FDA
ADVISORY COMMITTEES

Does Approval Mean Safety?

National Research Center for Women & Families

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Does Approval Mean Safety?

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National Research Center for Women & Families

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EXECUTIVE SUMMARY

FDA Advisory Committees: Does Approval Mean Safety?

The U.S. Food and Drug Administration (FDA) has the responsibility to determine if newly developed medical products are safe and effective. Whether it is a prescription medication, a medication sold over the counter, a medical device, a vaccine, or another type of biologic, the product can be marketed for general sale in the United States only if it has FDA approval.

FDA advisory committees are the most visible part of the FDA approval process. They meet in public to review the most controversial and cutting-edge medical products, examining applications for FDA approval. Committee members discuss the strengths and weaknesses of the studies and their enthusiasm or concerns about the medical product under review. At recent FDA advisory committee meetings on controversial drugs and medical devices such as Vioxx®, silicone implants, and antidepressants, the media have provided the Congress and the general public with a glimpse of the approval process.

Questions have arisen about committee members' financial ties to the companies submitting applications, their commitment to scientific scrutiny, the independence and objectivity of the deliberative process, and inconsistencies between the panel members' expressed concerns and their approval recommendations.

This report describes the results of a study conducted by the National Research Center (NRC) for Women & Families, providing the first objective analysis of the key role of FDA advisory committees as part of the FDA approval process. The purpose of this report is to better understand the strengths and weaknesses of the FDA's advisory committee process for FDA's two largest centers, the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH).

The study analyzes the voting patterns and committee discussions of a random sample of 6 of 16 drug advisory committees and 5 of 18 medical device advisory panels:

Drug Committees
Antiviral Drugs
Arthritis Drugs
Dermatologic and Ophthalmic Drugs
Gastrointestinal Drugs
Pulmonary and Allergy Drugs
Reproductive Health Drugs

Medical Device Panels
Immunology Devices
Microbiology Devices
Obstetrics and Gynecology Devices
Ophthalmic Devices
Radiological Devices

Data for these advisory committees were collected from the FDA Web site, based on transcripts of advisory committee meetings from January 1998 through December 2005. In that time, the 11 randomly selected advisory committees considered 89 prescription drugs and medical devices, including arthritis medications, LASIK devices, erectile dysfunction drugs, and devices to improve the accuracy of mammograms. There were 866 committee member votes.

Findings

As described by FDA officials, its advisory committees meet only to discuss the most controversial or innovative products, or products whose data are not clear-cut. The public might expect, therefore, that many of the drugs and devices reviewed by advisory committees would not be recommended for approval. he data indicate that this is true for some advisory committees, but not others. Overall, the 11 randomly selected advisory committees recommended approval for 79% of the 89 products reviewed between 1998 and 2005. The device advisory panels were even more likely to vote for approval than the drug advisory committees, recommending approval 82% of the time compared to 76% for drugs.

Despite the controversies surrounding many of these products, the votes for or against approval were rarely close. On the contrary, committee members agreed unanimously for 66% of the drugs and 75% of the medical devices that they recommended for approval.

Drug and Device Approval Recommendations

A review of the meeting transcripts indicates that advisory committee members frequently expressed strong concerns about the safety or the efficacy of the drug or device under review. However, those concerns were not necessarily reflected in their recommendations for approval. There were many examples of committee members who strongly criticized the studies or the medical products under review, and then recommended approval anyway. FDA officials at the meetings almost never expressed concerns about the disconnect between the committee members' explicitly expressed doubts about safety and effectiveness and their votes in favor of approval.

Of the 50 drug committee voting sessions in the study, 38 (76%) recommended approval of the drug. Most of the votes were unanimous, and almost all (93%) of those unanimous votes recommended approval.

Some of the committees were much more likely to recommend approval than others. The percentage of drugs they recommended for approval ranged from 50% for reproductive health drugs to 100% for arthritis drugs. The percentage of individual votes cast to recommend approval ranged from 50% for reproductive drugs to 98% for arthritis drugs.

What happens after the meetings are over? Of the 38 drugs recommended for approval by the drug advisory committees, all were subsequently approved by the FDA except one drug whose application was withdrawn before FDA made its decision. The FDA also approved four (36%) of the 11 drugs that the drug advisory committees voted against, including products that were opposed by almost all the committee members.

Of the 39 device panel voting sessions studied, 32 (82%) recommended approval of the device. Most of the votes were unanimous, with almost all (92%) of those unanimous votes recommending approval.

The percentage of devices that were recommended for approval ranged from 67% for microbiology devices to 88% for ophthalmic devices. The number of panel member votes cast to recommend approval ranged from 57% for microbiology devices to 91% for radiological devices. Three of the five randomly selected devices panels—the Radiological Devices Panel, the Immunology Devices Panel, and the Microbiology Devices Panel—had unanimous support for approval whenever they recommended approval during the eight years of the study.

Almost all (94%) the devices recommended for approval were subsequently approved by the FDA, and close to half (43%) of the devices that were not recommended for approval obtained FDA approval anyway.

Overall, the study found:

- Many advisory committees recommend approval for almost every product they review, usually unanimously;
- Individual committee members can have a disproportionate influence on approval recommendations;
- Voting patterns differ for drugs and devices, but not when we compare committee members with clinical, scientific, and consumer perspectives;
- Committee members describe pressure to conform and to recommend approval, and they candidly admit that their votes for approval may not be consistent with their concerns about safety and effectiveness;
- FDA officials passively acquiesce when they do not respond to committee members' statements indicating that votes recommending approval are not necessarily based on scientific evidence of safety and effectiveness; and
- The FDA almost always approves products recommended for approval but also often approves products that advisory committees reject.

Implications and Conclusions

The findings suggest that when the FDA schedules meetings for several of its advisory committees, the outcome is almost certainly going to be FDA approval for the products under review. In most cases the advisory committee will recommend approval, but even products that are not recommended for approval are frequently approved by the FDA. Even lopsided votes against approval apparently do not have much weight, since the FDA subsequently approved many of those products.

Although FDA officials describe the advisory committees as providing diverse perspectives and expertise, the large number of unanimous or nearly unanimous votes suggests that either the data are exceptionally convincing or that the committee members are reluctant to disagree with their colleagues or believe that the FDA wants the advisory committee members to come to consensus.

By combining information from the NRC study with studies of conflicts of interest on FDA advisory committees, it is possible to understand how a few committee members with conflicts of interest can have a disproportionate impact on approval recommendations. NRC's analysis of meeting transcripts indicates that many committee members' votes seem inconsistent with their concerns about the safety or efficacy of the drug or medical device under review. These transcripts clearly illustrate the pressures that committee members describe to conform to their colleagues or to be able to vote 'yes' even if it means changing the wording of the question so that they can do so in good conscience. The report includes examples of committee members directly trying to influence the views or votes of other committee members.

If the FDA is relying on advisory committees to help determine the conditions of approval, one would expect that FDA officials would provide explicit oral instructions about the types of conditions that the FDA is willing to impose, and that the FDA would impose most of the conditions and then enforce them. That is not the case, however.

Committee members frequently recommended unenforceable or vaguely worded conditions of approval and expressed their intention to recommend approval for products that they did not believe were proven safe or effective. Their candor suggests that they would welcome guidance from the FDA officials present, to make sure their recommendations were appropriate. Nevertheless, during committee discussions FDA officials showed remarkably little interest in providing oral guidance regarding the criteria for approval, or the realities of approval conditions to advisory committee members during the eight years of the study. Conditions of approval imposed by the FDA often did not reflect the conditions recommended by the advisory committees. Conditions that were imposed were rarely enforced.

Overall, the findings indicate that committee members, intentionally or unintentionally, move toward a consensus that often seems inconsistent with their differing views or perspectives in making decisions that may have life-or-death consequences for millions of Americans. Voting for approval contingent upon conditions is a popular compromise, but the FDA does not impose most of the specified conditions on the companies when it grants approval. The Committees' tendency toward approval seems to reflect the FDA's goals; in fact, the FDA appears to be even more geared toward approval than the advisory committees. The FDA approved almost all the prescription drugs and devices recommended by the advisory committee, and also frequently approved products that were opposed by the committee members.

Whatever the reasons, many of today's FDA drug and device advisory committees are rubber stamps for approval almost every time they meet. Moreover, even when an overwhelming majority recommend "non-approval," there is a good chance that FDA officials will approve the product anyway. Approval is even more likely for medical devices than it is for drugs.

Recommendations

If the FDA wants to restore confidence in the FDA, and restore the independence that FDA advisory committees were intended to provide, it is essential that the FDA make changes in the policies and process governing its advisory committees. The following recommendations are based on the assumption that the Congress and the FDA are committed to that end:

1. **The FDA should stop granting conflict-of-interest waivers for committee members, except under very restricted conditions.**
2. **The FDA should provide explicit and specific oral guidance whenever needed during advisory committee meetings regarding appropriate criteria for safety and effectiveness, and appropriate criteria for conditions of approval.**
3. **The FDA should demand more from advisory committee members, and then be more responsive to their concerns.**

INTRODUCTION

FDA Advisory Committees: Does Approval Mean Safety?

The U.S. Food and Drug Administration (FDA) has the responsibility to determine if newly developed medical products are safe and effective. Whether it is a prescription medication, a medication sold over the counter, a medical device, a vaccine, or another type of biologic, the product can be marketed for general sale in the United States only if it has FDA approval. This report is based on the first study to objectively examine the key role of FDA advisory committees as part of the FDA approval process. The purpose of this report is to examine the decision-making process and voting patterns of FDA advisory committees considering approval for new medical products or new medical indications for previously approved products at FDA's two largest centers, the Center for Drug Evaluation and Research (CDER) and the Center for Device Evaluation and Radiological Health (CDRH).[i]

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FDA advisory committees meet to review the most controversial and cutting-edge medical products. When these products are approved and later found to be more dangerous than expected, it is important to determine what went wrong.

