



PMA Advisory Panels: The Impact of FDA's Change in Policy on Voting Pattern

By Jeffrey N. Gibbs, JD and David A. Gibbs

This article provides a statistical analysis of Premarket Approval Application (PMA) data illustrating some new and interesting insights into the advisory panel process.

Introduction

The Food and Drug Administration (FDA) issues numerous guidance documents, policies and similar statements that apply to devices. These documents are not legally binding. Nevertheless, many of these documents are widely cited and incorporated into decision-making, both by FDA and industry.

Yet, although it is treated as a given—or at least widely accepted—that these documents affect industry and agency behavior, it can be difficult to discern *exactly* what their impacts are. The famous 1997 guidance on when to submit a new 510(k) for product modifications is a prime example.^{1} While the 510(k) guidance altered the way companies analyzed and documented product modification decisions, there is no way to quantify how many file/no file decisions were changed due to companies referencing that document or how it changed FDA's analyses.

Even for other narrower guidance documents, such as ones relating to the submission of marketing applications for a particular device, there is no opportunity to scrutinize the FDA decision-making process. FDA data can show the outcomes, e.g., how many 510(k)s of a single type were cleared after a guidance and the duration of review, but that is still only a modest surrogate marker for what one really wants to know: how did companies change their behavior in response and how was the actual review process affected? However, not all policy documents affect only decisions made in private. One forum where the decision-making process is fully visible is FDA's advisory panels on Premarket Approval Applications (PMAs).

PMAs represent a small minority of all applications received by FDA. 510(k) premarket notifications are far more common, representing more than 95% of marketing applications for 2016.^{2} Many devices which lack predicate devices bypass PMAs, going through the de novo authorization process. However, if the safety and effectiveness of a device cannot be reasonably assured through general and special controls, only the PMA route is available.^{3}

When Congress passed the *Medical Device Amendments* in 1976, it established a system for FDA to receive public input on PMAs from advisory panels. At that time, Congress decreed that PMAs “shall” go through panel review. That is no longer true. In 1990, Congress amended the law to let FDA bypass panel review when the agency “finds that the information in the [PMA] which would be reviewed by a panel substantially duplicates information which has previously been reviewed by a panel appointed under section 513.”^{4} Consequently, the number of PMA advisory panels convened is less than the number of PMAs received. In calendar year 2015, FDA held two PMA advisory panel meetings. In calendar year 2010, it held approximately nine. All of these advisory panel meetings are public.

Advisory panel meetings are high-stakes events. As a matter of law, FDA is not bound to follow a panel’s recommendations. After all, these are advisory panels, not juries. Yet, it is commonly stated and generally believed that the agency usually does follow panels’ advice. Accordingly, device companies spend a significant amount of time and money preparing for advisory panels. The agency also devotes significant resources to panel preparation. Financial analysts pay careful attention to FDA’s briefing packages, which are made public shortly before the meeting itself, and to the panel’s votes.

However, if a change in process caused a change in voting outcomes, the fates of devices, companies and the patients who could access the device could be altered. Thus, the process by which panels vote could be highly consequential.

And, in fact, FDA has changed that process. In 2010, FDA issued a new policy governing panel voting.^{5} Through this policy, FDA introduced several modifications.

First, FDA went to a blinded, simultaneous voting system. Previously, panel members would announce their vote sequentially around the table. The later voters heard how earlier panel members voted before stating their own positions. Under the current process, everyone votes at the same time. While panelists have heard comments by their colleagues throughout the day, nobody knows how anyone else has voted. The concern about the previous system was that first votes—and their accompanying explanations—would carry disproportionate weight.

Second, FDA changed the questions being voted upon. Previously, FDA had asked panel members to vote on one question: should the device be approved? Thus, the day-long discussion culminated in a decisive recommendation for or against approval. Under the new system, the panel no longer recommends for or against approval per se. Instead, panel members vote on three separate questions: 1. Is the device safe, 2. Is the device effective and 3. Do the benefits of the device outweigh the risks?

These changes seemingly relate only to process. Perhaps for that reason the changes were not very controversial. Yet, it is well-known that process can affect substance.

For example, a published study showed that a seemingly innocuous change related to panel seating affected votes at FDA drug advisory panels.^{6} It is also well-known that even subtle changes in question framing can affect answers, e.g., two statements that are mathematically equivalent: “would you take a drug with a 95% chance of surviving?” versus “would you take a drug with a 5% chance of dying?”^{7} The switch from “should the device be approved” to a trio of questions could have affected how much support sponsors received from panels.

