



Product Approvability Recommendations from FDA Advisory Committees: Inconsistently Sought, Indirectly Obtained

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“Product Approvability Recommendations from FDA Advisory Committees:

Inconsistently Sought, Indirectly Obtained.” Daniel & Martina Lewis Center for Healthcare Innovation at Fairleigh Dickinson University School of Pharmacy & Health Sciences, Madison, NJ, April 2017.

ABSTRACT

Divisions within the Food and Drug Administration (FDA) often convene meetings of advisory committees, also known as AdComm or Panel meetings. The purpose of many AdComm meetings is for the FDA to obtain outside advice and recommendations on whether to approve a new drug or medical device. Laws and regulations indicate that such Panels are to provide recommendations regarding the approvability of the drug or device by FDA. In this paper we examine recent AdComm meetings to find whether FDA is obtaining Panel recommendations on drug and device approvability in accordance with these laws and regulations. We find that Panel recommendations on approvability are often not obtained. We further find that, in most cases where Panel recommendations are obtained, voting procedures are such that those recommendations address product approvability in only an indirect manner. We recommend implementation of several practices to ensure that FDA succeeds in obtaining clear recommendations when it convenes Panels to address product approvability.

INTRODUCTION

Divisions within the Food and Drug Administration (FDA) often convene meetings of advisory committees, also known as AdComm or Panel meetings. The purpose of AdComm meetings is for the FDA to obtain outside advice and recommendations on difficult questions, such as whether to approve a new drug or medical device. As noted on the FDA website, the advisory committee program “is governed by a number of Federal laws and regulations that set forth standards for convening advisory committees.”⁴ At those AdComm meetings that are convened to evaluate a new drug or device, these laws and regulations indicate that the Panel is to provide recommendations regarding the approvability of the drug or device by FDA, and they set out guidelines for how formal voting is to be conducted at such Panel meetings.

In this paper we examine recent AdComm meetings to find whether FDA is indeed obtaining Panel recommendations on drug and device approvability in accordance with these

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⁴ <https://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/LawsRegulationsGuidance/default.htm>

laws and regulations. We find that Panel recommendations on approvability are often not obtained. We further find that, in most cases where Panel recommendations are obtained, voting procedures are such that those recommendations address product approvability in only an indirect manner. FDA thus only secures a direct recommendation on product approvability in a small minority of cases. We recommend implementation of several practices to ensure that FDA succeeds in obtaining clear recommendations when it convenes Panels to address product approvability.

BACKGROUND

Panel meetings are major public events in the development of a new drug or medical device. The FDA decides whether a specific New Drug Approval application (NDA), Biologics License Applications (BLA), Premarket Approval application (PMA), or 510(k) is brought before an AdComm. Typically, though not always, the first several products of a new class are brought before Panels; “me-too” follow-ons are typically not subject to Panel reviews. Panel recommendations to approve or not approve a drug or device are not binding on the FDA, but on the occasions when a Panel is held, most of the time the FDA’s ultimate decision is in line with the Panel recommendation. Panels held to review an NDA, BLA, PMA, or 510(k) are closely watched by many stakeholders, including the investment community, competitors, the medical community, and payers. As a report by the consulting firm McKinsey puts it, “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.”⁵ Indeed, the outcome of Panel meetings, and even their postponement or rescheduling, have far-reaching effects. For example, on September 2, the FDA cancelled a Panel meeting for Dynavax Technologies investigational hepatitis B vaccine Heplisav-B, sending shares in the drugmaker tumbling.⁶

Advisory committees for the purpose of providing recommendations to FDA regarding approval of NDAs and BLAs are established under Title 21 USC 355,⁷ and Panel meetings

5 Philip Ma, Navjot Singh, Jeff Smith, and Seth Townsend, “FDA Advisory Committee Outcomes,” 2013, McKinsey & Company, http://www.mckinsey.com/~/media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx. The authors find that, between 2001 and 2010, “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”(page 3).

6 Joe Barber, “FDA cancels advisory panel meeting for Dynavax’s experimental hepatitis B vaccine Heplisav-B,” FirstWord Pharma, September 2, 2016, <http://www.firstwordpharma.com/node/1413030>. The FDA said that the meeting was cancelled “to allow time for the FDA to review and resolve several outstanding issues” (<https://www.fda.gov/AdvisoryCommittees/Calendar/ucm518600.htm>). In January 2016, Dynavax reported that a Phase III study of the therapy met both of its co-primary endpoints versus GlaxoSmithKline’s Enerix-B (Joe Barber, “Dynavax’s experimental hepatitis B vaccine Heplisav-B hits late-stage study goals,” FirstWord Pharma, January 7, 2016, <https://www.firstwordpharma.com/node/1347872>).

7 “(n) Scientific advisory Panels: (1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under this section or section 262 of title 42, the Secretary shall establish Panels of experts...”

to provide recommendations regarding approval of PMAs for medical devices are established under Title 21 USC 360e.⁸ Panel recommendations on approvability are explicitly required in these statutes: “advice and recommendations...regarding approval for marketing” and “recommendation respecting approval of the application.” The Panel voting process is described in a guidance document issued by FDA in 2008.⁹

This document provides guidance on the procedures used for voting.

There are some advisory committee meetings at which votes are not taken. For example, votes are typically not taken at meetings to discuss the development of a clinical trial design or the development of a guidance document.

At other advisory committee meetings, members cast a formal vote on issues related to the approvability of a product submission. In others, different questions may be posed to a committee for a formal vote. Votes can be an effective means of communicating with FDA because they provide feedback on discrete questions. These questions are generally scientific in nature and can involve a range of subjects, including evaluation of post-market safety data or pre-market assessment of a product's risk/benefit profile. Since all members vote on the same question, the results help FDA gauge a committee's collective view on complex, multi-faceted issues. FDA recognizes that many of the questions voted on by advisory committee members are complex and that the discussion that accompanies the voting is important. The discussion, together with the votes, helps inform the agency's own deliberations on scientific and regulatory matters.

The guidance document states FDA's views on Panel voting procedures:¹⁰

FDA recommends adopting uniform voting procedures to help maximize the integrity and meaning of voting results. ...

The question presented for a vote should have minimal qualifiers, not be leading, and should avoid the use of double or triple negatives. ... The objective is to reduce any potential confusion and maximize the meaning of the voting results by ensuring that the votes are based on a consistent and collective understanding of the question at issue.

Why is formal voting at Panel meetings so important? Often, as a Panel meeting proceeds, it can seem to be solely a ‘gadfly session.’ Clinical experts are assembled to identify weak-

⁸ “(c) Application for premarket approval... (3) Upon receipt of an application meeting the requirements set forth in paragraph (1), the Secretary— (A) may on the Secretary's own initiative, or (B) shall, upon the request of an applicant unless the Secretary finds that the information in the application which would be reviewed by a Panel substantially duplicates information which has previously been reviewed by a Panel appointed under section 360c of this title, refer such application to the appropriate Panel under section 360c of this title for study and for submission (within such period as he may establish) of a report and recommendation respecting approval of the application, together with all underlying data and the reasons or basis for the recommendation.”

⁹ Food and Drug Administration, “Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings,” August 2008, <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125641.pdf>, page 4.

¹⁰ Ibid., pages 4 and 5.

nesses in the data and conclusions; they are there to identify problems, and so they do, often for the bulk of the meeting. Members often lament the way the clinical studies were performed and the endpoints that were analyzed. They frequently ask for additional analyses or follow-up to be performed in the course of the deliberations. Throughout a typical AdComm meeting, then, it can be difficult to determine whether the Panel members are in support of the product or are opposed to its approval.

Following the hours of review and consideration, however, the time to vote arrives—and the tenor of the session changes. The purpose at hand, along with the unspoken mood or spirit in the room, shifts, from: “Tell us everything wrong with this application,” to: “Now tell us, after all the hole-poking and lamentation, do you think we should approve this product? That is, would you want to use it in your patients?” Often, the most persnickety Panel members, who seemingly had been seeing the glass half-empty throughout hours of deliberation and review, are revealed to be the most ardent supporters of the approval of the new product. The formal vote on approvability is where the proverbial rubber hits the road—it is the single most important moment.

Casual observation, along with one overt policy change by the FDA, has suggested to us that in recent years Panels have been voting on product approvability less often than they did in earlier years. Here, in the next section, we examine the policy change, made in 2010 by the FDA’s Center for Devices and Radiological Health (CDRH), which reviews medical devices. Then, in the section after that, we present data on the frequency of approvability voting in Panels convened to examine new drugs and biologics, to test the impressions taken from casual observation.