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FDA advisory committees are the most visible part of the FDA approval process, meeting in public to examine applications for FDA approval, discussing the strengths and weaknesses of the studies and committee members' enthusiasm or concerns about the medical products. At recent advisory committee meetings on controversial drugs and medical devices such as Vioxx®, silicone implants, and antidepressants, media coverage has provided Congress and the general public with a glimpse of the approval process, and the advisory committee decision-making process has come under criticism. Questions have been raised regarding committee members' financial ties to the companies with applications before the advisory committee, their commitment to scientific scrutiny, the role of patients' subjective testimony, and apparent inconsistencies between the committee members' expressed concerns and approval recommendations.

FDA advisory committees meet to review the most controversial and cutting-edge medical products. When these products are approved and later found to be more dangerous than expected, it is important to determine what went wrong, and whether it is possible to strengthen the safeguards without delaying the availability of life-saving products. In order to understand the FDA approval process for specific medical products, however, it is essential to examine how advisory committees work in general.

By analyzing the committee members' voting records and public discussion of approval decisions, this report sheds light on how the advisory committee process trends toward consensus and approval, and how individual committee members can have a disproportionate influence on approval recommendations. The report examines how highly controversial products can generate little disagreement among accomplished professionals representing a wide range of perspectives and expertise. In addition, this report determines the extent to which voting patterns differ for drugs and devices, and for committee members with clinical, scientific, and consumer perspectives. Based on our findings, NRC for Women & Families recommends changes that will strengthen the scientific basis and influence of FDA advisory committee decision-making.

FDA Advisory Committees: The Basics

The company whose product is under consideration for FDA approval is responsible for providing data to the FDA that proves its product is safe and effective. For most medical products, the FDA makes an approval decision based on its internal reviews of available data, almost all of which is provided by the company. Agency scientists review the research data and other information, and FDA officials make the final decisions.

[i] The FDA refers to each advisory committee at the Center for Drug Evaluation and Research as a committee, and refers to the individual device advisory groups at the Center for Devices and Radiological Health as panels. For the purposes of this report, we make that distinction when possible but sometimes use those terms interchangeably.

Sometimes the FDA seeks additional advice, particularly on emerging technologies or controversial medical products. If the approval decision is unclear or controversial, or if there is substantial disagreement within the FDA, the FDA usually consults a scientific advisory committee whose members are selected and paid by the FDA but are not FDA employees. The FDA has 16 scientific advisory committees to review drugs and 18 to evaluate medical devices. The committees divide along product lines and body systems (such as arthritis drugs, reproductive drugs, reproductive devices, and ophthalmic devices) and review the products at public meetings that usually last one or two days. Members have overlapping terms for up to four years, and the terms are rarely renewed. The advisory committee meetings, open to journalists and the public, take place at hotels in the greater metropolitan Washington, D.C. area. Committee members receive data and analyses provided by the company whose product is under review, as well as a review memorandum and additional information provided by FDA scientists.[ii] Much of that information is publicly available online at least one day before the committee meeting.

Advisory Committee Meeting Agendas. During the public meeting, the company sponsor presents its data; the FDA scientists present their review; members of the public are invited to speak briefly during the "open public comment period;" and committee members ask questions of the sponsor, the FDA, and occasionally individuals who speak during the open public comment period. At most advisory committee meetings, most of the research-based presentations are by the company and its paid consultants, with less time for presentations by FDA scientists. Outside experts, such as government researchers or independently funded researchers, are sometimes invited to make formal presentations at an advisory committee meeting, but such presentations are not typical. In an announcement published in the *Federal Register*, members of the public are invited to sign up in advance if they want to speak. They must come at their own expense and usually are only given a few minutes to speak. Many meetings have no speakers during the open public comment period. At the most controversial committee meetings, where more than 100 individuals may ask to speak, each is likely to be given only two or three minutes. These time limitations are a disincentive to testify, since the cost of traveling to the meeting can be prohibitive; the hotel rooms where the meetings take place often cost more than $150 per night, and the hotels are frequently not near an airport or public transportation. In contrast, the company whose product is under review and others who support approval often pay transportation costs for patients, physicians, and others willing to testify on behalf of the product during the open public comment period. When they do so, part of the public comment period may be an extension of the company's strategy to get FDA approval.

After listening to the company presentation, the FDA presentation, and any public comments, committee members discuss and vote on questions that the FDA has prepared and provided to committee members in advance. The prepared questions for new medical products include whether the product is effective, whether it is safe, and "whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval." [1] The safety and effectiveness questions for medical device advisory panels are somewhat different. For devices, safety is defined as a reasonable assurance based on valid scientific evidence that the probable benefits to health outweigh any probable risks.

Effectiveness is defined as a reasonable assurance that a significant portion of the population will have clinically significant results.[iii] Additional questions often concern labeling information that committee members would recommend if the product were approved. In other words, although part of the meeting is to determine whether the committee will recommend approval, the committee members are told before the meeting that they will be asked to consider the conditions of approval, including what warnings or indications to put on the label. Depending on the wording, this has sometimes aroused criticism for giving committee members the impression that approval is expected, possibly creating a climate that pressures them to approve a product with conditions or restrictions, rather than rejecting it based on safety concerns.

[ii] For the purposes of this report, all individuals serving on a committee are referred to as committee members, although some are members of the standing committee and others were added to the committee for only one or more meetings. Meetings average 10 voting members.

[iii] These definitions are included in the charge to the medical device panels, and are read to the panel as part of a boiler plate set of instructions before voting begins.

Committee Members. Most committee members are physicians or scientists with expertise in the general area but not necessarily regarding the specific type of product under review. Advisory committees also include one industry representative and one patient or consumer representative. On medical device advisory panels, these representatives may ask questions and make comments but not vote. In the drug advisory committees, the patient or consumer representative is a voting member but the industry representative may not vote. In addition to the permanent members of the advisory committees, the FDA frequently will add one or more temporary members to each committee meeting with expertise relevant to the specific product under review.

According to Linda Ann Sherman, the FDA's director of advisory committee management and staff, the FDA's advisory committees' role is "to offer the FDA the very best advice possible on related questions posed by the Agency on a product of regulated industry." [5] She explains that "Scientific advisory committees complement the Agency's scientific expertise by bringing cutting-edge research, patient and patient caregiver concerns, and industry and consumer advocacy viewpoints to the table for discussion." In addition, the advisory committees "lend credibility to the FDA decision-making processes by having public discussions of controversial topics by the world's experts, the Agency staff, and the Agency's stake holders (industry and consumers)." FDA advisory committees are balanced demographically and scientifically, and are intended to be representative of the country in terms of age, race, sex, ethnicity, and other factors.

The decision to involve an advisory committee is usually at the discretion of the division director in one of the FDA's five product centers. Linda Kahan, deputy director of FDA's Center for Devices and Radiological Health, explains that the purpose of the advisory committee process is "to air issues that are controversial, complex, and do not have simple answers." [2]

The advisory committee process is expensive and time-consuming for the companies and the FDA, as well as for members of the public who take the time to travel to the meeting and participate. The FDA pays committee members' travel expenses as well as honoraria, but that reimbursement is unlikely to pay for all their time if they carefully review the data and documents before the meeting. The FDA Inspector General reports that about 21% of drug approvals were preceded by an advisory committee meeting[3] and the percentage is much lower for medical devices, since most medical devices are cleared for market without going through the Pre-market Approval (PMA) process, and therefore are exempt from scrutiny by FDA advisory committees.[4] Even so, in fiscal year 2003, FDA's advisory committee process "conservatively cost taxpayers more than $8 million." [5]

Although the FDA generally follows the advice of advisory committees, the agency is not required to do so.

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In some cases, such as the painkiller Vioxx®, the products were approved by the FDA after unanimous recommendations from FDA advisory committees.

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Controversy and Questions

One hundred years ago, the FDA was created in response to concerns about dangerous and ineffective medical products. In recent years, the FDA has come under scrutiny when numerous widely used FDA-approved drugs and medical devices were recalled or removed from the market in the wake of reported deaths and serious illness. In some cases, such as the painkiller Vioxx®, the products were approved by the FDA after unanimous recommendations from FDA advisory committees. The advisory committees have increasingly been criticized by Congress, the media, and consumer advocates because of questions about the committees' objectivity and scientific scrutiny. The focus, however, has been on drug approvals, not on medical devices. For example, an investigative journalist at *USA Today* found that at 92% of the drug advisory committee meetings from 1998-2000, at least one committee member had a financial conflict of interest.[6] Similarly, a more recent study published in the *Journal of the American Medical Association* found that at 73% of FDA drug advisory committee meetings from 2001 through 2004, the FDA announced that at least one voting member had a financial conflict of interest; at 22% of the meetings, more than half the advisory committee members had such conflicts.[3] The researchers pointed out that conflicts of interest could have influenced voting patterns because they "typically produced overall votes more favorable" toward the drug.

STUDY DESIGN

This report describes the findings of a study conducted by the National Research Center for Women & Families, which analyzed the voting patterns of a random sample of FDA advisory committees. The goal of the study, the first of its kind, is to evaluate the pattern of approval recommendations made by FDA advisory committees at two FDA centers, the Center for Drug Evaluation and Research and the Center for Device Evaluation and Radiological Health. A random sample of six of 16 drug advisory committees and 5 of 18 medical device advisory panels was analyzed in terms of voting patterns from January 1998 through December 2005.

Advisory committees typically are asked to answer specific questions about medical products under review by the FDA. Generally, FDA questions include whether the data indicate that the product is safe and effective, and whether the data on safety and effectiveness are adequate to support approval for marketing. Committee advice is not limited to questions related to new-product approval and marketing, however; committees also review new information about disease indicators and applications for new indications in FDA-approved medical products. Committee members may vote that the FDA require additional studies or make changes to a product's labeling. Sometimes advisory committees even make recommendations outside of the scope of the FDA's questions.