The question, then, is what impact, if any, did the changes have on voting patterns? Because the PMA advisory panel process is public, on the record and transcribed, it is possible to evaluate the impact of these seemingly small, subtle changes.

The widely shared expectation was that blind voting would lead to greater independence, or less agreement, among panel members. For example, one former panel member told us she expected the new process would lead to greater heterogeneity and voter independence because panelists would no longer be influenced by the explanation for their votes by strong-willed, vocal early voters. That is an entirely reasonable expectation. FDA itself explained, “[T]he ballot process allows each panel member to cast their vote without

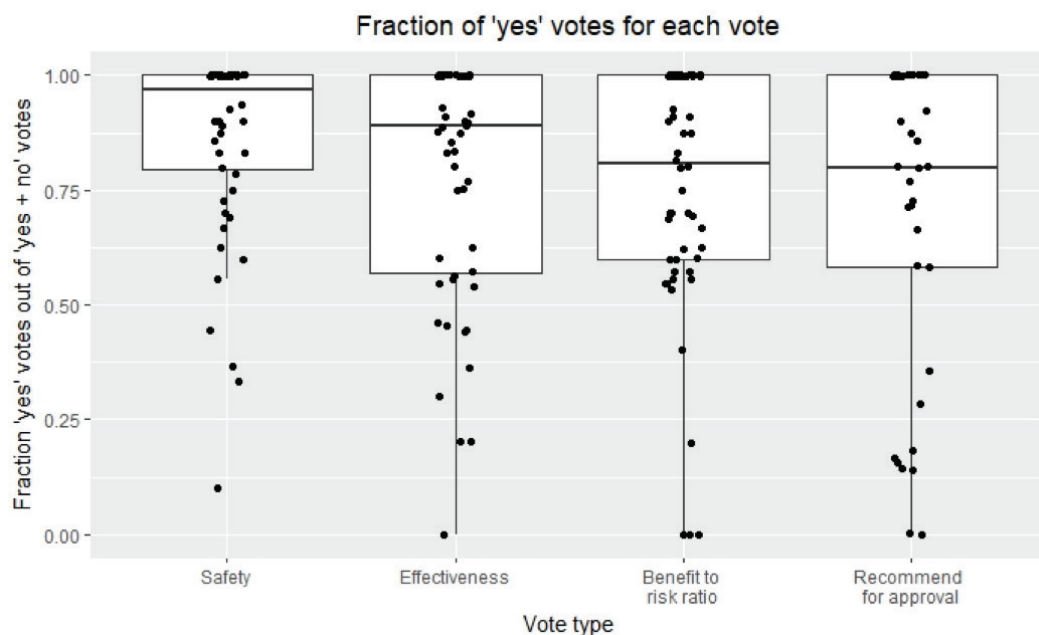
immediate influence by other votes.”^{8} If the new voting system resulted in less agreement (or more heterogeneity among panelist votes), all other things being equal, votes should have been more evenly split between “yes” and “no” under the new system.

To evaluate the new panel process, voting patterns were studied for all PMA advisory panels that were held between 1 September 2005 and 31 December 2016. (The few panel votes on Humanitarian Device Exemptions were not included.) During the study period, there were 89 advisory panels. Thirty-seven of these panels were held before the change and 52 after.

The analysis showed that vote outcomes did not become more heterogeneous or evenly split between “yes” and “no” under the new voting system. Instead, “yes” votes became more common in the new system. Under the old system, panels averaged 71% “yes” votes out of “yes” and “no” votes; under the new system, panels averaged 80% “yes” votes for all three questions combined (two-tailed t-test: $t=1.49$, $df=53.3$, $p=0.14$). This represents a modest effect of voting system on voting heterogeneity (Cohen’s $d=0.32$, 95% confidence interval= $-0.11-0.76$). Similar results were obtained using the percent of “yes” votes out of “yes,” “no” and “abstain” votes. (The fraction of abstentions doubled under the new system, but remained low: 2.7% of votes in the old system and 5.6% of votes in the new system.)

There were also differences between the percentage of “yes” votes among the four questions put to the panels (one under the old system, three under the new) (**Figure 1**). The average percentage of “yes” votes out of “yes” and “no” votes under the old system was 71% (+34% standard deviation). The average percentage of “yes” votes out of “yes” and “no” votes for safety, effectiveness and positive benefit to risk ratio (B:R) under the new system were 86% (+21%), 78% (+26%) and 75% (+27%), respectively. Thus, concurrence within panels was greatest for safety, followed by effectiveness, followed by the B:R. All of these had greater concurrence of votes than did the approve/disapprove question of the old system.

