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Quick Pulse

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WHAT TO EXPECT WITH FDA PDUFA TIMELINES AND COMPLETE RESPONSE LETTERS

John K. Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation & Research, FDA, recently discussed regulatory timelines for CDER and CBER with Trends-in-Medicine which may help in interpreting what some companies are saying about the approvability of their drugs and biologic agents.

Question: Do CDER and CBER follow the same PDUFA timelines?
Answer: Yes, we operate under the same PDUFA review process for CBER and CDER. There are some differences in statutory authority for NDAs vs. BLAs, but for PDUFA timelines and clocks, we operate under the same rules.

Q: Is there a difference between a "complete review letter" and a "complete response letter" -- and if so, what is it?
A: Under PDUFA, when we get an NDA, the agreement is we will do a complete review in a certain time period. At the end of that review, we can either approve the drug or tell the sponsor that it is not ready to be approved and there are things that need to be fixed. Under FDAMA, Congress directed the FDA to get rid of some of the old terminology for the letters if it was not an approval and to send Complete Response letters. Previously, we sent approvable and non-approvable letters.

CBER has already started sending out Complete Response letters because it was easy for them to follow the mandate, but it was not easy for CDER because the approvable and non-approvable letters are actually written into our regulations and intertwined in multiple areas. So, we have been working on revising the regulations to change the reference from approvable and non-approvable to Complete Response. In CDER we haven't instituted Complete Response letters; we still send approvable and non-approvable letters.

Q: Under what circumstances can the FDA extend the PDUFA data and for how long?
A: Currently, our review goals for standard applications are 10 months, and our review goals for priority applications are six months. Then, there are other rules if there is a re-submission. We don't have 12-month clocks any more in CDER, and that is also true for BLAs (at CBER). The PDUFA standard was 12 months, but PDUFA-2 changed that to 10 months...and for this year that (10 months) applies.

If a sponsor submits a major amendment – a major new study, new information, etc. – in the last three months of the review, we can decide if we will review the NDA as originally submitted and act by the PDUFA goal date, deferring review of the amendment to the next cycle, or we can extend the clock by three months and consider the amendment.

Q: If the FDA just needs more time or has a question, can that stop the clock?

A: Once an application is filed by FDA we are required to do a complete review and give a complete response for the application as submitted. If FDA asks for additional information during the review, this does not stop the clock and does not trigger an extension unless the sponsor's response to the request is a major amendment, then the rules discussed in the answer to the previous question apply.

The only situation in which FDA can suspend review of an application is if fraud is involved. If a company is being investigated for potential fraud, then we issue a public notice of that and suspend review of all applications.

So, we really don't have a provision that says we can stop the review or ask for more time. Sometimes it is incorrectly reported that the FDA extended the clock. The only way we can do that is if a company submits a major amendment. If we need more time, and we are not ready to make a decision at the time, then our option is to go overdue. We occasionally have to do that. PDUFA does allow that because it is predicated on a 90% success rate.

Sometimes, taking a few more days beyond the PDUFA goal date can allow FDA to approve the application rather than going to a new cycle. In these cases, even if the application is approved, it is counted as being overdue for PDUFA purposes. FDA uses this option only in rare and special cases.

Q: What happens if you issue a Complete Response letter?

A: A Complete Response letter means that we have completed our review, the application is not ready for approval, and the letter contains a comprehensive list of the deficiencies that must be addressed before the application can be approved. A Complete Response letter stops the clock for that review cycle.

Q: What if a sponsor takes three months to get back to you on the deficiencies in the Complete Response letter?

A: When a sponsor submits a complete response to a Complete Response letter, a new review cycle and a new review clock is started. The response must be complete for the clock to start; partial responses do not restart the clock.

Resubmissions are categorized as either Class 1 or Class 2. Class 1 resubmissions are those that respond to minor deficiencies, such as labeling comments and do not require review of large amounts of new data. Class 1 resubmissions receive a two-month clock. Class 2 resubmissions are those that contain more extensive new data for review, and they receive a six-month clock. FDA determines whether a resubmission is Class 1 or Class 2 based on criteria that are spelled out in the PDUFA Goals Letter.

Q: What happens when the sponsor responds to the FDA's Complete Response letter?

A: If we finish the first cycle before the original 10 months, that is done for history. The next cycle starts a new clock. There are Class 1 and Class 2 resubmissions. Class 1 are minor ---- that shouldn't take long. That is a two-month look. Class 2 are more substantial – maybe a new study which would take more time -- and that gets a six-month clock. So, the longest clock is six months, and in some cases it is two months. And the FDA makes the decision whether it is a Class 1 or Class 2 resubmission.