In this study, NRC for Women & Families analyzed only those votes dealing with the FDA approval of a New Drug Application (NDA) or new indication for a previously approved drug, or a PMA for devices. On those rare occasions when a committee member abstained, NRC did not include that vote in the analysis.

The advisory committees included in this study are as follows:

DRUG COMMITTEES
Antiviral Drugs
Arthritis Drugs
Dermatologic and Ophthalmic Drugs
Gastrointestinal Drugs
Pulmonary and Allergy Drugs
Reproductive Health Drugs

MEDICAL DEVICE PANELS
Immunology Devices
Microbiology Devices
Obstetrics and Gynecology Devices
Ophthalmic Devices
Radiological Devices

Data for these advisory committees were collected from the FDA Web site, based on transcripts of advisory committee meetings from January 1998 through December 2005. In that time, the six drug and five device advisory committees that were randomly selected considered 89 medical products at public meetings. There were 866 committee member votes.

Information about the products reviewed by these committees is included in Appendix C and Appendix D.

Advisory Committee Voting Patterns

As described by FDA officials, its advisory committees meet only to discuss the most controversial or innovative products, or products whose data are not clear-cut. Based on the FDA's concerns about the lack of "simple answers" for these products, the public might therefore expect that many of the drugs and devices reviewed by advisory committees would not be recommended for approval. The data indicate, however, that the 11 randomly selected advisory committees recommended approval for 79% of the 89 products reviewed between 1998 and 2005. The device advisory panels were even more likely to vote for approval than the drug advisory committees, recommending approval 82% and compared to 76% of the time for drugs.

Despite the controversies surrounding these products, the votes for or against approval were rarely close. On the contrary, 75% of the medical device approval recommendations were unanimous, as were 66% of the recommendations for drugs. The votes against approval were less likely to be unanimous: 29% of devices and 15% of drugs that the committees rejected were unanimous votes.[iv]

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The 11 randomly selected advisory committees recommended approval for 78% of the 87 products reviewed between 1998 and 2005. The device advisory panels were even more likely to vote for approval than the drug advisory committees, recommending approval 82% and 75% of the time, respectively.

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Scientists are taught to scrutinize and criticize data from the perspectives of their academic disciplines. Similarly, the popularity of 'second opinions' in medicine reflects the diversity of physicians' views on medical treatment and safety matters. Although FDA officials describe the advisory committees as providing diverse perspectives and expertise, the large number of votes that are unanimous or nearly unanimous suggests that either the data are exceptionally convincing — providing overwhelming evidence that the product is safe and effective — or the committee members are reluctant to disagree with their colleagues or believe that the FDA wants the advisory committee members to come to consensus.

For drugs and devices, most recommendations for approval were accompanied by warnings and restrictions on the label or specific conditions regarding additional research. In most device approvals there were numerous conditions, ranging as high as 14 for one device. Perhaps, therefore, the primary function of the advisory committees is to recommend restrictions and warnings on the labels and the conditions of approval, rather than to determine whether a product should be approved. This could explain the FDA's description of the use of advisory committees to examine complicated products and issues. However, if the FDA is relying on advisory committees to help determine the conditions of approval, including post-market research, one would expect that FDA officials would provide clear instructions to the advisory committees about the types of conditions that the FDA can mandate, and that the FDA would then enforce them.

One also would expect that the conditions of approval recommended by the advisory committees would be similar to those that the FDA required of the manufacturers. The findings do not support this.

In an effort to understand the advisory committee process, we examined the voting patterns of specific committees as well as individual members and types of members. The results indicate that certain advisory committees have recommended approval for every product they have reviewed for many years. There were individual committee members who never voted against approval of any product they reviewed. There also were

[iv] These differences were not statistically significant, reflecting the relatively modest sample size and the high proportion of recommendations for approval and unanimous recommendations in both device and drug advisory committees. The analyses were conducted using 2 x 2 *chi square* comparisons.

advisory committee members who never voted in the minority; in other words, if the majority voted against approval, they also voted that way, and if the majority voted for approval, they always voted that way.

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The results indicate that certain advisory committees have recommended approval for every product they have reviewed for many years.

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The Ophthalmic Devices Advisory Panel is an example of a panel that does not seem to be especially discriminating, having recommended approval for every medical device they considered for the last six years. The 10 medical devices they supported included implantable contact lenses, a capsular tension ring to aid in cataract surgery, and LASIK devices. Do the 100% approval recommendations mean that the ophthalmic devices reviewed by the FDA during those years were especially safe and effective, so that even the most controversial and complicated devices had data that clearly supported safety and effectiveness? On the contrary, in 2006, ophthalmic devices made the headlines when one of the major ophthalmic device manufacturers, Bausch & Lomb, withdrew one its newest contact lens solutions, ReNu® with MoistureLoc, from the market after reports of eye infections and blindness associated with its use. Did the FDA advisory panel fail to properly scrutinize this product?

Our analysis finds that the Ophthalmic Device Advisory Panel never reviewed ReNu® with MoistureLoc, because it was not considered a controversial product that needed careful scrutiny. On the contrary, ReNu® with MoistureLoc was cleared for market by the FDA as a medical device in 2003 under the 510 (k) program, which allows devices to be approved without clinical trials or advisory panel scrutiny if FDA agrees with the manufacturer that the product is substantially equivalent to other medical devices that are already on the market. The 510 (k) process provides much less scrutiny than the PMA process, and only the most controversial devices in the PMA process are reviewed by FDA advisory panels. Therefore, the medical devices reviewed by this advisory panel are considered much more controversial or innovative than ReNu® with MoistureLoc, which was subsequently removed from the market because of serious risks. Although the explanation of why ReNu® users developed rare eye infections has not been publicly revealed, FDA inspectors noted that the formula for the contact lens solution had been changed but that no clinical trials were conducted to determine if it was safe or effective if used as directed.[7] This example shows that ophthalmic devices have serious risks as well as important benefits, and certainly the most innovative and complicated ones, which are reviewed by the advisory panel, deserve careful scrutiny.

Diversity of Opinion: Who Votes For Approval?

As can be seen from the high proportion of recommended approvals, most advisory committee members recommend approval most of the time. Nevertheless, it is possible that committee members' training or perspectives may account for differences in voting patterns, with scientists potentially more skeptical about the data and practicing physicians more enthusiastic about new medical products because they can provide greater treatment choices. Consumer representatives might be especially concerned about risks or especially interested in getting new products approved and available. To evaluate differences in voting patterns, we categorized committee members in one of four groups: physician only (M.D. or D.D.S.); physician plus scientific degree (M.D. plus Ph.D. or master's degree); doctorate only (Ph.D., Sc.D., or Pharm.D.) and consumer representative (several of whom had R.N., M.P.H., or doctoral degrees). We analyzed the voting patterns of these four groups separately for the drug advisory committees and the device advisory panels. The few committee members with degrees that did not fall in these categories, such as law degrees, were not included in the analyses.

Drug Advisory Committees. The drug advisory committees included 155 committee members with medical degrees only; 46 with medical degrees plus a scientific degree; 62 with scientific degrees only; and 17 consumer representatives. We separately analyzed the data for the three patient representatives.

Of the 288 votes of the physician members, 210 (73%) were for approval. Of the 92 votes of doctoral level members, 67 (73%) were for approval. Of the 89 votes of the physician scientists, 71 (80%) were for approval. Of the 36 votes of consumers, 27 (75%) were for approval. There also were three patients who voted on these committees, and 100% were for approval. Clearly, our expected differences in voting patterns did not emerge; on the contrary, the doctors, scientists, and consumers voted identically, and the physician scientists were slightly, but not significantly, more likely to vote for approval. Although the 100% approval votes of the patients on the committees is interesting, the sample is much too small to draw any conclusions other than that patients tended to vote for approval as the other groups did.

Medical Device Advisory Panels. Consumer and patient representatives are not permitted to vote on device advisory panels, so we compared the 78 physicians, 14 physician scientists, and 31 scientists. Of the 207 votes of the physician members, 161 (78%) were for approval. Of the 72 votes of doctoral level members, 60 (83%) were for approval. Of the 32 votes of the physician scientists, 26 (81%) were for approval. As with the drug advisory committees, there is virtually no difference among the three groups.

Drug Advisory Committee Members Explain Their Votes

The FDA provides a full transcript of each committee meeting on its Web site, enabling our researchers to carefully review the questions and discussion, the concerns and enthusiasm expressed, and the reasons each committee member gave when voting. We assumed that overall, committee members expressing enthusiasm for a product would vote for approval and those expressing strong concerns would vote against approval. Therefore, we focused on the exceptions to that general pattern. We examined whether the surprisingly high proportion of votes in favor of approval could be explained by motivations other than confidence in the safety and effectiveness of the medical product under consideration. In this section of the report, we will focus first on comments from members of the Arthritis Drugs Advisory Committee, which had the highest proportion of votes for approval of all drug or devices advisory committees.

Arthritis Drugs Comments. The 33 members of the Arthritis Drugs Advisory Committee during 1998-2005 reviewed seven new drugs during the eight years of this study, two of which they voted on for two different indications in two different years. Of the 83 recorded votes they cast for these six drugs, 81 (98%) were for approval. Only two committee members ever voted against approval, and each did so only once.[v]

Given that advisory committees are convened for the most controversial or cutting-edge products, this near unanimity in voting is striking and worrisome. The findings are especially important because they included unanimous approval for Celebrex® in 1998 and Vioxx® in 1999, two drugs that subsequently were found to be associated with increased risk of heart attack and stroke. Vioxx® was subsequently removed from the market; Celebrex® remains on the market, but with strong warnings.