FORMAL VOTING BY PANELS ON MEDICAL DEVICES

Prior to May 2010, Panel members at AdComm meetings for medical devices had been instructed to make one of three recommendations—approval, approvable with conditions, or not approvable:¹¹

Panel Recommendation Options for Premarket Approval Applications

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (Act), as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications (PMAs) that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health {under conditions on intended use} outweigh any probable risks.

¹¹ See, e.g., https://www.fda.gov/OHRMS/DOCKETS/ac/05/briefing/2005-4162b1_02_Panel%20Recommendation%20Options.htm

Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use {when labeled} will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. APPROVAL – If there are no conditions attached.
2. APPROVABLE with conditions – The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.
3. NOT APPROVABLE – The panel may recommend that the PMA is not approvable if:
 - the data DO NOT provide a reasonable assurance that the device is safe, OR
 - the data DO NOT provide a reasonable assurance that the device is effective, under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

However, in May 2010, CDRH changed the manner in which Panels would vote on applications under review, a change seemingly in tension with the statutes that speak of Panel recommendations on approvability.¹² No longer would advisory committees vote on a recommendation of approvability of new products under review (approval, approvable, not approvable); rather, the Panels would be asked to vote on safety, effectiveness, and benefit-risk:¹³

For meetings focusing on a particular device that is under review in the agency to determine its approvability, *panel discussion has not always reflected a panel's final vote on approvability*. Under the new approach, instead of voting on the approvability of premarket approval applications, including conditions of approval, the panel will vote on the safety and effectiveness of a device and the device's risk versus its benefit.

By changing the voting procedure in this way, Panel members will *address key scientific issues* during their discussions, which will be reflected in their votes. This change will also allow panel members to address issues related to their scientific area of expertise instead of regulatory issues, with which they may not be so familiar.

So in the words of CDRH, the Panel meetings are convened to determine approvability, yet, votes on whether or not the Panel recommends the product for approvals will no longer be taken. This neither makes sense on the surface nor when one digs deeper, for it should be

12 See *supra* notes 7 and 8.

13 Food and Drug Administration, "Summary of Changes to CDRH's Advisory Committee Process," <https://www.fda.gov/advisory-committees/committees/meeting-materials/medical-devices/ucm208485.htm> (our emphases).

well understood that Panel votes on safety and effectiveness are not the same as votes on approval recommendations. Take Synercid, as an example—the AdComm chair stated, “There are two parts to our question. One is the safety and efficacy based on the data presented. The second part, that is clearly closely related, but not necessarily exactly the same, is whether or not the committee recommends approval recognizing that it is not us, but the agency that approves these drugs.”¹⁴ Interestingly, this Panel voted on four potential claims for the drug; votes on safety and effectiveness tracked well with votes on approval recommendation. On the fourth, however, the Panel voted three YES to seven NO that Synercid demonstrated safety and effectiveness for use in vancomycin-resistant enterococcus, but, it voted nine YES to one NO to recommend approval for the claim (see Table 1).¹⁵

Synercid potential claim	Safety / Effectiveness	Approval Recommendation
Skin and skin structures	7 yes; 2 no; 1 abstain	6 yes; 4 no
Community acquired pneumonia	0 yes; 10 no	0 yes; 10 no
Hospital acquired pneumonia	8 yes; 2 no	7 yes; 3 no
Vancomycin-resistant enterococcus	3 yes; 7 no	9 yes; 1 no

Table 1. Summary of AdComm voting at Synercid Panel Meeting.¹⁶

FORMAL VOTING BY PANELS ON DRUGS AND BIOLOGICS

Investigative method

In this section we develop data on the extent to which recent AdComms for new drugs and biologics have conducted formal votes on approvability. Our study, of the 2011–2016 period, can be seen as building upon data collected by McKinsey covering the 2001–2010 period (see Figure 1).¹⁷

Of the 543 total advisory committee meetings held for drugs in the 2001-2010 period, 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. ...

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.

¹⁴ Food and Drug Administration, “Anti-Infective Drugs Advisory Committee, 63rd Meeting, Open Session” (transcript, February 19, 1998), <https://www.fda.gov/ohrms/dockets/ac/98/transcript/3383t1.pdf>, page 200.

¹⁵ *Ibid.*, pages 220-221, 234-235, 251-252, and 284-285.

¹⁶ *Ibid.*

¹⁷ Ma et al., “FDA Advisory Committee Outcomes,” page 2.

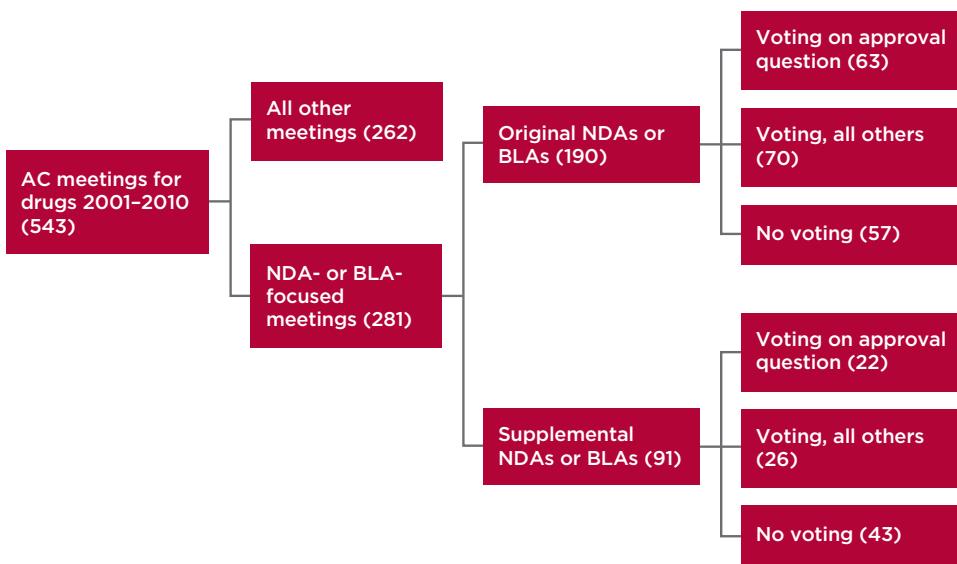


Figure 1. Characteristics of FDA Advisory Committees between 2001 and 2010.¹⁸

In 2001–2010, of some 281 AdComm meetings focused on products for which NDA or BLA (original or supplemental) were submitted and at which votes were taken, McKinsey found that approval recommendations were sought at just 85, or 30 percent.

We performed a review of all advisory committee meetings for drugs and biologics held between January 1, 2011 and August 31, 2016 that pertained to NDAs and BLAs (including supplements) for products, including new chemical entities and new indications for which meeting materials were available on the FDA website. We excluded fixed dose combinations for the same claims, combinations that did not contain new chemical entities or new use(s) of existing components, biosimilars, and over the counter drugs. We also looked at all PMA and 510(k) meetings during the period for medical devices.

We analyzed the extent to which advisory committee Panels voted on the approvability of the products under review, as provided for in the law, versus other parameters, for example, safety, efficacy, and benefit-risk.

As stated in the 2008 guidance document: “The question presented for a vote should have minimal qualifiers, not be leading, and should avoid the use of double or triple negatives.”¹⁹ Therefore, we also analyzed the wording of questions to determine the extent to which the recommendations from Panel members were solicited in a direct fashion, indirectly, or not at all. Examples of these three categories, for drugs/biologics and devices, are contained in Table 2.

