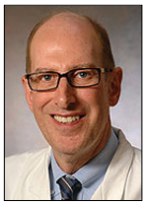
ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Serving on the FDA Oncologic Drugs Advisory Committee



Philip C. Hoffman, MD
Clinical Professor of Medicine
Section of Hematology & Oncology
University of Chicago
Chicago, Illinois

H&O What is the role of the Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA)?

PH ODAC is one of several FDA committees that provide advice on whether a sponsor's application for a drug approval meets the criteria for safety and efficacy. ODAC is an advisory committee. The FDA makes the final decision regarding a drug's approval.

ODAC reviews data for only a small minority of submissions to the FDA. The FDA's Oncology Center of Excellence decides whether to convene ODAC for a particular submission. The ODAC members are asked to vote on 1 or 2 straightforward questions. The questions might include whether an uncommon endpoint in a clinical trial is sufficient for FDA approval, or whether an unusual toxicity is serious enough to prevent approval. ODAC can also help decide whether a Risk Evaluation and Mitigation Strategy (REMS) is needed for a certain drug. That is, ODAC can vote on whether a patient must be informed in writing of a certain unusual risk or must undergo particular monitoring for toxicities during treatment.

H&O What types of clinicians are members of ODAC?

PH ODAC consists of a standing cadre of 12 to 14 members, mostly medical oncologists, but there is also a statistician, a nonvoting industry representative, and a consumer representative. I was a member from 2017 to 2021, and chair from 2019 to 2021.

Each meeting of ODAC also includes 4 or 5 ad hoc members who specialize in the area of the drug up for discussion. For example, if the application concerned a drug for prostate cancer, ODAC would invite several experts in genitourinary oncology to join the panel for that submission, to provide a closer understanding of the clinical need. A statistician might provide insight into subtleties regarding sample size or data analysis that might be missed by clinicians on the committee. As another example, about 2 years ago, ODAC reviewed the application for a myeloma drug known as Blenrep (belantamab mafodotin-blmf, GSK). This drug appeared to represent an important advance for certain patients with myeloma. However, it was associated with an unusual eye toxicity. ODAC invited input from several ophthalmologists. These ad hoc committee members provided insight into the seriousness of this toxicity to reassure the FDA that the benefits clearly outweighed the potential risks.

H&O What does the review process entail?

PH Meetings are convened several times a year. A half day is assigned for each application. First, the drug company presents its case in about 40 minutes. The representatives describe the perceived unmet need, the data that support the application, and any downsides. Next, the FDA presents its analysis. This presentation is not strictly a point/counterpoint rebuttal, but it does address the claims made by the drug company. For example, the FDA representatives might confirm the accuracy of the drug company's data, raise concerns that too many patients were censored from the analysis, or question whether the clinical benefit is sufficient to warrant approval.

After presentations from the drug company and the FDA, there is time set aside for open public comment. Because the agenda for the meeting is published well in advance, interested stakeholders can apply in advance to speak for about 8 or 10 minutes each, depending on the number of requests. Most of the time, these people are patients who have received the drug during a clinical trial, or family members of such patients. They often express gratitude for the opportunity to have received the treatment, stating that they might not be alive without it. These presentations are often emotional, but also very enlightening. They provide a worthwhile human perspective to the process. Sometimes practicing oncologists, in some cases those who entered patients into the key trials, lend their support for approval. In addition, a representative from a think tank will offer a perspective on whether an application is sufficiently compelling to merit approval or whether approval is premature.

After these presentations, members of the committee are able to question the representatives from the drug company and the FDA about specific points. Then there is some discussion among the committee members about issues they find either appealing or concerning about the application. Finally, the ODAC members vote, simultaneously, so no one is influenced by another's vote. Each vote is shown on a screen. Then all the committee members discuss one-by-one how they voted and the rationale behind their vote.

H&O What types of questions arise during the ODAC review process?

PH In some cases, a drug may be very useful, but only for a small subset of patients. For example, a drug for the treatment of pancreatic cancer may benefit a small number of patients who carry a *BRCA* mutation. Is that a good enough reason to approve it? Most of the time, the answer is probably yes, because why would we deny patients a drug that may be effective, even if the population eligible for it is small? The primary role of ODAC is to review safety and efficacy. This review does not consider the current state of the "market." For example, we once reviewed a treatment for lung cancer that was safe and efficacious for a particular subset of patients, but it was a "me-too" drug. Someone on the committee raised the question of whether physicians would administer this new drug, considering that the prevailing practice in the field had moved on. We concluded that the way companies choose to implement the approval is not our concern. Companies can advertise however they want. They can try to position a drug as an alternative standard of care that may be a better choice; offering patients and physicians choices can be a good thing, of course.

