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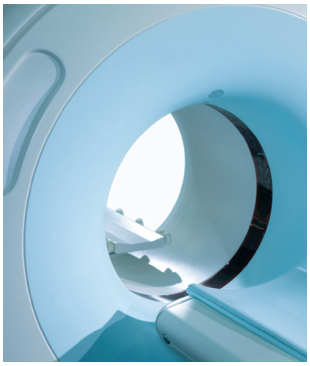
FDA Advisory Committee Outcomes



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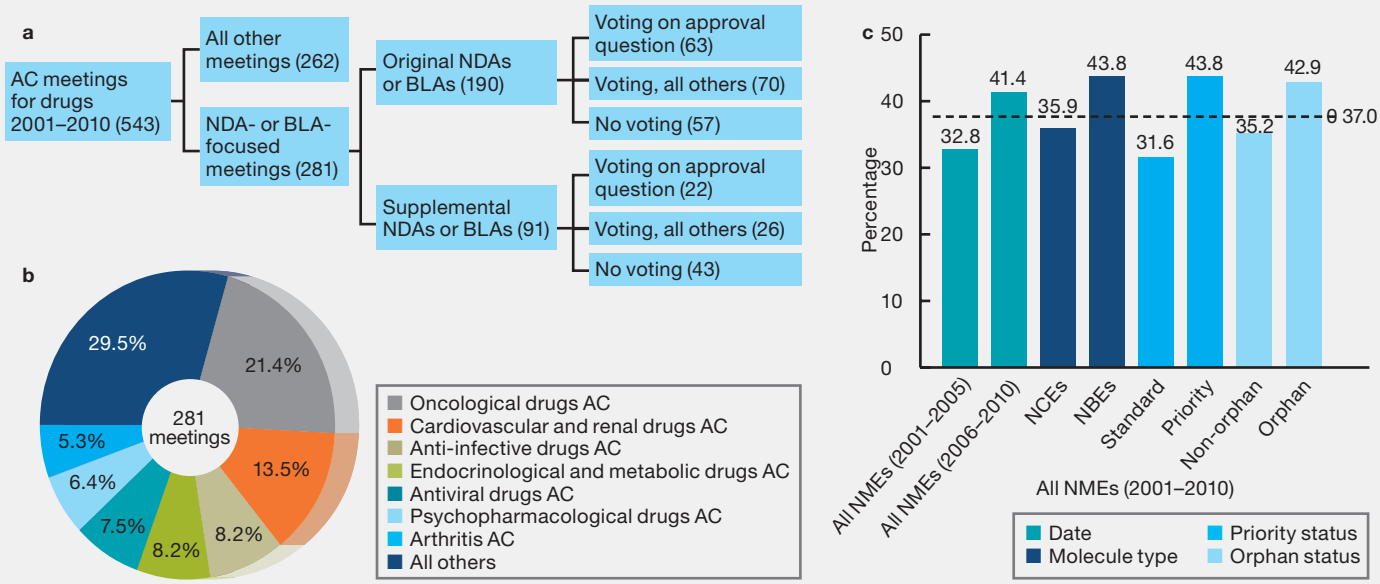
FDA Advisory Committee Outcomes

FDA advisory committee meetings are high-stakes interactions, with many years of effort, millions of dollars of investment, potential regulatory approval, and billions of dollars in potential sales for a new drug riding on the outcome. We have analyzed publicly available data and established a fact base that provides all stakeholders with a better characterization and greater transparency into the outcomes of advisory committee meetings. We also consider the implications for how sponsors can use this information to improve R&D decision-making.

During the pre-market review process for drugs and medical devices, many regulatory agencies seek unbiased advice from external experts to address areas of scientific or technical uncertainty. The US Food and Drug Administration (FDA) in particular has a well-defined process for obtaining expert input from its advisory committees and incorporating the input into its review processes. FDA reviewers complete an initial review of a product application and identify questions where external input is needed. The FDA then convenes an advisory committee meeting and obtains the requested input through a combination of presentations, discussion, and voting by committee members. After the meeting, FDA reviewers take into account the input received when making product approval decisions, although the recommendations of the committee are not binding.