18 Ibid., page 2, Exhibit 1a.

19 Food and Drug Administration, “Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings,” page 5.

Approvability question type	Drugs/biologics	Devices
Direct vote on approvability recommendation	Should Arymo ER be approved for the proposed indication?	With no further motions, it has been moved and seconded that the PMA P080013 for the DuraSeal Xact Sealant System be found approvable with three conditions the Panel has just approved. We will now vote on the main motion and that is to—that is approvable with conditions. With a show of hands, please indicate if you concur with the recommendation that the above-named PMA be found approvable with conditions.
Indirect vote on approvability recommendation	Does the efficacy, safety and overall benefit-risk profile of sugammadex support the approval of this application?	<p>VOTING QUESTION 1: Is there a reasonable assurance that the LAP-BAND® is safe for use in weight reduction for obese patients with a BMI of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions?</p> <p>VOTING QUESTION 2: Is there a reasonable assurance that the LAP-BAND® is effective for use in weight reduction for obese patients with a BMI of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions?</p> <p>VOTING QUESTION 3: Do the benefits of the LAP-BAND® for use in weight reduction for obese patients with a BMI of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions, outweigh the risks of the LAP-BAND® for use in weight reduction for obese patients with a BMI of at least 35kg/m² or a BMI of at least 30 kg/m² with one or more comorbid conditions, for purposes of approval?</p>
No vote on approvability recommendation	Considering all the efficacy data from Trials 004 and 020, do you agree that a clinically meaningful benefit has been demonstrated in adult patients with SBS treated with teduglutide?	Do you believe that the clinical data in the PMA (Deep Brain Stimulation System for Epilepsy – Medtronic P960009/S068) provide a reasonable assurance that the proposed device is safe and effective for the proposed indications and intended patient population, and that the benefits of the device outweigh the risks?

Table 2. Examples of approvability questions posed to drugs/biologics and medical devices AdComms: direct, indirect, and none.

Findings on direct approvability recommendations

We gathered data on one hundred forty-four AdComm meetings. Notwithstanding the law requiring that FDA obtain AdComms' recommendations regarding approvability, direct questions were asked at only twenty percent of Panel meetings (Figure 2). There was wide variability among the CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research) divisions, ranging from zero to one hundred percent.

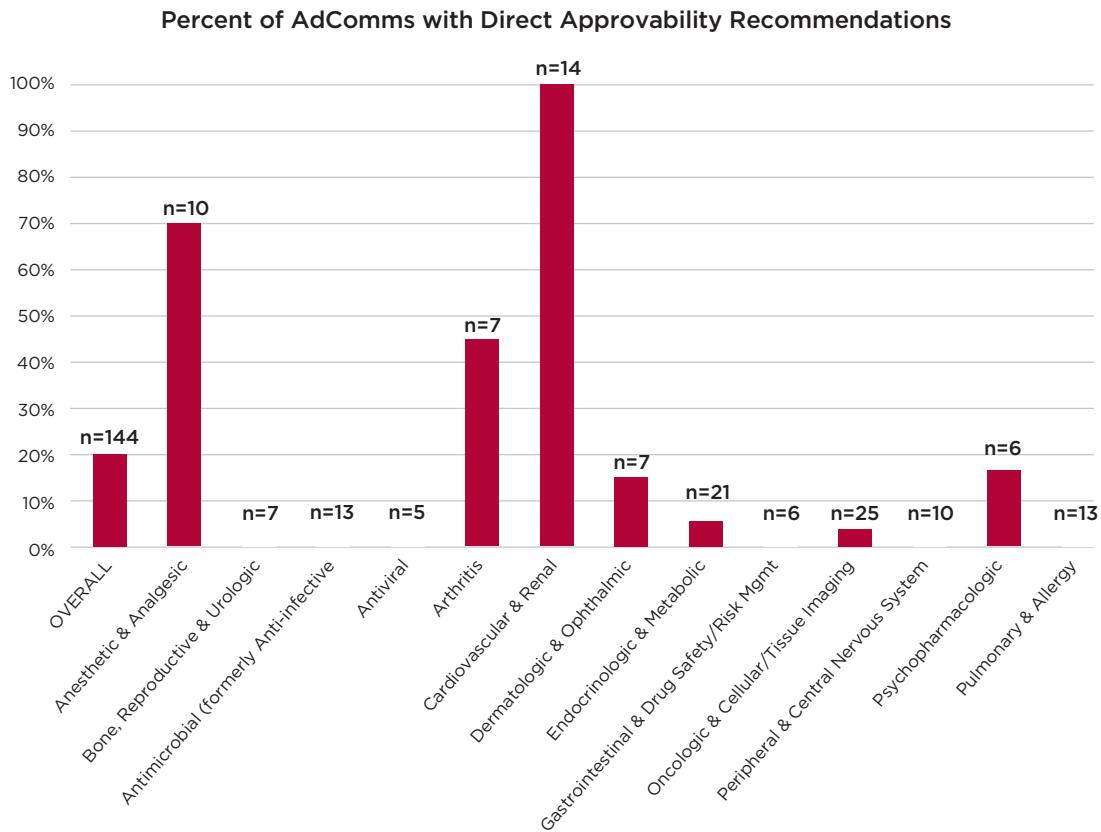


Figure 2. Drugs and biologics AdComms (January 1, 2011 thru August 31, 2016) voting - direct approvability recommendations

Only the Cardiovascular and Renal division asked direct questions regarding the AdComms' approvability recommendations at one hundred percent of Panel meetings. Five divisions (Bone, Reproductive, and Urologic Drugs; Antimicrobial Drugs; Antiviral Drugs; Gastrointestinal; and Peripheral and Central Nervous System Drugs) never asked a direct question regarding approvability of their Panels. The Oncologics Drugs division asked a direct question at just one of its twenty-five AdComm meetings.

Findings on direct and indirect approvability recommendations

Sixty-six percent of the AdComm meetings included direct or indirect questions regarding the Panels' approvability recommendation (Figure 3). There was wide variability among the review divisions, ranging from zero to one hundred percent.

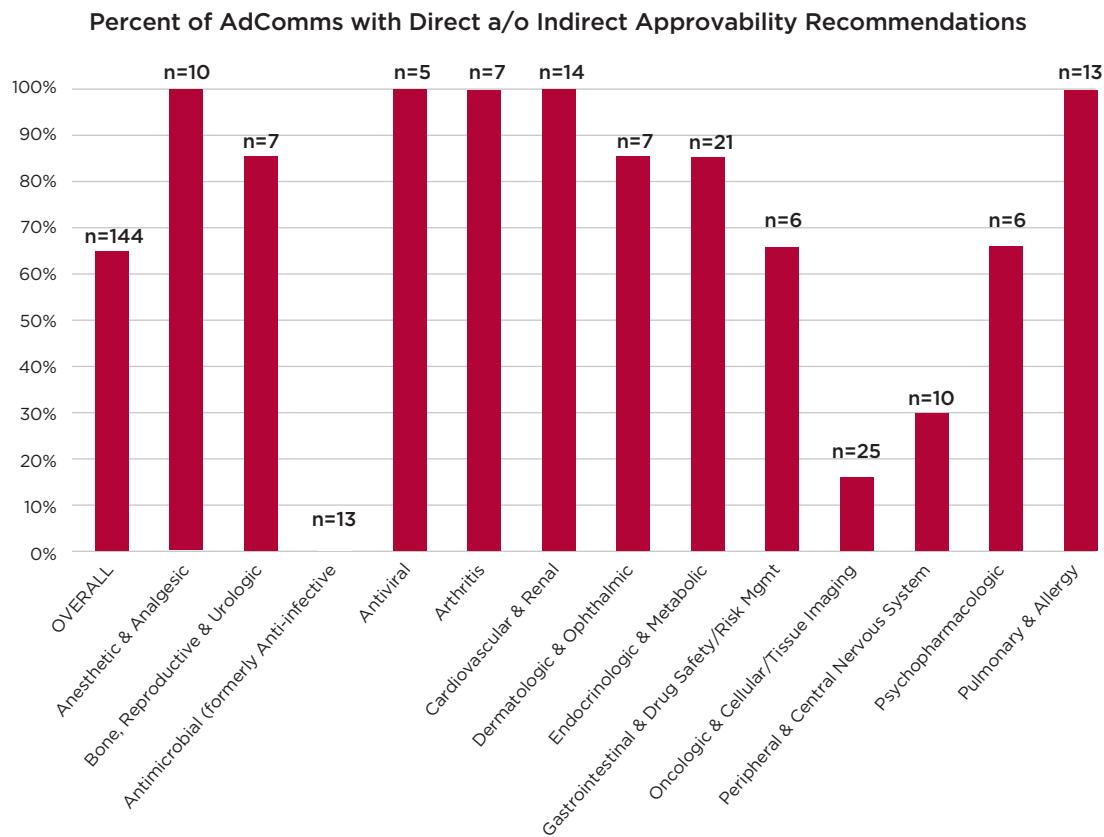


Figure 3. Drugs and biologics AdComms (January 1, 2011 thru August 31, 2016) voting - direct and indirect approvability recommendations

Five divisions (Analgesic, Antiviral, Arthritis, Cardiovascular, and Pulmonary) asked AdComms either direct or indirect questions regarding the approvability of products under review at every AdComm meeting. The Antimicrobial Drugs division asked neither a direct nor indirect question regarding product approvability; Oncologics and Peripheral and Central Nervous System divisions asked direct or indirect approvability questions at sixteen and thirty percent of the AdComms, respectively.