H&O Does the FDA usually follow recommendations from ODAC?

PH If the committee votes strongly to approve a requested indication, the FDA will typically follow this recommendation. Similarly, the FDA usually follows a strong vote against approval. There are also instances in which the vote reflects a split for and against approval. For these cases, the FDA may or may not proceed with approval.

In 2021, the FDA granted accelerated approval to a drug for Alzheimer's disease, although 10 of 11 members of an advisory panel voted that the research failed to show efficacy. (The eleventh member was uncertain.) There was a flurry of anger about this approval, and several members of the advisory committee resigned in protest. Although I can understand that members of that advisory committee might have been unhappy that the FDA's final decision was positive, I think they still needed to recall that the advisory committees are just that—advisory. Accordingly, I do not think that the resignations were necessary. Even if ODAC members vote strongly against an approval, we understand that it is the FDA's prerogative to approve a drug. Happily, this type of scenario did not arise during my tenure at ODAC.

H&O What are your views of the accelerated approval program?

PH Many drugs receive accelerated approval for certain indications based on early data that show improvement in progression-free survival and perhaps some early signals of better overall survival. The expectation is that subsequent trials will be performed to verify the initial data. An ongoing tension between the FDA and industry is that many drugs remain on the market under accelerated approval for extended periods because confirmatory trials have not been completed. In mid-2021, ODAC held a marathon 3-day meeting to discuss 6 applications that had previously received accelerated approval. We reviewed confirmatory data to decide whether these drugs should receive full approval. For 2 of the drugs, the companies withdrew the application for the particular indication because the confirmatory trials did not support the earlier results. (The drugs remained on the market for other indications.)

The accelerated approval program can help worthwhile medications reach the patients who need them. However, it is still an open question as to how to resolve the ultimate approval issue. We all need to remember that the world moves on. A confirmatory trial for a drug that received an accelerated approval in 2018 may no longer be relevant if better treatments or combinations have become available in the meantime. Doctors and patients

may decline to participate in a randomized trial to confirm the earlier results if that is the case.

The presentations at ODAC meetings offer a wealth of information about unmet needs, the current state of the art, future goals, and other aspects of care.

H&O How does the FDA address any potential conflicts of interest among the members of ODAC?

PH Before they join ODAC, members must provide extensive information about whether any of their investments and assets, or those of family members, could be construed as a conflict of interest in any way. Decades ago, there were some concerns that the FDA might be subject to too much outside influence. From my own experience in the past few years, however, the FDA is extremely cautious about avoiding any real or perceived conflicts. I could obtain a mortgage more quickly than I could join an FDA committee.

Before every meeting, ODAC members must complete a long conflict-of-interest form. The members must indicate whether they have any connection to the trials under discussion, to the pharmaceutical company, or to the makers of competitor drugs. The process is very rigorous. As an example, I was disqualified from certain meetings because my institution, the University of Chicago, participated in a trial under discussion. I did not have any patients in the trial, but still I was not permitted to participate in the meeting. The FDA aims to avoid any criticism that conflicts of interest might influence the approval process.

H&O Did you gain any insights into the drug development process from your work with the committee?

PH I was surprised by the complexity of the approval process. The stakes are of course very high for the drug company because of the large amounts of money involved. However, the stakes are also very high for the FDA, which has a heavy responsibility for assuring the public health and safety. Employees of the FDA work with extreme diligence to avoid approving a drug that could unexpectedly harm patients in the postmarketing period.

As an oncologist in an academic center, my focus is limited to certain cancers. While serving on the committee, I learned a tremendous amount about other malignancies. The presentations at ODAC meetings offer a wealth of information about unmet needs, the current state of the art, future goals, and other aspects of care.

This experience has also shown me that the people who work for the FDA are incredibly dedicated and smart. These unsung heroes are very analytical, detailed, and focused.

Disclosure

Dr Hoffman has no real or apparent conflicts of interest to report.

Suggested Readings

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