FDA advisory committee meetings are high-stakes interactions, with many years of effort, millions of dollars of investment, potential regulatory approval, and billions of dollars in potential sales for a new drug riding on the outcome. However, despite the fact that sponsors recognize the crucial nature of these meetings and are familiar with the processes, we have found limitations in the quantitative understanding of their outcomes. In this article, we have analyzed publicly available data on FDA advisory committee meetings with the aim of helping to address these limitations. We investigated several important issues, including the total number of meetings by type and therapeutic area, the frequency with which new product applications are subjected to advisory committee meetings, consistency between the advisory committee votes and FDA approval decisions, and the duration between an advisory committee meeting and the final FDA approval date for a product.

Exhibit 1 | Characteristics of FDA advisory committee meetings between 2001 and 2010.



a | Overall characteristics of 543 US Food and Drug Administration (FDA) advisory committee (AC) meetings held for drugs between 2001 and 2010.
b | Distribution by committee of the 281 meetings focused on new drug applications (NDAs) or biologics license applications (BLAs).
c | Percentage of approved new molecular entities (NMEs) that were the subject of an AC meeting. NBE, new biological entity; NCE, new chemical entity.

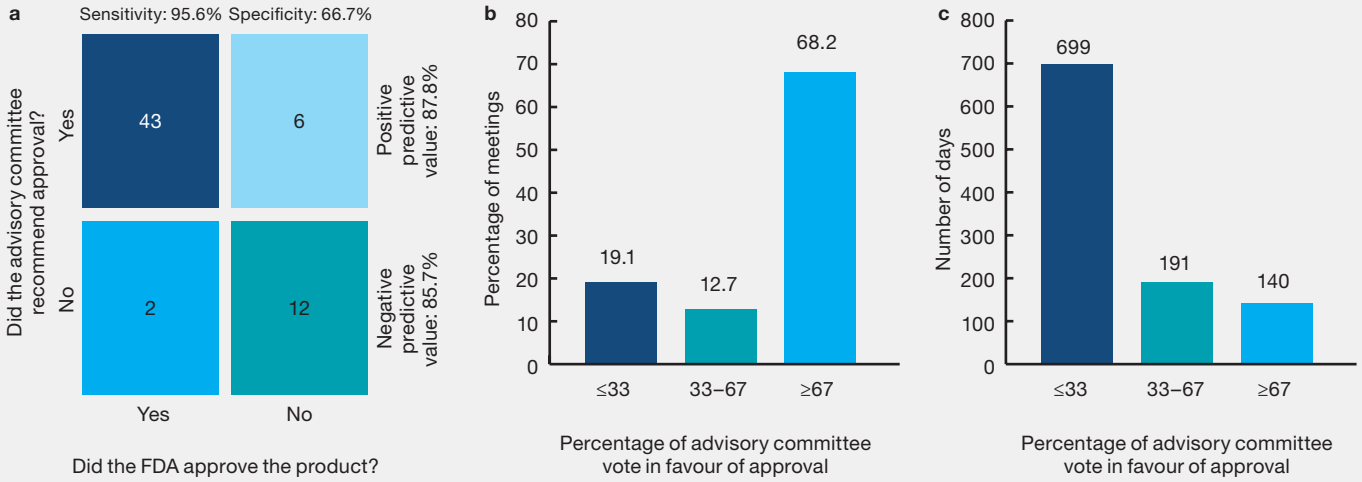
Analysis

We conducted an outside-in analysis of the outcomes of FDA advisory committee meetings held for drugs during the decade from 2001 to 2010 by reviewing publicly accessible materials, including meeting minutes, posted on the FDA's website.

