceptable. When it comes to 483s, the investigator may not have focused on a specific area and therefore had no observations. With Warning Letters, the content of the response may have led FDA to accept the response to a specific item, but on re-inspection, the field investigator may find some additional violations. Nothing is off limits.

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When FDA comes to re-inspect

A lot of times companies think that when FDA comes to re-inspect, they are only going to look at the systems that were cited in the Warning Letter. Many companies fall into this trap thinking that when FDA comes back, they are only going to verify corrective actions. This is just not true. FDA will focus some of the inspection on the corrective actions, but will also, generally, perform a full inspection. The issues identified in the Warning Letter may have been corrected, but new potential issues may be noted. While some of the issues may not warrant additional action, they may lead to a delay in lifting the Warning Letter.

Some companies aren't interested in getting the Warning Letter lifted

Some Warning Letters may not be lifted simply because the company has either abandoned the U.S. market, or has gone out of business. A small percentage of Warning Letters simply go unanswered, particularly when there isn't any product on the U.S. market. Other companies, particularly when an Import Alert is in place, may make an initial response, but then discontinue products, move facilities, etc., with the result being no opportunity for the Warning Letter to be lifted. We have no way of knowing how many of the open letters fall into that category.

Warning Letters are FDA's practice to allow for firms to take voluntary and prompt corrective actions before initiating a drastic enforcement action such as a seizure or injunction. It goes without saying that firms should demonstrate to FDA their willingness to address the issues raised in the letter in as short of a time frame as is possible, not only to get their Warning Letters lifted as soon as possible, but also to minimize disruption of supply of products to patients. Many companies who have received a Warning Letter have expressed that they desire to have it lifted in a year or less. Given the data, this would be an aggressive exception to recent close-out timeframes. While it is theoretically possible to do so in such a short interval, the likelihood of this happening is not high. In addition, because it is critical to demonstrate to FDA that the issues raised in the Waning Letter are being handled, a superficial fix by a firm to reduce time frames could lead to escalated regulatory action by FDA. **CP**