Potayto—Potahto? The Meaning of the FDA’s “Complete Response” Letters

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On August 11, 2008, the Centers for Drug Evaluation and Research (CDER) of the US Food and Drug Administration (FDA) officially changed the way the division is responding to new drug applications (NDAs), raising mild alarm in some circles by stating that in the future, rather than respond with “approvable” letters or “not approvable” letters, the division would be responding with “complete response” letters.

This led many observers to wonder what this switch would mean for stakeholders in the process. Others have asked whether the move clouds rather than supports the goal of transparency in the approval of new drugs, while still others yawn and wonder if this switch means anything substantive at all. After all, the Center for Biologics Evaluation and Research (CBER) has been sending out complete response letters for 11 years now. Has the approval of biologics been impaired as a result compared with the track record of small-molecule drugs?

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Before CDER’s announcement on July 9, 2008, about the switch (which became effective on August 11), there were a few outcomes possible in response to the NDA: first and best was an approval letter. Second, was the far-less welcomed approvable letter, which although it was not an approval, did signal that the company had made a good effort and that the FDA might approve the compound if the drug sponsor met some particular goals. Finally, of course, was the dreadful not approvable letter, which almost always meant what it said—that an NDA could not be approved as submitted, causing the sponsoring companies’ investors to lose heart in many cases.

Now, with the switch to “approvable” or “complete response” letter, there are only 2 scenarios for which all stakeholders—the company, the physician community, the patient, and the investors—need to prepare.

What prompted this change? According to the announcement by the FDA, “These new regulations will help the FDA adopt a more consistent and neutral way of conveying information to a company when we cannot approve a drug application in its present form,” said Janet Woodcock, MD, director of the agency’s CDER. “Thorough and timely review of drug applications is a priority of the FDA, and these new processes will make our communications with sponsors of applications more consistent.” From a communications perspective, this is an interesting comment, given that Dr Woodcock uses 2 sentences to announce that this is an effort to be consistent, and uses the word twice, without explaining with what the division is seeking consistency.

The answer is that CDER is moving to be consistent with CBER. The question that follows is: Why did it take CDER 11 years to make the switch that CBER made in no time at all? The agency first made the commitment regarding complete response letters as part of the user-fee performance goals established in conjunction with the enactment of the FDA Modernization Act of 1997 (Public Law 105-115) (the user-fee provisions of this act are known as “PDUFA II”), and this commitment was repeated in conjunction with the enactment of the Prescription Drug User Fee Act of 2002.

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In any case, the rule has been finalized and is now in use. The rule includes:

1. Additional regulations regarding changes to the FDA’s ability to defer the review of amendments
2. Extensions of the review cycle due to the submission of a major amendment
3. Classification of responses to a complete response letter (ie, class 1 and class 2 resubmissions)
4. Timelines for submitting a response to a complete response letter and administrative actions for failure to respond
5. The definition of an efficacy supplement.

Under the old system, an approvable letter stated that an NDA was basically approvable if certain issues were resolved, indicating that the NDA substantially meets regulatory requirements and the FDA could approve if the applicant submits additional information or agrees to specific conditions. A not approvable letter meant that the application could not be approved and might describe deficiencies.

A complete response letter will state that the FDA cannot approve an NDA in its current form, and will describe specific deficiencies in the application. The deficiencies described therein can be minor (labeling) or major (new clinical trials). When possible, CDER recommends actions that might be taken to place the application in an approval standing.

So what is the difference? For many, this boils down to a matter of transparency. The contents of an approvable letter and a complete response letter are considered proprietary, and the FDA does not divulge the contents of such letters, nor does it issue a press release. Rather, it is in the purview of the sponsoring drug company to release as much information as it wants, with as much specificity as it wishes.

Under the old system, when a company received an approvable letter, although the company might not have said much about the contents, the fact that an approvable letter was received instead of a not approvable letter signaled that the NDA at least had some merit, and that if the company was willing to fulfill certain tasks, the application would likely be approved.

But under the new system, no such subtle signal is being sent. Especially for investors, that means there is an unprecedented reliance on what the company says, and how it may speak about the complete response letter it has received; reading between the lines of a press release may be very telling, if vague, assuming the company says anything substantive about the release. A statement that the company would be working with the FDA in the future could signal that there is a pathway set up in the letter for eventual approval, and that the company is going to take it, or it could mean that the company is just going to call the FDA and complain.

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If a press release alludes to a specific issue, such as one of the comparators used in the study, it may signal that more studies are needed. If, however, the matter is simply one of labeling, there might be language in the press release that indicates a short-term fix.

Or, as some are advocating, there could be a push to release the entire contents of complete response letters. That solution may be one that companies come around to on a voluntary basis, or it is possible that it could be included in what is, no doubt, a substantial amount of FDA and pharmaceutical marketing reforms that are distinct possibilities for Congress during 2009.

Reference


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