DISCUSSION

Should advisory committees provide FDA with direct recommendations on approvability? To this point our paper has effectively presumed that they should, but perhaps soliciting a Panel's direct recommendation is often *not* a good idea. That would even potentially

explain the findings of the preceding section: Perhaps FDA knows when soliciting direct recommendations is a good idea and when it's not a good idea, and it acts accordingly when organizing Panels.

But why would FDA often believe it is not a good idea to get a Panel's direct recommendation on approvability? If FDA needs Panel help to make a decision on approving a new product, why wouldn't it want a clear recommendation?

When CDRH changed its policy in May 2010, the FDA provided the following rationale for the change:²⁰

For meetings focusing on a particular device that is under review in the agency to determine its approvability, *panel discussion has not always reflected a panel's final vote on approvability*. Under the new approach, instead of voting on the approvability of premarket approval applications, including conditions of approval, the panel will vote on the safety and effectiveness of a device and the device's risk versus its benefit.

By changing the voting procedure in this way, panel members will address key scientific issues during their discussions, which will be reflected in their votes. This change will also allow panel members to address issues related to their scientific area of expertise instead of regulatory issues, with which they may not be so familiar.

We find this rationale not particularly compelling, for scientific issues raised by the FDA were very often extensively discussed, considered, and reviewed by AdComms prior to the May 2010 change in voting procedures. Consider the discussion questions at AdComms for the WATCHMAN® Left Atrial Appendage device, both prior to (April 29, 2009) and after (December 11, 2013) the change in voting implemented by CDRH, shown in Table 2.²¹ The extent to which these AdComms were called upon to "address key scientific issues" is similar.

As far as we can determine, the changes by CDRH have not provided for an enhanced ability of the FDA to engage AdComms on scientific issues; rather, they simply put an end to obtaining direct and unequivocal approvability recommendations.²²

20 Food and Drug Administration, "Summary of Changes to CDRH's Advisory Committee Process" (our emphasis).

21 See <https://www.fda.gov/ohrms/dockets/AC/09/briefing/2009-4434b1-03.pdf> and <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM377932.pdf>.

22 Under the new CDRH procedure, Panel Questions (discussion items) are often separated from Voting Questions by this statement: "The following questions relate to the approvability of [the device]. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today" (see, e.g., <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM490458.pdf>, page 4). Then, votes on safety, effectiveness, and benefit-risk are taken. However, these are not votes on the AdComms' recommendations regarding approvability, as required by law, but rather they are votes on elements that the FDA will consider in its decision.

April 23, 2009	December 11, 2013	<p>Examples of scientific/discussion questions</p> <p>Key primary effectiveness results for the updated 900 patient-year dataset are shown in Tables 1 and 2. Do these data, in addition to the original 600 patient-year data, provide a reasonable assurance that the WATCHMAN device can be used as an effective alternative to standard warfarin treatment for reduction of stroke, death, and systemic embolization?</p> <p>Please discuss the confounding effect of adjunctive antithrombotic drugs that were given to patients in the device arm of the trial.</p> <p>Do the data provided from the PROTECT AF study provide a reasonable assurance of safety? In your discussion, please specifically comment on the incidence and significance of the pericardial effusions associated with use of this device. Please also comment on the incidence of device embolization and thrombus present on the device.</p> <p>The pivotal trial demonstrated that qualified physicians need to carefully place this device in order to minimize acute procedural complications. Is the applicant's proposed training program adequate for training a new set of physicians in this procedure?</p> <p>The acute safety of the WATCHMAN device was a major concern in the PROTECT AF trial dataset discussed at the previous Panel meeting. There were 5 procedural ischemic strokes (3 due to air embolism), a 5.3% (24/449) rate of procedure-related serious pericardial effusions and cardiac perforations in randomized Device subjects, a 9.1% (41/449) rate of failed implant attempts, and an impression that the operator learning curve can be significant for new operators and sites. The sponsor subsequently worked on addressing these issues in the CAP registry and the PREVAIL trial. Procedural success was improved vs. PROTECT AF in both the CAP registry and PREVAIL trial, with procedural success rates of 94.3% and 95.1%, respectively. The rates of acute stroke and pericardial effusion were also lower in the CAP registry and PREVAIL, as shown in Table 1. Please comment on whether the new data presented in the CAP registry and PREVAIL trial address these concerns regarding acute WATCHMAN implantation procedural outcomes.</p> <p>The WATCHMAN device did not meet the non-inferiority criterion for the first primary endpoint (18-month rate of stroke, systemic embolism, and cardiovascular or unexplained death), as shown in Table 2. The individual components of the first primary endpoint composite are shown in Table 3. When interpreting the PREVAIL trial outcomes, the following issues should be considered:</p> <ul style="list-style-type: none"> • Deaths accounted for at least 50% of all events, which were likely unrelated to the procedure, the WATCHMAN device, or oral anticoagulation therapy. • The stroke (ischemic and hemorrhagic) rate in control subjects was lower than expected, with only one ischemic stroke and no hemorrhagic strokes in the control arm (Table 2). • The non-inferiority rate ratio criterion of <1.75 was set lower than the criterion used in PROTECT AF (<2.0), but is higher than that used in typical drug trials of anticoagulants used to prevent stroke and systemic embolism in subjects with nonvalvular atrial fibrillation. Please comment on the clinical significance of these results.
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Table 3. Comparison of questions posed to Watchman Left Atrial Appendage device AdComms before (April 2009) and after (December 2013) CDRH changed the AdComm voting procedures.
(Continued on next page)

April 23, 2009	December 11, 2013
<p>Voting questions</p> <p>The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (Act), as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory Panel on designated medical device premarket approval applications (PMAs) that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as reasonable assurance, based on valid scientific evidence that the probable benefits to health (under conditions on intended use) outweigh any probable risks. Effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use (when labeled) will provide clinically significant results. Your recommendation options for the vote are as follows:</p> <ol style="list-style-type: none"> 1. APPROVAL - If there are no conditions attached. 2. APPROVABLE with conditions - The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel. 3. NOT APPROVABLE - The Panel may recommend that the PMA is not approvable if: the data DO NOT provide a reasonable assurance that the device is safe, the data DO NOT provide a reasonable assurance that the device is effective, under the conditions of use prescribed, recommended, or suggested in the proposed labeling. Following the voting, the Chair will ask each Panel member to present a brief statement outlining the reasons for their vote. 	<p>Voting Question 1: Is there reasonable assurance that the Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy is safe for use in patients who meet the criteria specified in the proposed indication? Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy Panel Meeting Voting Questions Page 2 of 2</p> <p>Voting Question 2: Is there reasonable assurance that the Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy is effective for use in for patients who meet the criteria specified in the proposed indication?</p> <p>Voting Question 3: Do the benefits of the Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?</p>

Table 3 (continued). Comparison of questions posed to Watchman Left Atrial Appendage device AdComms before (April 2009) and after (December 2013) CDRH changed the AdComm voting procedures.

We note here also one other public statement suggesting a rationale for not obtaining a Panel's direct recommendation on approvability. At the Panel meeting to review the BLA of necitumumab in July 2015, the Oncologics Drugs AdComm (ODAC) was not asked to provide an approvability recommendation, nor was any vote taken at all. The Panel was instead prompted with two questions for discussion of necitumumab, both posed in "benefit-risk" terms. The FDA's Richard Pazdur said at the end of that meeting: "One of the reasons we did not have a vote—I keep on emphasizing we're more interested in your underlying reasons and the discussions here rather than a vote. The agency will make a determination on this application."²³

A potential rationale perhaps implied in Pazdur's statement is that a significant separation is now thought to exist between issues that AdComms can or should address and issues that the FDA should address. Given our findings in this study plus the context for quotation from Pazdur, perhaps the nature of the separation is that Panels are now believed to be capable of addressing safety and effectiveness, benefit and risk, etc., but not approvability, which is an issue for FDA to address. But is it plausible that Panel members cannot, given their knowledge, meaningfully address approvability?