Of the 543 total advisory committee meetings held for drugs in the 2001-2010 period (Exhibit 1a), 281 were focused on a single product, of which 190 were for original new drug applications (NDAs) and biologics license applications (BLAs), and 91 were for supplemental NDAs or BLAs. The distribution of meetings by therapeutic area is shown in Exhibit 1b. With regard to novel drugs, 37% of FDA-approved new chemical entities or new biological entities in the 2001–2010 period were the subject of an advisory committee meeting (Exhibit 1c). This percentage increased from 32.8% in the 2001–2005 period to 41.4% in the 2006–2010 period, suggesting a slight increase in the FDA's use of advisory committee input to help inform product approval decisions. Additional data analysis shows that new biologics, priority status applications, and orphan drugs were the subject of more meetings, on a percentage basis, than new chemical entities, standard applications, and non-orphan drugs.

We considered in detail a subset of 63 of the 190 meetings related to original NDAs or BLAs, at which committee members were asked to vote for or against approval of the drug of interest. In the analysis, we looked at the voting record to determine whether the committee provided an endorsement for the approval of the drug (identified as a simple majority of votes recommending approval). We then identified whether the FDA

Exhibit 2 | Analysis of a subset of 63 FDA advisory committee meetings that included votes for or against the approval of a new drug between 2001 and 2010.



a | Summary of US Food and Drug Administration (FDA) advisory committee recommendations and approval decisions.
b | Clarity of outcome of voting decisions. We considered the effect of the strength of the advisory committee endorsement by creating three equal categories: ≤33% endorsement for approval; between 33% and 67% endorsement for approval; and ≥67% endorsement for approval. In 87% of committee meetings, the result was either a clear "yes" or "no" vote.
c | Association between the strength of the endorsement by the advisory committee, as measured by the percentage of panel members voting for approval, and the median duration between the meeting and the FDA approval date. The duration varies inversely with the strength of the endorsement.

approved the drug, and for those drugs that were approved we also identified the duration of time between the meeting and the approval date.

As shown in Exhibit 2a, the FDA's approval decisions have been broadly consistent with the recommendations of its advisory committees. The FDA approved 88% of the original NDAs or BLAs that were endorsed by its advisory committees, and did not approve 86% of those that the committees did not endorse. In addition, in those instances when the approval decision made by the FDA differed from the recommendation of the advisory committee, the FDA did so at the same rate regardless of whether the panel endorsed approval. The sensitivity and specificity of advisory committee recommendations as a test for FDA approval is 96% and 67%, respectively. In addition, at 78% of advisory committee meetings the members recommended drug approval.

Exhibit 2b shows that in 87% of committee meetings the result was either a clear "yes" or "no" vote. One possible explanation for this observation is that the committee members have a deep expertise in their field and can readily address the areas of uncertainty in the application. An alternative explanation could be a "herding effect" in advisory committee meetings, where one or more influential members convince other panel members of their point of view. The open, role-call voting system of most meetings could further contribute to this effect. In practice, it seems likely that both explanations contribute to this observation.

The association between the strength of the endorsement by the committee (as measured by the percentage of panel members voting for approval) and the duration between the advisory committee meeting and FDA approval date is shown in Exhibit 2c. As might be anticipated,

the duration varies inversely with the strength of the endorsement, suggesting that strongly endorsed products tend to be approved on the first review cycle, whereas products that are not as strongly endorsed could be associated with multiple review cycles. Our results also show that advisory committees endorse approximately the same percentage of products for approval as the FDA approves applications (~75%). This suggests that the FDA is not disproportionately pre-screening either clear approvals or rejections prior to selecting applications to review at an advisory committee meeting. Instead, the results are suggestive of a two-cohort model of applications based on whether FDA reviewers feel they have sufficient input and knowledge to make approval decisions without an advisory committee meeting. This supports the notion that advisory committees have a crucial role in providing necessary input to FDA reviewers during the pre-market review process.

Implications

We believe that these results have important implications for companies that are preparing for potential advisory committee meetings. Given the characteristics of advisory committees that we have described here, we believe that the use of bodies akin to advisory committees could be considerably expanded by industry, and could be a major driver for improved decision-making. Companies currently use mock advisory panels to help rehearse and prepare for advisory committee meetings. However, given the sensitivity and specificity of the approach, companies may be better served by incorporating the approach into decision-making, not merely preparation. This could be applied at different points in the life cycle of a product where important investment decisions are made—for example, following Phase II development—in addition to pre-submission.

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