There are several possible reasons why drugs would unanimously be recommended for approval and then later be found to be more dangerous than expected:

1. Committee members might have relatively lenient standards for approval, lack understanding of statistical or scientific shortcomings of the data, or both;

2. The research findings provided to committee members might be reassuring and convincingly presented and the risks may not be fully determined until the product is used long term or on patients that differ in age, health status, or other traits that influence safety; or

3. Committee members might feel pressure to recommend approval for the product or pressure to conform with colleagues on the committee who support approval.

[v] When the advisory committee met to review a new indication for the previously approved Enbrel® in 2000, the vote was stated as 7-2 for approval in the meeting transcript. However this vote was not included in the study statistics because it was not a roll call vote and committee member votes were not recorded in the transcript.

As we consider whether the committee members are relatively lenient in their standards for approval, the question arises as to whether they carefully scrutinize the statistical analyses that are the basis of proving safety and effectiveness. Since most of the votes are cast by physicians, and physicians who do not have research degrees do not necessarily have statistical training, it is possible that the lack of statistical expertise could make it difficult for some committee members to scrutinize the inferential statistics presented.

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"Since I'm ignorant of most statistical issues, in my ignorance I can be very impressed with the data."

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The FDA meeting transcripts do not indicate how often this happens, but several committee members clearly stated their lack of understanding of the data. For example, at the August 1998 Arthritis Advisory Committee meeting on Arava®, Dr. Steven Abramson stated: "Since I'm ignorant of most statistical issues, in my ignorance I can be very impressed with the data." [8] Although other committee members also had difficulty understanding the data analyses, most were not as candid.

Within a few years of this advisory committee meeting, Arava® was associated with 130 severe liver reactions, including 56 hospitalizations and 22 deaths.
As a result of these publicized adverse reactions, the Arthritis Advisory Committee met in March 2003 to determine if "the benefit to risk profile" of Arava® was acceptable for the current indications. At that time, Dr. James Fries expressed his view that risk information should not be considered unless the data are conclusive. He explained, "I have this sort of gorge that rises when we have groups which are watchdogs for the public interest who may be hurting the health of the public by raising what turn out to be false positive red flags. Now, I'm in favor of eternal vigilance, but until we actually have something that rises up out of background I don't think we ought to mention it." [9] Once again, the committee voted unanimously to maintain approval. Arava® is still on the market, but the FDA now warns patients that the drug can cause "rare cases of severe liver injury, including death" as well as inflammation of lung tissue. Patients taking Arava® must have their livers tested before use, and regularly while they are taking the drug.[10]

In August 2001, the Arthritis Advisory Committee met to review Kineret® for treatment of rheumatoid arthritis. During that meeting, several committee members indicated that they understood that FDA's standards for approval do not require proof of safety and efficacy. For example, Dr. Jennifer Anderson remarked that she questioned whether the data "demonstrate an appropriate safety and efficacy profile as a treatment. I don't think that has been shown yet, but that is not what we are voting on." [11] Despite those doubts, she concluded that "the data are adequate, it seems, for approval given the way the guidelines for these things are written by the FDA." The patient representative, Leona Malone, expressed her uncertainty and ambivalence, stating "I am anxious for anything to come out that is going to offer some help" to patients but "I am not familiar with clinical data enough to really cast a vote in the same type of league with you people, but it does fulfill the requirements that FDA set up. So, I would say a very quiet yes." In a response that was unique for the advisory committee meetings in the study, Dr. Jay Siegel, an FDA employee participating in the meeting, disagreed with the committee members' comments and clarified FDA requirements for approval, saying, "Wait a second. The law requires that a drug be safe and effective for approval, and there seems to be a lot of confusion about these guidelines and what they mean, because there have been three comments that this meets the standards for approval, but we are not sure about whether it is actually good."

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"Wait a second. The law requires that a drug be safe and effective for approval, and there seems to be a lot of confusion about these guidelines and what they mean, because there have been three comments that this meets the standards for approval, but we are not sure about whether it is actually good."

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Dr. Siegel's comments were highly unusual, and at other meetings, FDA officials did not respond when advisory committee members clearly expressed their intention to vote for approval of products that they were not sure were safe or effective. The standards for products

already on the market may be especially lenient and the pressure to agree with committee members who vote for approval even greater, based on the numerous concerns expressed about a new indication for Enbrel® at the April 2000 advisory committee meeting. During the discussion before voting, Dr. David Felson did not comment, but after Dr. Steven Abramson expressed concerns about the lack of long-term safety data and said "I would still wait another year" before approval, Dr. Felson agreed, admitting "I didn't have the courage to say what you said. I've sort of been leaning on the fence in terms of thinking about this problem because I think there's wonderful efficacy data here, and the safety data is genuinely reassuring, I think, despite all the concerns we all had. But the truth is I wouldn't want to give a patient with early rheumatoid arthritis this treatment without some better data on long-term safety. I wouldn't want to sentence them to potentially having a really dangerous long-term side effect without knowing more, especially since there's nothing keeping them from ultimately getting it [since it is already approved]…I think that remains my concern. I'm still not sure, though. I think I could be convinced either way." [12]

At the same meeting, Dr. Nigel Harris stated that since Enbrel® was already approved and already in use, "Indeed, if there is a risk that we don't know, the risk will exist and occur anyway.…You know, let us approve it as a first line — not first line but as a first stage. If there's trouble down the road, you're going to get it anyway. We've approved it, and the trouble will occur. So really, I think that, one way or another, the concerns about safety really are not important in terms of what we are considering today." [12]

When Dr. Lee Simon expressed his desire "to see if I can sway you one more time," Dr. Abramson interrupted, saying, "I was already swayed. I didn't want to be like a wimp and be inconsistent." The comments for Enbrel® suggest that new indications may be held to an even less stringent standard than new products, since it is widely assumed that they can be used off label for other indications anyway.

These are just a few of the comments that indicate that Arthritis Drugs Advisory Committee members sometimes voted for approval despite strong concerns. It is notable that FDA officials usually made no effort to encourage stricter approval standards. Nor is this pattern unique to the Arthritis Drugs Advisory Committee. The comments of members of other advisory committees with less extreme voting patterns expressed similar concerns and the FDA was similarly acquiescent. A few of the many examples are quoted for each committee.

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"If we don't expect certain standards, then the message gets out that someone else can come in and not do a good job or not present these things, and that also bothers me."

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Antiviral Drugs Committee Comments. Several members of the Antiviral Drugs Advisory Committee also indicated that they were bowing to pressure to conform. At the January 1998 meeting on CellCept®, the committee voted unanimously to recommend approval, despite very strong concerns. For example, the consumer representative, Susan Cohen, stated: "Since I'm not a political person, I really have tremendous problems with the samples they used….It really troubles me a great deal. I think they were chosen to be favorable, and so I'm not comfortable with that. The other thing I have to say that makes me uncomfortable — being [a] consumer member is a lot different. If we don't expect certain standards, then the message gets out that someone else can come in and not do a good job or not present these things, and that also bothers me; because I'm here representing consumers, and that's what it's about, and thank God someone mentioned at this table consumers….I think I'm going to have to vote yes, but with a lot of reservations and concerns that this doesn't send a message out to every other pharmaceutical company, well, you know, in the long run you can get it passed, but I am troubled about how you put your samples."[13]

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"I'm going to have to vote yes, but with a lot of reservations and concerns that this doesn't send a message out to every other pharmaceutical company, well, you know, in the long run you can get it passed."

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Doctors on the committee also described the pressure to conform and please colleagues. At the July 1999 meeting of the Antiviral Drugs Advisory Committee to review Rapamune®, Dr. Lawrence Hunsicker stated, "So one of the things that has to be put on as a caveat is that we do not know the safety of this drug beyond one year. Now, when mycophenolate was presented I almost lost all my friends by proposing that we actually put a one-year limit on the labeling. And I was talked out of it by my friends who told me that if they didn't talk me out of it they'd outvote me anyway. So I'm not going to make that recommendation."[14]

The advisory committee members' desire to approve drugs is sometimes so strong that they change the criteria for approval, ignoring whether a product is efficacious. For example, at the February 2001 Antiviral Drugs Advisory Committee meeting reviewing Valcyte®, a drug to treat eye disease related to HIV infection, committee members were asked if the data supported the efficacy of the drug for maintenance therapy. Several committee members stated that the data did not support efficacy of the drug, so Dr. Ram Yogev asked if the word "efficacy" could be replaced with the word "use" so that they could instead vote on whether the data supported the "use" of the drug. Rather than clarify the criteria for approval, as Dr. Siegel did at the Arthritis committee meeting that same year, Dr. Debra Birnkrant, the Acting Director of FDA's Division of Antiviral Products, agreed to the change. The committee chairman then asked if replacing "efficacy" with "use" would make committee members happy, and Dr. Yogev replied, "Much happier, because then I could say yes….I don't know the efficacy."[15] The committee subsequently recommended the drug for approval by a vote of 11-1.