Certainly, the members of a Panel have different competencies, training, and so forth, than do the FDA regulators—those differences are of course the reason for convening Panels in the first place. In some regards, the differences are relevant and important, but in other regards they may not be. For example, one area where the differences matter is terminology and language. Panel members will of course not be familiar with some of the jargon of regulatory decisionmaking. Panel members' lack of familiarity with regulatory terms of art is a good reason to ask straightforward questions using clear language.²⁴ A lack of familiarity with regulators' terminology, however, does not mean that the Panel cannot be asked to address substantive questions about regulation.

And it seems to us that approvability is a substantive question that Panel members are qualified to address, and even a question where their different competencies, training, etc., aid them in rendering good judgments. The essence of the approvability question is whether

23 Food and Drug Administration, "Oncologic Drugs Advisory Committee (ODAC): Thursday, July 9, 2015, 7:59 a.m. to 12:05 p.m.," <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM459508.pdf>, pages 184-185.

24 One of the authors (Gulfo) attended the AdComm meeting for bezlotoxumab on June 9, 2016. The sole voting question posed to the Panel was "Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of C. difficile infection recurrence in patients aged 18 years and older?" The Panel chair was among the minority voting No. He argued that while there is a "preponderance of evidence" that bezlotoxumab is safe and effective, he did not feel there is "substantial evidence," which would be especially important to have for a first-in-class product. But it seems to us that the Panel chair was confused by the term "substantial evidence" in the question posed by the FDA. *Substantial evidence* is a term of art in the statute that means that the clinical evidence supporting approval consists of results from "adequate and well-controlled investigations." Substantial evidence does *not* apply to the results, rather the robustness and execution of the studies used to generate the data—without doubt, the Merck studies were robust and well-conducted. The "preponderance" of the data to which the chair refers has to do with the clinical results. "Substantial evidence" used by FDA in the question has to do with the kind of studies and how they were conducted, not the results, themselves. So, the chair conflated the two and was confused by the question. The chair applied a trial law standard to the "evidence," as if a preponderance of evidence were to mean at least fifty-one percent of the facts weigh in a certain direction and substantial evidence means that at least ninety percent (for example) weighs in that direction. Neither apply when it comes to AdComm meetings.

a drug should be available to physicians for prescribing to patients. AdComm members are predominantly physicians, and often a Panel will be almost entirely comprised of physicians. A great deal of the value in the perspectives that physicians provide—indeed, of the value of the AdComms themselves—relates directly to their understanding and real-world application of standards—“safe and effective,” “benefit-risk,” and so forth—that the FDA purports to use. If the physicians on a Panel think that a particular drug which meets such standards *should not* be available, or that a particular drug which does not meet such standards *should* be available, that absolutely is knowledge that the FDA should possess and consider.²⁵

The current structure of the AdComm process may inadvertently generate feelings that Panels are being led toward a conclusion preferred by the FDA. In particular, the great extent to which FDA has been afforded discretion over many facets of the process creates myriad opportunities for skepticism to fester, as often the FDA may hardly be able to avoid biasing the process in one direction or the other. Consider:

1. The FDA decides whether to convene AdComms. This is the case even for novel products. For example, palbociclib, the very first Cyclin D-CDK4/6 inhibitor, was approved without an AdComm. The target is the central molecule contained in all cells, which coordinates signals from the external environment and governs the decision whether a cell will divide. Yet, no AdComm was held for its review.
2. The FDA determines Panel composition—standing members, selection of the chair, temporary members, and voting members—and it takes no input from industry, which is powerless to object to Panel member participation. There is likely strong inclination among Panel members to identify and adopt the FDA’s preferences—Panel members enjoy the prestige and optics of AdComm participation, so it can be in their interest to fall in line with the FDA, especially on gray areas. Also, Panel members naturally view information provided by the FDA as impartial, so it is weighted to a much greater extent than information provided by sponsors.
3. The FDA drafts discussion questions that guide Panel deliberations, with no input from industry.
4. The FDA decides which information is shared with the Panel prior to the meeting, often preventing sponsors from amending Panel packages. The pre-meeting briefing documents often may seem to communicate a direction that the FDA is leaning, which can influence the Panel to a great extent.
5. The FDA also decides whether alternative claims can be presented to the AdComms.

²⁵ The FDA did not obtain a direct recommendation on approvability from the Panel convened on April 25, 2016 to consider the drug eteplirsen. Several months later the FDA approved the drug, in a decision that was controversial largely because it seemed to contravene negative votes by the Panel. But there is reason to believe the Panel may have voted in favor of approving eteplirsen, had it only been asked that question directly, and that result would have saved the FDA from much criticism (see Appendix for details).

6. USC Title 21 360c(b)6(A) states that the sponsor is to have the same access to data and information submitted to the Panel, yet this is not practiced—the FDA as a matter of course interacts with Panel members without sponsor participation.
7. USC Title 21 360c(b)6(C) states that Panel meetings “shall provide adequate time for initial presentations and for response to any differing views...and shall encourage free and open participation by all interested persons.” However, in practice, this is grossly distorted—sponsors are not afforded sufficient opportunity to rebut statements made by the FDA to the Panel, or to counter positions that the FDA advances as embodied in the discussion and voting questions that are posed to the Panel.²⁶

One way to summarize the main points in the preceding list is to draw an analogy between an AdComm meeting and the proceedings in a criminal court. In AdComms as they are presently conducted, following this analogy, the Panel is the jury and the sponsoring firm is the defense, but the FDA is both judge and prosecution. Panel members—jurors—are selected by the FDA, as is the Panel chair, and the FDA can also invite temporary and non-voting Panel members; there is no equivalent of a voir dire process by which the sponsor could object and disqualify Panel members. The FDA also formulates the discussion items and voting questions submitted to the Panel—these comprising the ‘case’ or the ‘charges.’ Like competing attorneys, the sponsor and the FDA—in its ‘prosecution’ role—are supposed to have equal access to the Panel. In its ‘judge’ role, the FDA is not supposed to influence the Panel or make known any desired outcome of the AdComm meetings.

The analogy is valuable particularly in understanding that, in important respects, AdComms cannot be made procedurally ‘fair’ to sponsors and to products, at least not to the same extent that a criminal trial is procedurally fair to defendants. The central difference is that it is almost certainly not feasible to create a functional separation within the FDA between a ‘district attorney’s office’ and a ‘judiciary,’ because both would need a high level of case-specific knowledge for each Panel. As a result, the Panel process unavoidably leans to a significant extent against the sponsor and product: It is as if the prosecution and judge in a trial had common organizational attitudes and presumptions plus a tendency to view the case similarly. That shared foundation means that the FDA-presented critique of a drug will tend to align and interact naturally with all aspects of the Panel process, whereas the sponsor’s presentations will tend to be marked by more awkwardness and conflict. In instances where the FDA is entirely neutral with regard to the merits of a drug or device, then, a sponsor likely will face a somewhat uphill battle at a Panel meeting.

26 For example, at the MelaFind AdComm meeting in November 2010, the FDA presentation contained thirteen statements about melanoma that were medically wrong, in addition to many other misstatements pertaining to the studies, regulatory history, results, and analyses. However, the sponsor presentations had concluded, so, there was no way to rebut these falsehoods except at the final ten-minute summation, which takes place at the conclusion of the AdComm meeting. I requested additional time, to which the Panel chair responded, “The Sponsor will have a summation, comments and clarifications at this time. We understand that the Sponsor has asked for additional time and I’d like to read into the record now that we’re going to give an additional 5 minutes, so a total of 15 minutes for summation. That’s going to be a hard endpoint.” I was forced to select the mistruths that we thought were most damaging, as well as present a summation of the PMA and Panel proceedings (Joseph V. Gulfo, *Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances*, 2014, Post Hill Press, pp. 129-136). This is hardly consistent with the regulations, which allow for “adequate time” and encourage free and open participation.

It is worth recalling that the law authorizing FDA regulation in general has a default position in favor of *approval* of new drugs. The law is premised on an assumption that the development process is a harsh critic and that by the time an NDA (or BLA, or PMA) is filed, it is more than likely approvable. The FDA is thus not required to delineate reasons to approve new products, which would be the case if the presumption was that the drugs submitted for NDA approval were toxic snake oil. No, just the opposite: The FDA is charged with delineating its rationale for *not* approving NDAs and BLAs:

*If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; *he shall issue an order refusing to approve the application*. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application.²⁷*

AdComm meetings are critical hearings, coming at the end of the lengthy, difficult, and expensive processes by which drugs and medical devices are developed. During these sessions, all the data available after years and years of testing are summarized and debated. The new products are thoroughly reviewed—the safety and effectiveness data and all shortcomings of the development process. After all is said and done, after the good, the bad, and the ugly has been aired and debated for hours, it is most appropriate to have a final straightforward vote on whether clinicians on the Panel want to use the drug, that is, recommend its approval. That is precisely what the law governing Panels intends.