Q: Do you determine that a resubmission will be Class 1 or Class 2 review up-front, before it is filed?

A: No, because sometimes it depends on how the company chooses to respond to the deficiencies. If it is only a labeling issue, it might be a Class 1, but to get more favorable labeling the sponsor may want a new study, and that might require more information, so it could get a Class 2.

Q: If a company gets a response letter from the FDA that is not deemed to be a Complete Response Letter, under that scenario, does the clock simply stop, or does that trigger the beginning of a new six-month clock?

A: The answer is no. That really can't happen. Once we file the application, unless a company withdraws its application during the review cycle, we are required to give an Action Letter at the end when we give the review. Once we file an application, we are obligated to complete the review and send the comprehensive letter unless the company voluntarily withdraws. If a company withdraws during the review, when it resubmits, it gets a full clock.

Q: Do you ever make arrangements with companies to extend the PDUFA date?

A: We sometimes get sponsors who suggest, "Now the goal is coming up, and we agree to extend the clock." They can't do that. The only way to do that is with a major amendment submission. I have to remind my staff that just because the company is okay with an extension doesn't mean we can do that. There are ways we work with companies to be efficient,

especially if a product looks effective for a serious and life-threatening disease, but they can't grant us extensions in time.

Q: It seems there is a lot of confusion over what a Complete Response letter means.

A: One of the frustrations for the public is that Complete Response letters are not made public, so you can't see what the FDA said about the application. Wall Street analysts sometimes get frustrated because the way a company portrays the letter may not be the same as when they finally see it.

While Congress directed us to get rid of approvable/non-approvable letters, a lot of the outside community like those because there is some difference. With a non-approvable letter, you can feel pretty confident that there are substantial issues before approval, whereas an approvable letter says the application has the potential for approval if the company fixes the deficiencies. Those deficiencies can be anywhere from minor to a whole list, but it says the FDA made a preliminary judgment that the application can be approved, a preliminary finding of safety and efficacy if the outstanding issues are addressed. Unfortunately, the media often portray an approvable letter as tentative approval.

There are drugs that get a non-approvable letter that eventually get approved. A non-approvable letter doesn't say go away forever, it just says there is not enough information to make even a preliminary determination that it is approvable. Non-approvable means the drug has significant problems but not that they can't be overcome. I've had situations myself where we sent an approvable letter on one cycle, get back information, and then decide to send a non-approvable letter on the next cycle. So, there is no guarantee.

In CBER, with BLAs, they are already issuing Complete Response letters which lead people on the outside to not know what is in there. We don't comment on what's in a Complete Response letter.

Q: Are there cases in which a first-in-class item may not have to go to an FDA advisory committee, particularly if there is no FDA panel with expertise in that area?

A: We make the decision on panels based on a number of different factors. So, while an NME or a first-in-class are some of the criteria, there is no requirement that every one go to an advisory committee. Often, it depends on the science and on clinical issues. Do we feel we need input from an advisory committee before making a decision? Historically, about half of priority applications have been presented to an advisory committee. We haven't been faced with a situation where we didn't think we had a panel with the needed expertise. We have broad flexibility in bringing in consultants to support the panel.

Q: Do very new, innovative things most often go to an advisory panel?

A: In general, things that are very new and innovative are high on the list (to go to an advisory committee). But there are situations where they don't go because maybe the data is so clear cut or the advantage is so obvious that taking it to committee might not add value and might slow down approval. We do take some things to an advisory committee because they are new and innovative, and we think it is not only necessary to get expert opinions but also to increase public knowledge on the review, so the public knows our process. It is often very good for the public to know how the FDA came to a conclusion, the factors the FDA considered.

Q: The FDA generally wants two clinical trials before approving a drug. Can one be monotherapy and one combination therapy or do they both have to be in the same setting?

A: Generally, the standard of evidence for an approval is two adequate and well-controlled trials. FDAMA changed that, in certain circumstances, to one adequate and well-controlled trial along with other supporting information. When we do see two trials, they don't have to be identical, or even in the same specific patient population. Sometimes two trials complement one another, such as single therapy and combination therapy. Or, there might be situations where a slightly different age group or stage of disease is studied. We don't normally see one study in breast cancer and another in lung cancer for the same drug to get both indications, though in cancer one study is often enough to support an indication for that particular type of cancer. If we saw a drug for asthma, we wouldn't accept one trial in asthma and one in allergy; both would have to be in asthma.

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