Dermatologic and Ophthalmic Drugs Comments. Similar pressures were expressed at the March 2003 review of Vitrase®, a drug to treat bleeding in the eye, by the Dermatologic and Ophthalmic Drugs Advisory Committee. When the committee was asked if they thought there was evidence that the drug was effective, eight committee members voted no and only four voted yes. Nevertheless, when asked if the benefits outweighed the risks, they voted 7 to 5 for approval. In other words, three committee members voted that the benefits outweighed the risks even though they had voted that the drug had no proven benefits. Dr. Scott Steidl admitted the contradiction, explaining, "I am a little confused about this question, personally. But…my feeling is similar to what Stephen Feman stated that, although I said no to the first [question regarding effectiveness], I am thinking about the last question in a broader sense. So I guess you could put me as a yes. I think there probably are subsets and patients where I would consider it so I kind of feel that I would have to say yes to this even though it may seem contradictory."[16] The votes would seem less contradictory if the product had no risks, but that was not the case; the FDA required the Vitrase® label to list numerous risks, and later criticized the company for failing to provide adequate warnings about these substantial risks in their advertising.[17]

Gastrointestinal Drug Comments. Sometimes the pressure to save time also may undermine the process and result in consensus rather than argument. That consensus can be for or against approval. For example, at the June 2000 meeting of the Gastrointestinal Drugs Advisory Committee, one member, Dr. Stephen Hanauer, interrupted himself as he was about to read the warnings regarding Zelmac®, a drug for irritable bowel syndrome, saying, "Gee, I really don't want to read this whole thing. It is on the bottom of page 6...." and Dr. Christina Surawicz interrupted, reassuring him: "We have read it. It is good."[18] The committee then voted 1 to 7 against approval. Although the FDA sent an approvable letter to the company, indicating that the drug was likely to be approved, the drug has never been approved.

At a March 2003 meeting of the same advisory committee to review Emend®, votes for approval did not always reflect confidence in the product. For example, Dr. Robert Levine admitted, "I'm uncomfortable with it, but I will say yes. From these other experiences with post-marketing, as all of you are saying, these are very serious consequences. Therefore….I would say yes."[19]

Pulmonary and Allergy Drug Comments. At times, advisory committee members are explicit in their uncertainty of how to vote. In September 2003, the Pulmonary and Allergy Drugs Advisory Committee reviewed Ariflo®, a drug to improve pulmonary function. Dr. Carroll Cross couldn't decide how to vote and stated, "My answer is maybe but I have to decide which way to go. Can I pass for now and listen to other comments as we go around the table?"[20] Although it is certainly desirable for committee members to learn from the views of colleagues with different perspectives, generally that sharing of ideas should take place during the many hours of presentations, questions, and discussion. His request to delay his vote illustrates how the votes of committee members with strong opinions can directly influence the votes of their colleagues.

Reproductive Drug Comments. The Reproductive Drugs Committee was least likely to vote for approval, but even so committee members sometimes voted for approval after expressing very strong concerns. For example, at the April 2000 review of Uprima® by the Reproductive Drugs Advisory Committee, Dr. Robert Califf described the low standards for approving the erectile-dysfunction drug, saying, "Specifically with regard to the 2-milligram dose, it seems to me that as a specific question, it's kind of like old-fashioned medicine: It's not much good, but it probably won't do much harm either." He later indicated that any advantage of the product might be more psychological than physiological, suggesting, "Maybe it would be best to start with placebo."[21]

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"It's kind of like old-fashioned medicine: It's not much good, but it probably won't do much harm either."

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The committee members' comments regarding Uprima® clearly show that a vote for approval does not necessarily mean that advisory committee members believe that a product should be approved. For example, Dr. Peter Kowey admitted, "If you came back and told me several months from now that you decided not to approve this drug, it would not break my heart because I think there are two ways to handle this kind of problem. One way is to not approve the drug. Period. And the other way is to approve it and then label the hell out of it. I voted yes with the proviso that you understand that there's got to be a tremendous amount of work done on labeling for this drug. I favor a black box warning in bold letters that says, that if you take this drug, you may pass out and if you pass out, you may injure yourself and you may injure yourself severely."[22]

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"I voted yes. But don't take that to mean that I don't have grave concerns about the safety of this drug."

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Dr. Kowey also indicated that his vote was influenced by physicians on the committee when he explained "I said yes because I was listening to these guys who take care of these patients who would like to see this drug available. And I agree that they're a desperate lot of patients and they do need to have that drug, and I'd like to see it on the market. That's why I voted yes. But don't take that to mean that I don't have grave concerns about the safety of this drug, and if it's not communicated properly to the physicians, what's going to happen is you're going to run into the same withdrawal problems that you had with other drugs somebody mentioned earlier. So, I feel very strongly about that."[22]

Nevertheless, Drs. Califf and Kowey voted with the majority on the committee to recommend approval for the drug at the 2-milligram and 4-milligram doses. Their concerns were apparently well founded; the manufacturer withdrew its application for the drug before FDA announced a decision about approval.

Device Advisory Committee Members Explain Their Votes

Our analysis of the device advisory panel discussions focuses on the most extreme example first, the Ophthalmic Devices Advisory Panel, which recommended approval 88% of the time, usually unanimously.

Ophthalmic Device Comments. As was the case in the drug advisory committees, the device transcripts indicate that members sometimes voted for approval despite serious concerns about the data or the product. For example, at the January 2002 meeting regarding a capsular tension ring for use in cataract surgery, Dr. Allen Ho voted for approval and summarized his views as follows: "Poor study, poor execution, flawed from the beginning, I think." [23] Similarly, in the May 2003 review of CrystaLens® (an artificial lens to correct visual impairment after cataract surgery), Dr. Arthur Bradley explained his vote and expressed his ambivalence as follows: "I think this is an exciting new product. I was disappointed with the quality of the data but I think it has demonstrated efficacy. Although somewhat marginally so. That's why I voted to approve." [24] The panel voted unanimously for approval.

The panel members' comments often show self-deprecating humor about their uncertainty, concerns, and peer pressure, but patients and consumers are not aware of the concerns that were expressed. If the FDA subsequently agrees with the recommendations and approves the product, patients and consumers assume that the product is safe and effective. Patients certainly would wonder, for example, why Dr. Joel Sugar recommended approval for the STAAR Implantable Contact Lens, if they heard him admit at the October 2003 panel meeting that although "I feel that the efficacy has been well demonstrated, the safety remains a concern." [25] They might not be reassured by Dr. Sugar's explanation that when he voted for approval, he hoped that longer term data would eventually indicate that the product is safe. They might be similarly surprised by the comments of Dr. Timothy McMahon, who admitted, "I've waffled through the day with regard to my vote for approvability" but explained he was convinced by "the reassurances that the Sponsor will look at the follow-up data in a responsible manner….And hopefully, this will turn out for the best for all of us."[25] Based on these concerns, it is fortunate for patients that, in one of its rare instances of not approving a medical device recommended by the advisory panel, the FDA did not approve this product.

In the November 2001 review of the Viewpoint CK system for the treatment of spherical hyperopia, Dr. Michael Grimmett said, "I unenthusiastically voted approvable with conditions, as I believe the procedure is reasonably safe, yet only marginally effective. I'm uncomfortable with the lack of stability of the procedure." He nevertheless voted for approval with the hope that labeling would help consumers "have an adequate chance of achieving the appropriate information in order to make an informed consent about this procedure."[26]

Similarly, at the February 2004 meeting regarding the ARTISAN Myopia Lens, Dr. Richard Casey indicated his willingness to vote for approval on the basis of wishful thinking: "While the data may not have been conclusive, I think certainly the trend was that it probably is efficacious and probably is safe." [27]

The Ophthalmic Devices Panel approved every device it reviewed during the last six years of our analysis, but even before that uninterrupted approval pattern started in the summer of 1999, individual members described surprisingly low standards for approval in their panel discussions. For example, for the February 1998 review of the Kremer LASIK device, Dr. Janice Jurkus, explained that she voted for approval "because I did not see from the data that this was totally unsafe or totally ineffective." [28]

Radiological Device Comments. Other device panels were similarly willing to vote for products that they recognized as questionable. One of the many examples is the December 2002 Radiological Devices Panel meeting assessing a device for thermal imaging for breast biopsies. Dr. Geoffrey Ibbott voted for approval. When the motion failed, he voted against approval, stating, "Well, I voted in favor of the first motion, but, like Dr. Tripuraneni, I'm quite comfortable with the approval of the second motion [against approval]."[29]

Obstetrics and Gynecology Devices Panel Comments. It is not unusual for individual members to be outspoken in their criticisms and yet consistently vote for approval. For example, in January 2001, the Obstetrics and Gynecology Devices Panel unanimously recommended approval for the FirstOption Uterine Cryoblation Therapy System for treating abnormal uterine bleeding. There were strong concerns about the device, however, and Dr. Michael Diamond suggested the need for careful post-market surveillance. When challenged by other panel members that the risks of the product were not unique, Dr. Diamond explained, "Well, the difference between this device and the other ones … [is] we haven't had a 25% or higher failure rate with a device as part of the clinical trial, which we do have here."[30] Despite these strongly worded concerns, Dr. Diamond voted for approval.

Similarly, in the same panel's review of an endometrial ablation system in June 2003, Dr. Diamond recommended that the medical device be approved without conditions despite "recognizing all the things that we have talked about and the nine questions we went through, which to me seem like we have pretty unanimous thoughts throughout them of how they needed to be modified or addressed." [31] In response to the suggestion from others on the panel that those modifications and concerns should be specified as conditions for approval, Dr. Diamond agreed.

At the same panel's review of a fetal heart monitoring system in June 2005, Dr. Jay Iams opined that the company should be required to study if its device increased the Caesarean-section rate among women who used it. Dr. Julian Parer asked, "What happens if, at the end of two years, the [Caesarean] section rate has doubled, the rate of acidemia has tripled and we say, 'My God, we made a terrible mistake approving this device?' What option do we have?" [32] An FDA official candidly explained that "theoretically, FDA can withdraw PMA approval. In practice, that virtually never happens." Nevertheless, Dr. Parer and everyone else on the panel voted to approve the product.

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"What happens if, at the end of two years, the [Caesarean] section rate has doubled… and we say, 'My God, we made a terrible mistake approving this device?'"

