Filing Review is About More Than Checking the Boxes; or Is It?

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Things sometimes change fast. Our original article described one company's recent announcement that the Food and Drug Administration refused to file its new drug application as a reminder that the agency's filing review may be more than a check-the-box exercise to see if the sponsor has submitted something for each required category of information. But, then, earlier this week, the company announced FDA had taken the very unusual step of rescinding that decision and agreeing to review the application without the submission of additional data.

Background

An NDA sponsor announced earlier this month that it had received a "Refuse to File" letter in response to its NDA for its candidate psychiatric drug. The sponsor described FDA as taking the position that it was unable to complete a substantive review of the application "based on insufficient evidence of overall effectiveness for the proposed indication, and that additional well-controlled clinical trials are needed prior to resubmission."[1]

Then, earlier this week, the company announced that FDA had reversed course and agreed to file the application for review and rescind the earlier letter.[2] The company stated that FDA's actions followed "productive interactions with the Agency in which [the company] clarified certain aspects of the NDA submission," and noted that no additional data or analyses were submitted to FDA.[3] In keeping with the confidential nature of an NDA and communications between a sponsor and the agency, FDA did not comment on the actions. We can't know exactly what lead to the reversal, and what, if any, the administration's declared support of getting more drugs approved was a factor.

Although this Refuse to File letter was rescinded, it still serves as a reminder that FDA *may* not limit its filing review to only ensuring that something has been submitted for each required element of the NDA (i.e., a technical review); it may look at the sufficiency of the information from a substantive perspective.

FDA describes when it may refuse to file an NDA (among other submissions) in its guidance, *Refuse to File*: *NDA and BLA Submissions to CDER Guidance for Industry*, which was issued as a Procedural Guidance in December 2017.[4] The Guidance focuses, in particular, on when the agency may refuse to file "when the NDA is incomplete because it does not on its face contain [the] information required".[5] One might conclude that FDA's filing review is limited to evaluating whether the sponsor has submitted something for each element that is required, and that the filing review does not delve into the adequacy of the data or information submitted.

FDA appears willing, however, to utilize the Refuse to File process to communicate to sponsors that the data submitted are not adequate to support a finding of safety and effectiveness. It seems likely that FDA did not base this conclusion solely on its 60-day administrative review of the NDA, but that it was aware of the clinical trial issues it identified in the Refuse to File letter before the application

1 Press release available at http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=2340507
2 Press release available at http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=2342624
3 Id.
4 Available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588242.pdf
5 Id.

was submitted.[6] Again, although this particular letter was rescinded, we don't really know the specific reasons why, and cannot assume there may not be circumstances in which FDA may consider substance of the submission.

AGG Observations

- It goes without saying that an application must have included in its NDA information or data for each required category, and there is no substitute for painstakingly confirming each of these boxes can be checked off. Even when an omission can be relatively easily fixed, the result will be time lost and, perhaps, a need to publicly disclose the receipt of Refuse to File letter.

- Beyond the administrative details, sponsors need to know that if FDA has been sending strong signals that some element of the package is not likely to be sufficient to support approval, the agency may take the step of refusing to file the application (perhaps to save itself the pain and time of reviewing an application it knows will not be approved). We don't have the background in the case reported to know what FDA may have previously communicated or that the company knew that it would receive a Refuse to File letter, but it is important to listen to what the agency is saying, even if it is not necessarily what the company wants to hear.

- In some cases, FDA will file the application, but will identify items in the 74-day letter it has identified "as review issues." A sponsor receiving such a letter may want to reach out to FDA for additional clarification if any of those issues are a surprise or not clearly understood.

- This company's success in having the Refuse to File letter rescinded serves equally as a reminder that not all FDA decisions are final and in some cases, can be changed.

- We note that some sponsors who receive such a Refuse to File letter may decide to further develop data to augment the application before resubmitting. Given that the company in the case described here did not submit additional data, the agency may still have the substantive concerns with the data that lead to the Refuse to File letter.

6 Under Prescription Drug User Fee Act (PDUFA) goal timelines, the Center for Drug Evaluation and Research (CDER) makes a filing decision within 60 days of receipt and provides the sponsor with notice of its conclusion on filing within 14 days, issuing what is commonly referred to as a "74-day letter."

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