²⁷ 21 USC 355(d); our emphases.

Uncertainty is the most powerful deterrent with respect to investment in life sciences companies. Since real medical innovation occurs mostly in small companies that are dependent on financing from private and public markets, uncertainty stifles innovation. Rules and standard procedures help investors and drug developers understand and navigate unknown terrain. Consistent enforcement of the rules “de-risks” the process. There are many unknowns in the costly, arduous, and time-consuming drug development process; one of them should not be how the FDA will run the company’s AdComm meeting.

It is certainly necessary, often, for the FDA to have latitude to exercise discretion at different points in the drug development and review process, and, accordingly, FDA is accorded great discretion in many matters.²⁸ But we do not believe that whether approvability questions are posed at AdComms, or the manner in which they are asked, should be matters that are subject to agency discretion. Importantly, the law does not require the FDA to follow Panel recommendations; therefore, conducting approvability voting in a direct and unambiguous manner does not pose a risk of undermining FDA’s authority. Removing FDA discretion over approvability voting should have healthy outcomes: It will help ensure that Panels are what they purport to be, which is a means of securing genuinely needed external recommendations, and thus it should heighten respect for FDA and its processes.

RECOMMENDATIONS

FDA law calls for AdComms that are convened to review product approval applications—NDAs, BLAs, PMAs, and 510(k)s—to provide recommendations with respect to approvability. Only one FDA division, Cardiovascular and Renal Drugs, has abided by the letter and spirit of the law, obtaining AdComm recommendation via succinct, unambiguous, direct, and unencumbered questions. In order to comply with the letter and spirit of the law, it is critical that all FDA review divisions institute a policy of obtaining Advisory Committee recommendations regarding the approvability of new drugs, biologics, and devices. In order to achieve this, we propose that the following practices be implemented:

1. Panel discussion questions must be reviewed with the sponsor in advance of the Panel meeting. After reviewing the proposed discussion questions, the sponsor must be afforded the opportunity to amend pre-Panel meeting documents that are distributed to the AdComm members by the FDA in advance of the meeting.

²⁸ The great extent to which FDA is empowered to exercise discretion is a recurring theme in Daniel Carpenter’s influential study *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton University Press, 2010). An example of a matter over which it is often important for FDA to have discretion is with regard to timing and deadlines (see Daniel Carpenter, Jacqueline Chattopadhyay, Susan Moffitt, and Clayton Nall, “The Complications of Controlling Agency Time Discretion: FDA Review Deadlines and Postmarket Drug Safety,” *American Journal of Political Science* 56(1): 98–114). Frances Kelsey, for instance, was able repeatedly to extend the time available for FDA review of thalidomide by declaring the sponsor’s applications to be incomplete (Rock Brynner and Trent Stephens, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine*, Cambridge, Mass.: Perseus Publishing, 2001, pp. 48–55).

2. FDA should make some allowance for sponsors to 'challenge' the selection of AdComm members, i.e., institute some process that serves a function similar to jury selection in courtroom trials.
3. Prior to the vote on approvability, sponsors must be afforded sufficient time (one hour) to refute and clarify points that have been raised by the Panel in response to FDA discussion questions that are debated after the company's initial presentation.
4. Approvability voting questions will be limited to the approvability of specific claims:
 - a. the indication being sought by the sponsor and supported by inclusion criteria in trials from which clinical data reviewed by the Panel are derived, and/or
 - b. limited claim(s) based on the data (safety and effectiveness) from the clinical trials reviewed at the AdComm meeting, and/or
 - c. claims for narrow groups of best responders (post hoc) that are deemed appropriate by the Panel based on the data reviewed during the AdComm.

The question(s) must be succinct, with no qualifiers, and structured in the following manner: "Do you recommend approval (or accelerated approval) of _____ for the treatment of patients with _____."

5. The approvability voting question may be followed with questions regarding AdComm recommendations for labeling in order best to ensure safe use.
6. The AdComm will also be asked to vote on whether post-approval studies are recommended, as well as the nature of the post-approval studies:
 - a. Observational study or studies, only
 - b. Randomized, blinded—specific hypotheses and endpoints (If the study is negative, whether the initial claim should be withdrawn)
 - c. Registry study

APPENDIX: ADDITIONAL FINDINGS ON DIVISIONS THAT RARELY OBTAIN APPROVABILITY RECOMMENDATIONS

It was surprising to us that Antimicrobial and Oncology Drugs divisions seldom obtain Panel recommendations regarding approvability, yet these disciplines deal with some of the most vexing medical problems, including the emergence of antibiotic-resistant organisms and the inexorable progression of cancer. We would have expected that these divisions, more than others, would want to know from clinical experts on the front lines of patient care whether they, indeed, would want to use the new products under review. To learn more, we reviewed additional AdComm meetings, from before January 1, 2011, conducted by the Antimicrobial Drugs and Oncologics divisions, as well as the Peripheral and Central Nervous System division.

Antimicrobial Drugs division

We looked back through 1998 to determine whether the Antimicrobial division ever solicited approvability recommendations from its AdComms. During the period January 1998 thru August 2016, we found only three Panel meetings at which a direct or indirect question regarding product approvability was asked. Two had direct questions posed to the Panel: (1) Synercid in February 1998 ("Does the committee, all things considered, recommend approval of Synercid for the indication of skin and skin structure infections?"); and (2) Artesunate in 2010 ("Given the overall benefits and risks, do you recommend approval of single dose artesunate rectal suppository?"). The third instance, an indirect approvability question, was for Artesunate in 2002 ("Is the safety information and safety profile of artesunate sufficient to support the approval of artesunate for use as initial therapy in patients without other therapeutic alternatives"). We were surprised to observe different questions for the same product; we were also surprised that the development sponsor of the Artesunate NDA was the World Health Organization. Therefore, at only one Panel meeting for a corporate-sponsored product between 1998 and August 2016 did the division solicit an approvability recommendation.

An example of the current model used by the Antimicrobial division is the isavuconazole Panel meeting (January 22, 2015) for the treatment of invasive aspergillosis: "Has the applicant demonstrated substantial evidence of the safety and efficacy of [name of drug] for [indication]?" The AdComm's recommendation regarding the drug's approvability is not solicited in the question, either directly or indirectly.

Case in point: bezlotoxumab

Two of the authors (Gamie and Gulfo) attended the Bezlotoxumab AdComm meeting on June 9, 2016.²⁹ The antibody is intended to reduce the re-infection rate of patients suffering from *C. difficile* enteritis; it acts by binding to and neutralizing *C. difficile* toxin B. The

29 Minutes for this meeting are available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM510472.pdf>.

antibody is administered while patients are receiving antibiotic therapy to eradicate the *C. difficile* infection, however, it is intended to reduce the recurrence rate in those who achieve clinical cure on antibiotics. Merck presented data on two phase 3 randomized trials, MODIFY I (1452 patients; 403 received bezlotoxumab) and MODIFY II (1203 patients; 407 received bezlotoxumab). The primary efficacy endpoint of both studies was *C. difficile* infection recurrence (CDIR), and both studies were positive. The combined analysis revealed that treatment with bezlotoxumab resulted in a 37% reduction in CDIR; patients treated with placebo had a CDIR rate of 27% compared with 17% for patients receiving bezlotoxumab ($p < 0.0001$). In the more clinically appropriate subset, CDIR dropped from 33% to 21% ($p < 0.0001$), a 36% reduction. And the drug did not have a negative impact on clinical cure rates. Although not prospective endpoints in the study, bezlotoxumab resulted in 2-day reduction in length of in-hospital stay and a 5.7% reduction in readmission rate. Looking at safety, 61% of patients on placebo (781 total patients) and 62% of patients receiving bezlotoxumab (786 total patients) experienced at least one adverse event. More patients treated with bezlotoxumab experienced cardiac adverse events, suggesting that bezlotoxumab should be used with caution in patients with underlying cardiac problems.