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Immunology Device Comments. The Immunology Devices Panel considered no new devices between 1999 and 2004, but in 2005 it met to review the AlzheimAlert® test, a laboratory assay designed to measure proteins in urine specimens of patients with suspected Alzheimer's disease. The panel recommended against approval, but the two doctors who voted for approval indicated reasons that were not consistent with the FDA stated standard of proven safety and efficacy. For example, Dr. Oscar Lopez explained his support because "as a neurologist, and as somebody who works in the field of dementia, I believe that anything that increases awareness of the disease is positive and is important. So I think that would be very important to have something in the community… to have a tool that can increase their awareness of the disease. The problem that I have with the study is that it's not — I'm not convinced that it works in Alzheimer's disease."[33] Dr. Terrance Lichtor, a neurosurgeon who also voted in support of approval, stated, "It's not really identifying patients with Alzheimer's disease. It's more … help and management of patients with dementia who do not have Alzheimer's disease. And that's more of what I see. But I feel that this test does add some information, and only time will tell whether or not this will pan out to be helpful." This was an opportunity for FDA officials on the panel to clarify the criteria for approval, but they remained silent.

Microbiology Device Comments. At the March 2002 Microbiology Devices Advisory Panel meeting review of an HPV DNA test, panel members disagreed about the conditions for approval but voted for approval with those conditions anyway. For example, Dr. George Birdsong stated: "I'm going to say yes. I'm mixed on that one actually."[34] and Dr. Frederick Nolte was even blunter: "I voted in favor of the resolution. I guess I'm learning how to play politics … but I think basically the test has value."

Approval Recommendations

Of the 50 drug advisory committee voting sessions in the study, 38 (76%) resulted in a recommendation for approval of the drug, not counting the one tie vote. Of those 50 voting sessions, 27 (54%) ended in unanimous votes, with 25 (93%) of those unanimous votes recommending approval. Overall, 50% of the time the drug advisory committees unanimously recommended approval of the drug application.

Of the 39 medical device panel voting sessions surveyed, 32 (82%) voted to recommend approval of the device. Of those 39 sessions, 26 (81%) of the votes were unanimous, with 24 (92 %) of those unanimous votes recommending approval. Overall, the majority (62 %) of the medical device advisory panels unanimously recommended approval of the device under consideration.

The next section of this report provides the specific data on voting patterns for each drug and device advisory committee.

Drug Approval Recommendations

Each of the drug advisory committees in the analysis recommended approval at least half the time. The percentage of drugs that were recommended for approval ranged from 50% for reproductive health drugs to 100% for arthritis drugs. The percentage of individual votes cast to recommend approval ranged from 50% for reproductive drugs to 98% for arthritis drugs.

The Arthritis Drugs Advisory Committee also was most likely to recommend approval unanimously: eight (89%) of the nine committee votes recommending approval between 1998 and 2005 were unanimous.

While 76% of 50 drug committee voting sessions recommended approval, 396 (75%) of the 527 votes cast by committee members were for approval.

Of the 11 drugs that drug advisory committees voted against between 1998 and 2005 (not including the one tie vote), the FDA subsequently approved four (36%) of them as of July 2006, including two that were rejected by the Dermatologic and Ophthalmic Advisory Committee (Cyclosporine, rejected 1-5 and Methyl Aminole, rejected 2-9), one rejected 3-6 by the Gastrointestinal Advisory Committee (Serostim®), and one rejected 4-13 by the Antiviral Advisory Committee (Relenza®).

Of the 38 drugs recommended for approval by the drug advisory committees, all were approved except one drug whose application was withdrawn before FDA made its decision, as described previously in this report.

It is notable that although the drug advisory committees rarely rejected applications, the FDA was 12 times more likely to follow the recommendations for approval than those against approval. This is surprising, since one might assume that the few drugs that were rejected must have particularly great risks or particularly poor safety and efficacy data. The fact that the FDA was so willing to overturn those recommendations adds to the impression that the FDA committee meetings are intended primarily as a mechanism for drug approval rather than for close scrutiny regarding whether approval is appropriate.

The voting patterns for specific drug advisory committees are presented below.

Antiviral Drugs. There were 98 Antiviral Drugs Advisory Committee members who cast 215 votes, 172 of which (80%) were for approval. Voting on 18 products, they recommended approval for 15 (83%), and 11 of these approval decisions (73%) were unanimous.

Of 36 committee members who voted for more than one product (a maximum of eight products), 13 (36%) always voted for approval. The more active members were less likely to vote for approval every time: of 19 who voted at least four times, only two (11%) always recommended approval.

Arthritis Drugs. Of all the drug and device committees in the study, the Arthritis Drugs Advisory Committee members members were the most likely to recommend approval. Its 33 committee members cast 83 votes for new drugs or new indications, 81 of which (98%) were for approval. They voted on seven drugs, two of which they voted on separately for two different indications. All nine (100%) votes were for approval, and they recommended approval for eight of the nine (89%) unanimously.

Since almost all the committee members voted for approval every time, it is not possible to distinguish among committee members who voted for or against approval.

Although our analysis did not examine conflicts of interest, it is notable that the conflicts of interest among members of this advisory committee have been scrutinized in an article published in the *Journal of the American Medical Association* in 2006. The authors reported, for example, that at a 2005 advisory committee meeting to evaluate the risks of Cox-2 inhibitor pain medication, 93% of the votes cast by members who had received consulting fees from at least one of the drug makers favored the drugs, compared with 55% of the votes by individuals without conflicts.[3] Since our report only analyzes roll call votes for products being considered for approval for the first time or for a new indication, we did not analyze the votes from that 2005 advisory committee meeting. However, the substantial number of Arthritis Drugs Advisory Committee members with financial ties to manufacturers certainly could help explain the extremely consistent pattern of support for approval for almost all the products this committee reviewed since 1998. Based on the voting patterns for that committee, it is likely that if several committee members vote for approval for any drug, the remaining committee members will vote the same way.

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93% of the votes cast by members who had received consulting fees from at least one of the drug makers favored the drugs.

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Dermatologic and Ophthalmic Drugs. There were 44 Dermatologic and Ophthalmic Drugs Advisory Committee members who cast 69 votes, 40 of which (58%) were for approval. They voted on eight products, and recommended five (63%**)** for approval. Two of those (40%) were unanimous. The votes against approval were not unanimous.

Of 17 committee members who voted for more than one product (six was the maximum), only five (29%) always voted for approval. Only three voted at least four times, none of whom always voted for approval.

Gastrointestinal Drugs. There were 44 Gastrointestinal Drugs Advisory Committee members who cast 62 votes, 43 of which (69%) were for approval. They voted on six products, and recommended four (67%) for approval. Two (50%) of these votes were unanimous. The votes against approval were not unanimous.

Of 16 committee members who voted for more than one product (three was the maximum), five members (31%) always voted for approval.

Pulmonary and Allergy Drugs. There were 38 Pulmonary and Allergy Drugs Advisory Committee members who cast 58 votes, 40 of which (69%) were for approval. They voted on five products, three (60%) of which they recommended for approval, and two (67%) of the three were unanimous. The votes against approval were not unanimous.

Of 10 committee members who voted for more than one product (four was the maximum), four (40%) always voted for approval. Of three who voted at least four times, only one (33%) always voted for approval.

Reproductive Health Drugs. There were 28 Reproductive Health Drugs Advisory Committee members who cast 40 votes, 20 of which (50%) were for approval. They voted on only three products, one of which was voted on separately for two different dosage levels. Committee members recommended approval of the one drug at both dosage levels, thereby recommending approval of two (50%) of the four indications but only one (33%) of the three drugs. None of the votes for approval were unanimous, although one of the votes against was unanimous.

Of 12 committee members who voted twice, eight (67%) voted for approval both times. None of the committee members voted more than twice.

The small number of advisory committee meetings and the diversity of votes reflect substantial controversy involving the membership of this advisory committee, which in recent years included Dr. David Hager, a physician whose outspoken ideological opposition to some reproductive drugs has generated opposition to his membership on this committee.[35]

Device Approval Recommendations

All of the medical device advisory panels in our analysis recommended approval most of the time. The number of products that were recommended for approval ranged from 67% for microbiology devices to 88% for ophthalmic devices. The number of panel member votes cast to recommend approval ranged from 57% for microbiology devices to 91% for radiological devices. The microbiology panel was the only one where less than three-quarters of the products were recommended for approval or where less than three-quarters of the votes were in favor of approval.

Three of the five randomly selected device panels — The Radiological Devices Panel, the Immunology Devices Panel and the Microbiology Devices Panel — were always unanimous in their support for approval. The Radiological Devices Panel was most likely to recommend approval unanimously whenever they voted: six of the seven devices it reviewed between 1998 and 2005 (88%) were unanimously recommended.

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Three of the five randomly selected device panels — The Radiological Devices Panel, the Immunology Devices Panel and the Microbiology Devices Panel — were always unanimous in their support for approval.

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While 82% of the 39 devices were recommended for approval, 272 of 339 individual device panel members' votes (80%) supported approval.

The FDA subsequently approved 30 (94%) of the 32 devices recommended by the advisory panels. However, the FDA also approved 43% of the devices that the panel voted should not be approved.

Immunology Devices. There were 21 panel members who cast 29 votes, 24 of which (83%) were for approval. They voted on four products, three (75%) of which they recommended for approval, and all approvals were unanimous.

Only four of the panel members voted for more than one product (three was the maximum), but all (100%) always voted for approval.

Microbiology Devices. The Microbiology Devices Panel members were the least likely to recommend approval, although even they recommended approval most of the time. The 12 panel members cast 21 votes, 12 of which (57%) were for approval. They voted on three products, two (67%) of which they recommended for approval, and one (50%) of which they recommended unanimously.

Experience seemed to encourage panel members to vote against approval; panel members who participated in more panel meetings were more discriminating in their voting. Six of the panel members voted for more than one product (three was the maximum), and none of them always voted for approval.

Obstetric and Gynecological Devices. There were 43 panel members who cast 87 votes, 66 of which (76%) were for approval. They voted on nine products, seven (78%) of which they recommended for approval, and five of the approvals (71%) were unanimous.