Figure 1 - Fraction of “yes” votes for each vote type. Left three are from the new voting system (n=52); right-most is from the old voting system (n=37). Each point is a panel.

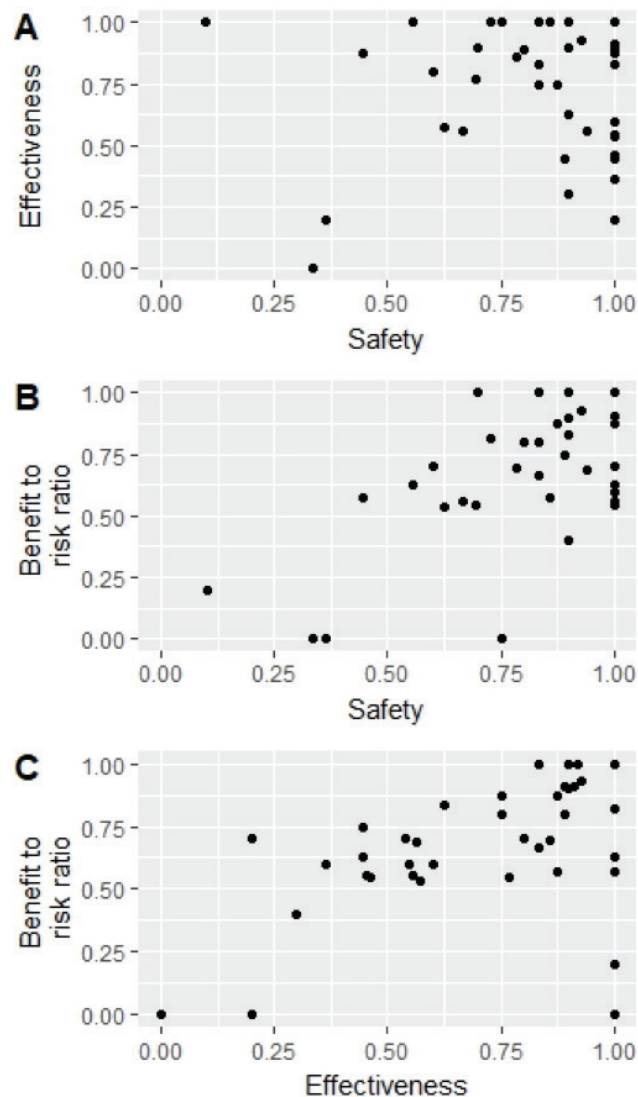


Finally, we looked at what extent the fraction of “yes” votes (out of “yes” and “no” votes) was correlated between questions across panels in the new system (**Figure 2**). That is, for example, did applications that received more “yes” votes for safety also receive more “yes” votes for effectiveness or were “yes” votes for effectiveness associated with “yes” votes for a positive B:R? It was found that the fraction of “yes” votes was

weakly positively correlated for safety and effectiveness (**Figure 2A**, Spearman $\rho=0.16$, where a Spearman ρ of -1 is a perfect negative correlation, 0 is no correlation and 1 is a perfect positive correlation), but moderately positively correlated for B:R and safety (**Figure 2B**, $\rho=0.55$) and B:R and effectiveness (**Figure 2C**, $\rho=0.65$). This means that applications that received more “yes” votes for a positive B:R also tended to receive more “yes” votes for safety and effectiveness.

The relationship between safety and effectiveness is different, however. In Figure 2A, the votes are clustered in a triangle in the upper-right of the plot; there is no clear association between safety and effectiveness “yes” votes. Given that there can be a trade-off between a device’s safety and effectiveness, that outcome may not be as counter-intuitive as it might initially seem.

Figure 2 - Fraction of “yes” votes (out of “yes” and “no” votes) for each vote. Each point is a panel (n=52).



Thus, since the change was made, panel votes have not become more heterogeneous as seen in the percentage of “yes” votes being greater for safety, effectiveness and benefit-risk than it was for the unitary question of approval.

This change in voting pattern is not necessarily attributable to the change in voting policy. There have been many other changes in the PMA process over the years. For example, the higher percentage of “yes” may be due to FDA’s setting higher standards for the

PMAAs that proceed to panel. The applications going to panel may be higher quality, which could account for more “yes” votes than under the old policy. Yet, there is an 11 percentage point gap in “yes” votes between the safety and B:R questions. The potential impact of changing the procedural manner in which votes are cast on substantive voting patterns should be carefully considered before changes are made in the future.

The significance of advisory panels ultimately does not come from the votes per se. What matters most is the PMA outcome. Looking at panel votes provides some windows into the PMA process, both as to likelihood of approval and timing. That will be the focus of our second article.

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