The FDA expressed its displeasure with Merck (in the pre-meeting documents distributed to the Panel and during the FDA presentation) because the company insisted on utilizing the recurrence rate as the primary endpoint before initiating trials, not Global Cure, which the FDA wanted. Merck did this because their drug does not modulate active infection; rather, it prevents recurrence, and therefore Global Cure is not the appropriate way to measure its effectiveness.

One voting question was posed to the AdComm:

Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence in patients aged 18 years and older?

- a. If yes, please discuss your rationale and provide any recommendations concerning labeling.
- b. If no, please discuss your rationale and what additional studies/analyses are needed.

The Panel voted ten in favor and five opposed, with one abstention.

Of particular interest to us are comments from the Panel chair, who voted in opposition. He made three points: (1) a total of 800 patients treated with the drug was not sufficient because *C. difficile* is not an orphan disease, rather it affects 500,000 patients per year;³⁰ (2) although there is a “preponderance of evidence” that bezlotoxumab is safe and effective, he did not feel there is “substantial evidence,” which would be especially important to have for a

³⁰ As defined by the FDA, orphan diseases affect 200,000 patients or less. Drug studies for the approval of orphan claims typically include 50 to 100 patients. So, eight hundred patients that received bezlotoxumab, the experimental drug, seems to us a large and appropriate number, especially considering that the placebo comparator arm was just as large.

first-in-class product; and (3) the two studies that Merck performed are best considered Phase 2b studies, and phase 3 studies using a different endpoint should be conducted. The first and third point are not the kinds of comments that clinical experts generally offer at Panel meetings, because these comments speak to regulatory, not clinical, issues. These points to us raise the concern that the FDA made its wishes clear to the Panel chair. The second point, meanwhile, seems to demonstrate that the chair was confused by the term “substantial evidence” in the question posed by the FDA.³¹ At least as, if not more, disturbing is that another Panel member stated that he trained under the Panel chair, therefore, not surprisingly, he feels the same as the chair.

The *data* are the reason AdComms are convened—to ask members whether, based on the data that have been generated, approval is recommended. Interestingly, the chair did say that he wants to use the drug: “I think there is a preponderance of evidence, but the issue of substantial evidence, to me, is a very high bar for a first-in-class, novel therapy for which we have no experience and which we have a lot of hope, and desire, and need, *and I want my patients to have this...*” If the Antimicrobial division used the paradigm that it applied for Artesunate in 2002 or 2010, it seems obvious that the vote would have been resoundingly in favor of the drug. Ideally, all divisions should use the succinct and direct paradigm, in accordance with the regulations, employed by the Cardiovascular division (for example, “Do you recommend the approval of bezlotoxumab for reducing *C. difficile* recurrence”), which obviates any possibility of confusion.

Oncologics Drugs division

The Oncologics Drugs AdComm (ODAC) was asked to provide product approvability recommendations at just four of the twenty-five Panel meetings that were conducted in the 2011–2016 period. The Oncologics Drugs division asked no voting questions, for example, at the ODAC to review the BLA of necitumumab in July 2015. As reported in the media, “ODAC was not asked to cast an official vote in favor or against the application for the EGFR antibody; instead, [Richard] Pazdur, director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research, sought the insight and thoughts on the application through discussion of the clinical trial results.”³² Two discussion questions were asked:

1. Please discuss whether the INSPIRE trial results in the non-squamous NSCLC population impact the benefit-risk assessment of necitumumab for squamous NSCLC.
2. Please discuss whether the efficacy and safety results of SQUIRE in squamous cell NSCLC support a positive benefit-risk assessment of necitumumab in combination with gemcitabine/cisplatin in the proposed population.

31 See on this *supra* note 24.

32 Silas Inman, “ODAC Supports Necitumumab for Squamous NSCLC,” OncLive.com, July 9, 2015, <http://www.onclive.com/web-exclusives/odac-panel-supports-necitumumab-for-squamous-nsclc>.

The regulations are clear: The FDA can solicit the Panel's insights, but it must also obtain its approvability recommendations. But, at the end of the meeting, Pazdur asserted strongly that FDA will make decisions, and that he was not interested in Panel votes.³³ The notion that not securing the Panel's approvability recommendation somehow affords the FDA a greater opportunity to obtain their medical and scientific insights is preposterous.

Eltrombopag provides an example of the Panel's approvability recommendation not being solicited in a voting question: "Do the current clinical data demonstrate a favorable benefit-risk profile for the use of eltrombopag in the 'short term' treatment of patients with chronic ITP?"³⁴ A favorable benefit-risk profile does not mean that the Panel recommends approval any more than a negative benefit-risk profile necessarily means that the Panel would not recommend approval, at least in some types of patients. In order to obtain clear feedback and to comply with FDA regulations, the question should be worded in this manner: "Do you recommend approval of eltrombopag in the 'short term' treatment of patients with chronic ITP?"

The Oncologic Drugs division certainly knows how obtain the unequivocal view of ODAC. It did so in the case of satraplatin, in July 2007, where the division also seemingly led the Panel to the conclusion it wanted to obtain: "Should the FDA wait for the final survival analysis of the SPARC trial before deciding whether this application is approvable?" ODAC voted twelve to zero in favor of waiting for the final survival analysis.³⁵

There seemed to be little consistency in the manner in which questions were asked of the ODAC. Consider the voting questions for three drugs (brentuximab, laromustine, and rociletinib) that were being considered for accelerated approval, that is, approval based on Phase 2 surrogate endpoint data with a subsequent requirement for Phase 3 confirmatory trials. If data from nonrandomized Phase 2 trials are not compelling enough, then sponsors must complete Phase 3 randomized trials for approval.

Brentuximab.³⁶

Should the FDA grant accelerated, regular, or non-approval for Brentuximab vedotin for the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant? [Vote: ten to zero for accelerated approval; July 2011]

33 See page 15 above. As part of the Cancer Moonshot Program, Pazdur has been put in charge of the new Oncology Center of Excellence, meaning that all oncologics products that come before the FDA—drugs, biologics, devices, and diagnostics—are now under his purview.

34 <https://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4366m1-Final.pdf>

35 <https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4309m1-Final.pdf>

36 <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM268123.pdf>

Laromustine:³⁷

Should a randomized study defining the efficacy and safety of laromustine in the population proposed for the indication be completed prior to approval of laromustine? [Vote: thirteen to zero for requiring a randomized study; September 2009]

Rociletinib:³⁸

Should the results of the randomized clinical trial (TIGER-3) be submitted before FDA makes a regulatory decision on this application? [Vote: twelve to one for requiring results of the randomized study; April 2016]

Why were straightforward votes on approvability of laromustine and rociletinib not obtained, consistent with the model of brentuximab? It is plausible that the FDA wanted the additional studies for those two drugs (but was positively inclined toward brentuximab), and therefore the ODAC was given no opportunity to affirm their approvability.

Another example of a leading voting question was seen with Pixantrone dimaleate. The Panel was asked: “Is this single incomplete trial adequate to support approval?” The study in question had been debated throughout the entire ODAC session up to the time of voting. Why did the FDA include “single incomplete” in the question? Did they feel the ODAC would not remember what had been said about the product over the preceding several hours? Did they forget the language of the guidance document: “The question presented for a vote should have minimal qualifiers, not be leading, and...?” The Panel voted No on this question, nine to zero.³⁹

Peripheral and Central Nervous System division

The Peripheral and Central Nervous System Drugs AdComm was asked to provide product approvability recommendations at just three of ten Panel meetings that were conducted during the 2011–2016 period, and at all three, indirect approvability questions were asked. Two of the three were seen in 2011, Amyvid (florbetapir F18) and Gadavist (gadobutrol), and the third in 2013, that being Lemtrada (alemtuzumab). However, the Panel meeting in 2013 was for a Supplemental BLA application, that is, an additional claim for a drug that

37 <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM183036.pdf>

38 <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM510286.pdf>

39 <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM207638.pdf>

was already on the market.⁴⁰ The last time the Peripheral and Central Nervous System division asked a direct question regarding approvability recommendation was for Sabril (January 2009).

Case in point: eteplirsen

At the eteplirsen AdComm meeting on April 25, 2016,⁴¹ Panel members were clearly confused by the wording of the questions posed by the FDA, which were leading, to say the least.

Two examples:

2. Has the Applicant provided substantial evidence from adequate and well controlled studies that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit?
7. Do the clinical results of the single historically-controlled study (Study 201/202) provide substantial evidence (i.e., evidence from adequate and well-controlled studies or evidence from a single highly persuasive adequate and well-controlled study that is accompanied by independent findings that substantiate efficacy) that eteplirsen is effective for the treatment of DMD?