Of 23 panel members who voted for more than one product (maximum of six), nine (39%) always voted for approval. Of four who voted at least four times, two (50%) always voted yes. The most active members of the panel always voted for approval (five times out of five, and six times out of six).

Ophthalmic Devices. Thirty-two Ophthalmic Devices Advisory Panel members cast 157 votes, 129 of which (82%) were for approval. They voted on 16 products, 14 (88%) of which they recommended for approval, and 10 (71%) of these were unanimous. This panel has not rejected any devices since July 1999.

Of 25 panel members who voted at least twice (with a maximum of 12 votes), only five (20%) always voted for approval. Of 20 who voted at least four times, only three (15%) always voted for approval.

Radiological Devices. There were 38 Radiological Devices Advisory Panel members who cast 45 votes, 41 of which (91%) were for approval. They voted on seven products, six (86%) of which they recommended for approval, and all (100%) were unanimous.

Of 10 panel members who voted for more than one product (five was the maximum), four (40%) always voted for approval. Of three who voted for at least four products, only one (33%) always voted for approval.

Labeling, Conditions of Approval, and FDA Approval Decisions

When committee members vote for approval, they often include caveats as a condition of approval or specify the risks of the product that should be included on the label. They may also ask that the label describe restrictions in the use of the product, for example, whether it is intended for individuals in certain age groups and whether the product is proven safe for pregnant women.

The advisory committee meeting transcripts indicate that when committee members have concerns about the safety of a product, they often vote for approval but also vote for conditions or restrictions that reflect those concerns. In fact, all but one of the approval votes for the device panel meetings were votes in favor of "approval with conditions." The conditions were sometimes numerous and quite burdensome, including studies to be conducted after the product was approved to examine long-term safety or efficacy. While providing clear guidance to the FDA about committee members' concerns, conditions of approval may serve another function: a compromise that helps persuade reluctant advisory committee members to vote for approval, so that they do not require better data to prove the product is safe or effective before approval is granted.

For example, at the June 2004 meeting of the Obstetrics and Gynecology Devices Advisory Panel that reviewed a high intensity ultrasound system called ExAblate 2000® for uterine fibroids, Dr. Grace Janik stated, "there are a number of us that have insecurities if efficacy is truly demonstrated here" and recommended that the company do more research before the product is approved.[36] She was told that a pre-market study was "not really germane" to the discussion because they were voting on conditions of approval; if a pre-market study was needed, then the product should not be approved. Another panel member asked "can we be at a point in discussing conditions if we haven't decided approval or disapproval?" and was told by the panel chair, Dr. Kenneth Noller "Yes, that's what we do." At that point, two panel members suggested that Dr. Janik propose the study as a post-market study instead of a pre-market study, which Dr. Janik declined to do. Dr. Janik subsequently voted against approval, but the product was recommended with seven conditions of approval, on an 8-5 vote.

The advisory panel members recommended conditions that they considered essential for approval. However, the only one of those seven conditions of approval that was specified in the FDA's letter to the company was a post-approval 3-year study, which would include more African-American women.[37] African-American women are at much greater risk of uterine fibroids than white women, but the product — used for the treatment of uterine fibroids — was approved despite African-American women being "under-represented in the pivotal study."[vi]

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The panel agreed to 14 often very technical conditions of approval, but most of those conditions were not imposed on the company in the letter of approval. Instead, the FDA informed the company that they must register all patients.

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Although advisory panels often spend considerable time voting on conditions of approval in an effort to provide essential safeguards, an analysis of the final FDA approval letters indicate that most conditions of approval specified by advisory panels were not imposed on the companies.[vii] Another example of what happens to these conditions is the approval decision regarding CrystaLens®, the implantable intraocular lens that was recommended for approval with 14 conditions at a May 2003 Ophthalmic Devices Advisory Panel meeting. The FDA meeting transcript indicates that the panel agreed to 14 often very technical conditions of approval, but most of those conditions were not imposed on the company in the letter of approval. Instead, the FDA informed the company that they must register all patients "in a data base to be maintained indefinitely, or until the applicant is otherwise notified."[38] The FDA also specified that any "warranty statements must be truthful, accurate, and not misleading."

The data suggest that most conditions recommended by advisory panels are not included in the final FDA decision. A separate issue is whether the conditions are enforced. That will be dicussed in the next section of this report.

In addition to changing and deleting many of the recommended conditions of approval, the FDA can make approval decisions that are different from the recommendations of their advisory committees. For the new medical products or new indications reviewed by advisory committees from 1998 through 2005, 79% were recommended for approval, and even more — at least 84% — of all those reviewed were approved by the FDA. The percentage of approvals is even higher than the percentage recommended for approval because while 96% of those recommended for approval were subsequently approved, 39% of those that were not recommended were approved anyway. The chance of a "non-approval recommendation" being overturned by the FDA in favor of approval was 36% for drugs and 43% for devices. In fact, the FDA was 10 times more likely to approve drugs and devices that were recommended for non-approval than they were to reject drugs and devices that were recommended for approval. These numbers are underestimates because there are medical products that were reviewed in this study that may yet be approved by the FDA, particularly those reviewed in 2005.

[vi] If the health of African-American women was considered important, these women should have been studied more carefully before the product was approved.

[vii] The specific conditions of approval are included in the letter to the company. A "Conditions of Approval" document accompanies the letter; that document includes general instructions about post-approval reports and adverse reaction and device defect reporting, as well as the need for a PMA supplement if the company makes substantial changes to the product.

Overall, the findings suggest that when the FDA schedules most of its advisory committee meetings, the outcome is almost certainly going to be FDA approval for the product under review. The outcome is less certain for drugs than devices, and much less certain for some committees than others.

There is no doubt that FDA advisory committee meetings focus not only on an up or down vote for approval, but also on the labeling and other conditions of approval, such as delineating post-market research and surveillance. However, if these conditions are a primary purpose of the advisory committee meetings, it is surprising that the conditions are so frequently omitted or drastically revised in the final approval decisions.

Are the conditions of approval that the panels recommend feasible and enforceable? FDA officials rarely provide information during the meeting about the limitations of FDA authority to mandate certain types of restrictions or to enforce post-market research or surveillance. As a result, the conditions of approval may be unrealistic.

On the other hand, even when the FDA reduced the conditions to ones they considered essential and enforceable during the eight years of our study, the FDA often failed to monitor or enforce those conditions. Scientists at FDA's Center for Devices and Radiological Health could not find information on most (58%) of the Condition of Approval Studies required as part of the PMAs approved between 1998 and 2000.[39] FDA's record for enforcing post-market drug commitments is similarly lax. According to a report released by the FDA in March 2006, drug companies had failed to initiate 65% of required post-market study commitments.[40] Only 14% of open post-market study commitments had been submitted.

Numerous official documents and quotations by FDA officials praise the advisory committee process as an objective, scientific review by independent, outside experts who are reviewing the most controversial and cutting edge medical products to determine whether they should be approved, and if so, under what conditions. Based on the FDA's official description, the advisory committee meetings are viewed as an important part of the process and committee recommendations are assumed to be influential, with media reminding readers that 'the FDA does not have to follow the recommendations of their advisory committees, but they do so 90% of the time.'[41]

The results of this study contradict that public image for many of the committees. While it is impossible to say what percentage of drugs and devices would be recommended for approval under ideal conditions with careful scientific scrutiny, the findings of this report are worrisome. The percentage of approval recommendations is very high, the percentage of unanimous approvals is very high, and advisory committee members are regularly admitting that they are voting for approval despite serious misgivings about safety or efficacy. Many committees are relying on post-market studies when they consider the pre-market studies inadequate, but the post-market track record is very poor for drugs and devices.

The drug advisory committees have less extreme records of recommending approval than the device advisory panels. Although all drug advisory committees recommended approval at least half the time, only two recommended approval more than two-thirds of the time. However, those two committees, reviewing antiviral drugs and arthritis drugs, reviewed most of the new drugs from 1998-2005 for the six committees studied.

In contrast, all medical device panels recommended approval at least two-thirds of the time, and four of the five recommended approval at least three-quarters of the time, frequently unanimously.

For several of the committees in this study, the vast majority of prescription drugs and medical devices will be approved, apparently regardless of the concerns of committee members. The conditions of approval that are recommended will rarely be imposed. Moreover, although the FDA follows advisory committees' recommendations for approval more than 90% of the time, they are much less likely to follow recommendations for non-approval. This suggests that advisory committee votes for approval reflect pressure for approval coming from the FDA. It seems likely that for many of these advisory committees, staff time and resources could be better spent on a better advisory committee process.

Conflicts of Interest and Biased Experts

There are many possible reasons why the current advisory committees recommend approval most of the time, even when members have substantial concerns about safety or efficacy. The possible explanation that has attracted the most attention in recent years — in the media, in Congress, and among consumer advocates — is the existence of financial conflicts of interest among FDA committee members. For example, in an analysis of advisory committee meetings that was published in the *Journal of the American Medical Association*, the FDA reported at least one voting committee member with a financial conflict of interest at more than 80% of the meetings that reviewed specific products, and 22% of the conflicts were with the company whose product was under review.[3] Committee members with financial ties to a competitor were even more supportive of approval than those with financial ties to the company making the product. That surprising finding was highlighted by the FDA in a response to the article, claiming that since committee members were voting in favor of competitors' products, the financial conflicts must not be biasing the votes.[42]

The study presented in this report differs from previous FDA advisory committee studies in many important ways; for example, the *USA Today* study and the *JAMA* study analyzed conflicts of interest. Both of those studies analyzed all drug advisory committee meetings for several years, whereas our study analyzed a random sample of drug and device advisory committees for more years but included only new drug or device approvals, and our study analyzed only the votes regarding approval or non-approval, not other votes pertaining to safety, efficacy, or labeling. Equally important, the *JAMA* study excluded from analysis any votes that were unanimous, since it was interested only in explaining voting differences on each committee.