A majority of the Panel voted against the drug on each of these questions: Seven “No” to six “Yes” votes on Question 2, and seven “No” to three “Yes” votes on Question 7. Panelists voting “No” on Question 2 cited a lack of substantial evidence of effect on the key surrogate marker, dystrophin, which patients with Duchenne Muscular Dystrophy (DMD) completely lack due to one of several mutations. The drug is intended to treat patients with the exon 51-skipping variant of DMD, representing about 13% of patients with a DMD diagnosis.

The incidence of DMD is just one in forty-five thousand patients per year in the US. It is, however, the most common and debilitating form of disease arising from mutations to the large DMD gene, located on the X chromosome. It is caused by inactivation of the gene product, dystrophin, and afflicts boys almost exclusively; there is no cure. Affected individuals are typically non-ambulatory by the age of twelve. Contractures develop as the disease

40 We are aware of one instance that is suggestive of differing approaches to AdComms held for supplemental applications and those held for new-drug applications. On April 26, 2012, the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) met to discuss two products for the treatment of retinopathy: ranibizumab (Lucentis) during the morning session and ocriplasmin (Jetrea) during the afternoon session (see <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM320122.pdf>). The voting questions to the DODAC for ranibizumab were quite appropriate—direct and specifically soliciting the Panel’s approvability recommendations. However, the voting questions to the DODAC for ocriplasmin did not obtain the Panel’s approvability recommendations. Perhaps the reason DODAC was asked two different types of questions on the same day is that it was considering a Supplemental BLA application for ranizumab and a new BLA application for ocriplasmin. The law, however, does not distinguish between supplemental and new-product applications with respect to the requirement to obtain AdComm recommendations regarding approvability.

41 The meeting transcript is available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM510390.pdf>.

progresses, and in the absence of optimal care, including corticosteroid treatment, physical therapy, and nocturnal assisted ventilation, most patients succumb to the disease by the age of 20 years as the result of respiratory and/or cardiac complications.

Data were presented on 12 patients who took eteplirsen for four years; their results were compared to matched control patients from Italy and Belgium. A randomized study was not possible to conduct due to ethical constraints: Administering placebo to patients while requiring multiple muscle biopsies over an extended period offers no possible benefit.

Results of a six-minute walk test indicated that boys taking eteplirsen walked 162 meters further than the control group, and ten of the 12 boys on the drug were still able to walk after four years, versus only three of 13 in the control group. FDA commented: "Know that if these results were from a well-designed and interpretable trial, there likely wouldn't be much to talk about." In other words, the data were quite compelling, but from the wrong kind of study, in FDA's view.

The data were indeed compelling to Jerry Mendell, director of the center for gene therapy at Nationwide Children's Hospital in Columbus and lead investigator in Sarepta's study. "Fifteen-year-old boys like Billy don't maintain ambulation by accident" Dr. Mendell told the AdComm, after showing a video of one 15-year-old on the drug. AdComm member Aaron S. Kesselheim, associate professor at Harvard Medical School in Boston, said "The studies provided by [Sarepta] were not adequate and well controlled." But he acknowledged that it remains an "open question" whether eteplirsen produces a clinical benefit to patients who take it. Bruce I. Ovbiagele, chairman of neurology at the Medical University of South Carolina, voted against approval but said: "Based on all I heard, the drug definitely works, but the question was framed differently."

Panelists were instructed to consider only data from well-controlled studies, which flies in the face of FDA's initiative to capture the voice of the patient in decisionmaking.⁴² "Well-controlled" implies randomized, multi-arm studies. But, randomized multi-arm studies are not the only trials that are considered capable of providing substantial evidence; historically-controlled trials are adequate according to the law.⁴³ Further, competing standards were given to the Panel: One calls for a safety determination first followed by an effectiveness determination, while the other calls for the effectiveness determination first followed by safety. This is important for eteplirsen, which is very safe, but the effectiveness data from controlled clinical trials are not considered definitive by many. According to the first standard, as long as the drug is proven to be safe, any clinical benefit is meaningful and should result in approval.

There seems to us little doubt that had the FDA posed direct approvability questions to the Panel, akin to the manner in which the Cardiovascular division asks questions—for example,

⁴² Family members shared anecdotes demonstrating obvious positive clinical effects of eteplirsen. As one Panel member remarked, "Unfortunately, what I would consider meaningful evidence from the testimony of the families is not properly measured in the study."

⁴³ See 21 CFR 314.126.

"Do you recommend the approval of eteplirsen for the treatment of patients with exon 51-skipping variant of the Duchenne Muscular Dystrophy (DMD)?"—the vote would have been very positive and the drug would have been approved (and helping many patients with this universally fatal and debilitating condition) much sooner.

Further, if the FDA were to have solicited approval recommendations from the Panel, they would have avoided the furor that ensued following their decision to approve the drug on September 19, 2016,⁴⁴ effectively going against the Panel votes taken on confusing questions. Many have criticized the FDA for the decision, lamenting that this signals a lowering of approval standards, which prompted a "civil war" within the agency.⁴⁵ Adding fuel to the fire is that the week before the approval, Ronald Farkas, the team leader of the review of the eteplirsen NDA (and a vocal detractor of eteplirsen), left the agency.⁴⁶ It was Janet Woodcock, the Director of the CDER, who overruled staff and approved eteplirsen on an accelerated basis, and who was subsequently harshly criticized for the decision.⁴⁷

The seeds for the furor that erupted in the wake of FDA's decision were certainly sown at AdComm meeting. Simply put, because the FDA asked the AdComm confusing questions, FDA was later put on the defensive in explaining its rationale for the approval. The Panel had obvious difficulty in interpreting Question 2. Woodcock attempted to clarify the question by stating:

Yes. This is the standard for accelerated approval. So this would be a vote on whether or not that surrogate endpoint of dystrophin is reasonably likely to predict clinical benefit. *So this is a question about approvability*, and my point is that you have to factor in the clinical data in this discussion, what weight you think it gives to the reasonably likely decision. So you're talking about, first, whether question 1A, which you already discussed, whether or not dystrophin was increased. Now, reasonably likely, as you've already discussed and I've mentioned in my opening remarks, there is no standard established. And for this condition, there is no threshold established because there's never been a drug to do this. So people don't know. They've looked at natural experiments such as Becker's, and you see that there is a range of response as was said earlier. So the question that you're being posed, if you follow me, is does the clinical experience in these trials, with these patients, lead you to believe, if you believe dystrophin was increased, that that increase is reasonably likely to predict a clinical benefit? Do you follow me? Okay.

⁴⁴ Food and Drug Administration, "FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy," September 19, 2016, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm>.

⁴⁵ Matthew Herper, "Approving a Muscular Dystrophy Drug Ignites a Civil War at the FDA," *Forbes.com*, September 20, 2016, <https://www.forbes.com/sites/matthewherper/2016/09/20/approving-a-muscular-dystrophy-drug-ignites-civil-war-at-the-fda/>.

⁴⁶ John Carroll, "The FDA Confirms That Sarepta Nemesis Ronald Farkas Has Left the Agency," *Endpoints News*, September 14, 2016, <https://endpts.com/the-fda-confirms-that-sarepta-nemesis-ronald-farkas-has-left-the-agency/>.

⁴⁷ Sheila Kaplan, "'Tough as Nails': Storm Swirls Around FDA Drug Cop Who Approved Controversial Drug," *STAT*, September 20, 2016, <https://www.statnews.com/2016/09/20/janet-woodcock-sarepta-fda/>.

Interestingly, she said that Question 2 is about approvability. If so, why did the question not contain explicit wording regarding the approval recommendation? Judging from Ovbiagele's comments ("Based on all I heard, the drug definitely works, but the question was framed differently"), the Panel did not consider this question to be about approval. In two letters to the FDA dated May 20, 2016⁴⁸ and September 16, 2016,⁴⁹ the US Senate Committee on Homeland Security and Governmental Affairs raised concern about the awkward and confusing manner in which the FDA posed questions to the Panel and how that affected the final vote.

48 <http://www.hsgac.senate.gov/download/senators-johnson-and-coats-letter-to-fda-commissioner-califf>
49 <https://www.hsgac.senate.gov/download/johnson-alexander-letter-to-fda>