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Commitee members vote 'yes' even if it means changing the wording of the question so that they can do so in good conscience.

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The FDA conducted its own survey to examine the views of advisory committee members and individuals attending 11 advisory committee meetings in 2003.[43] The results were quite favorable about the advisory committee process at the meetings attended, although many respondents expressed concerns about conflicts of interest and most disagreed with the statement "The meetings do not favor certain people or organizations above others." The usefulness of the data are limited, however, because the survey response rate was only 21%. Moreover, 82% of those who participated in the FDA survey stated that they were paid to attend the advisory committee meeting, but the survey results did not specify whether they were paid by the company whose product was under review, by the federal government, or by other sources that might have influenced their views.

Despite the substantial differences in methodology, the information from the previous studies has interesting implications for this report, and vice-versa. Since our findings indicate the tendency for committee members to come to consensus rather than vote their differences, the fact that so many committee members have financial ties to the companies involved could have an enormous impact, disproportionate to the specific numbers of committee members with such conflicts. In fact, just one or two committee members whose votes are influenced by their financial ties could easily influence the recommendations of their entire committee, even resulting in unanimous recommendations for approval. This would be especially likely if the person with the financial ties were to be very active in the committee discussion, since there is often considerable agreement in the discussions. It would be even more influential if an individual with financial ties to the company made the motion for approval, since unanimity follows those first votes most of the time, especially for medical devices.

Peer Pressure?

This study includes quotations from committee members whose votes seem inconsistent with their concerns about the safety or efficacy of the drug or medical device under review. These quotations are not representative of the entire discussion, but they clearly illustrate the pressures that committee members describe to conform to their colleagues or to be able to vote 'yes' even if it means changing the wording of the question so that they can do so in good conscience. Their candor suggests that they would welcome guidance from FDA officials to make sure their recommendations are appropriate.

We also found examples where committee members directly tried to influence the views of votes of other committee members. One especially telling example is when a committee member wanted the panel to require an additional study be completed before approval was granted, to make sure the product was effective. She was then urged by other committee members to instead ask that the study be recommended as a post-market study. That compromise would enable panel members to vote for approval and also ask for the study, but with no guarantee that the study would be conducted and the results would indicate that the product was effective. The explicit pressure to change her mind is an example of how the process pushes toward the most common endpoint: approval with conditions.

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If FDA officials are unhappy with the overwhelming approval pattern of these committee votes, or the conditions that are recommended, they are doing very little about it.

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Most members of FDA committees serve for several years and are sometimes invited to temporarily serve on other committees as well, while other individuals are repeatedly invited to serve as consultants with temporary voting privileges. Based on those patterns of individuals participating on several committees, FDA officials who decide whom to invite often know in advance (or could easily find out) if those committee members tend to vote for or against approval. It is therefore possible that many committees are "stacked decks," with approval virtually inevitable. It is not possible to tell from this study whether "stacked deck" committees that always vote for approval were intentionally selected to achieve that outcome, or if that outcome was not intentional. However, a 2006 survey of FDA scientists by the Union of Concerned Scientists (USC) reported that such manipulation was sometimes intentional.[44]

FDA Advice: Part of the Solution or Part of the Problem?

The UCS 2006 survey of FDA scientists and an internal FDA survey quoted by UCS suggest that there is pressure within the agency to stifle risk information and to approve new medical products despite safety concerns. Such pressures could influence the advisory committee recommendations, since the committees depend on the FDA scientists for objective analyses of the data. The wording of the questions that FDA prepares for committee members to vote on also influences whether the votes will support approval or not. Certainly, there is no indication that FDA officials are unhappy with the overwhelming approval patterns of most of these committee votes, or the conditions that are recommended. In fact, committees that vote for approval the greatest percentage of the time tend to meet more often than committees where the votes are less likely to be for approval.

The transcripts indicate that when committee members expressed their intention to vote for approval despite lack of safety or efficacy data, FDA officials did not urge committee members to make careful recommendations based on research evidence. An FDA official might read rather lengthy boiler-plate instructions that include the definitions of safety and effectiveness, but FDA officials almost never respond to drug or device committee members' often lax interpretations of approval criteria. An FDA official's one clear reminder that committee members should vote for approval only if a product was safe and effective, at an Arthritis Drugs Advisory Committee meeting in 2001 that was quoted earlier in this report, stands out because it is so unusual. Moreover, an Internet search on the FDA Web site indicates that the FDA staff involved, Dr. Jay Siegel, has not participated in any FDA advisory committee meetings to review new medical products or new indications since that 2001 meeting.

Perhaps FDA officials generally avoid such comments because they do not want to unduly influence the advisory committee, which is intended to be an independent voice in the FDA approval process. If that is the reason for their silence, however, it is misguided. As shown in the section of this report quoting committee members, many are quite outspoken about their concerns and about their interpretation of the criteria for approval being less than clear evidence of safety or effectiveness. All committee meetings include FDA staff at the dais with the committee members, with numerous FDA officials in the audience as well. When committee members express their willingness to vote for approval despite strong concerns about whether the product is safe or effective, their comments are generally met with silence from FDA staff and officials. This is likely to be interpreted as FDA agreement with their statements.

The pro forma recitation of boiler-plate instructions does not seem to provide useful guidance for FDA committee members during the course of their deliberations. Moreover, the silence of FDA staff and officials when committee members indicate their intention to vote in ways that are inconsistent with their stated views, sends the message that whatever assumptions the committee members express about the decision-making process are correct. Similarly, the conditions of approval that are discussed and voted on during committee meetings attract very little guidance from FDA officials who are at the dais or in the room. Committee members propose conditions that in some cases would not be seriously considered by the FDA, or could not be enforced by the FDA, but the proposed conditions receive little feedback from the agency while these discussions and votes are underway. Instead, FDA officials simply do not impose most of them when final decisions are made.

Overall, FDA officials showed remarkably little interest in providing guidance to advisory committee members during the eight years of committee meetings analyzed in this report. Certainly this gives the impression that FDA officials are satisfied with the current process, one where committee members intentionally or unintentionally move toward a consensus that often seems inconsistent with their differing views or perspectives in making decisions that may have life-or-death consequences for millions of Americans.

Regardless of the reasons, many of FDA's advisory committees seem destined to recommend approval almost every time they meet. Moreover, even when a very strong majority recommends "non-approval," FDA officials may approve the product anyway.

In recent years, this pattern of approving medical products in spite of serious concerns has resulted in a large number of well-publicized cases when FDA-approved products were found to have high risks of death and serious injury. Whether the products are voluntarily or forcibly removed from the market or temporarily recalled, these situations undermine the credibility of the FDA and the trust of the American public. If the FDA wants to restore confidence in the FDA and restore the independence that FDA advisory committees were intended to provide, it is essential that the FDA make changes in the policies and process governing their advisory committees. The following recommendations are based on the assumption that the Congress and the FDA are committed to that end.

1. **The FDA should stop granting conflict-of-interest waivers for committee members, except under very restricted conditions**.

Research on conflicts of interest among FDA advisory committee members has focused on the votes of members with conflicts of interest. As long as voting members with conflicts of interest did not outnumber the other voting members, it was assumed that the conflicts did not matter. However, the findings in this report clearly show that one or more members on each advisory committee can easily sway the entire committee's vote.

Committee members with financial conflicts of interest may have more expertise regarding a new medical product, but research indicates that they are also more likely to be more supportive of FDA approval. Their expertise is likely to also make them more outspoken, leaders on the committee rather than followers. The role of committee members with financial ties to the product is illustrated by the Arthritis Drugs Advisory Committee, which has included many members with financial ties to the products under review, and also shows an overwhelming pattern of voting in favor of approval of almost every medication that comes before it. For example, even after numerous reports of deaths linked to Vioxx®, many committee members continued to defend its use despite the availability of many safer, less expensive alternatives.[45]

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Many of FDA's advisory committees seem destined to recommend approval almost every time they meet. Moreover, even when a very strong majority recommend "non-approval," FDA officials may approve the product anyway.

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In July 2006, the FDA announced its intention to improve its advisory panel process by making information about conflicts of interest more transparent. Although transparency is useful, there is no evidence that transparency would reduce the likelihood of biased advisory panel members influencing FDA approval decisions. If panel members are aware, for example, that a colleague on the panel has served as a generously paid consultant to the company whose product is under consideration, that might make them more skeptical of the consultant/committee member's comments. However, it would be unlikely to have much impact on the consultant/committee member's influence on voting, given the collegial atmosphere of advisory committee deliberations. The study findings indicate that if the consultant/committee member is very enthusiastic about a product, that enthusiasm will be contagious, and if he or she is the first to recommend approval, the product would likely be recommended for approval, probably unanimously.

2. **The FDA should provide explicit and specific oral guidance whenever needed during advisory committees meetings appropriate regarding criteria for safety and effectiveness, and appropriate criteria for conditions of approval.**

The Center for Devices and Radiological Health requires only a "reasonable assurance" of safety and efficacy rather than proof, and panel members interpret this to mean that neither safety nor effectiveness is required. In recent years, FDA safety criteria regarding drugs and devices have increasingly emphasized the need to manage risk, rather than a more traditional concept of safety.[46] The message has been heard loud and clear by committee members, some of whom explicitly indicate that they believe the FDA standard for approval does not require a product to be proven either safe or effective. The widely shared acknowledgement that all products have adverse reactions for some individuals under some circumstances has been used to justify ignoring concerns about potentially serious risks for large numbers of patients. This seems to be especially true for committees that virtually always vote for approval despite strong concerns. Meanwhile, advisory committee members often support approval on the condition of post-market research and surveillance, apparently not informed that FDA officials have acknowledged that the FDA officials to review and analyze adverse reaction reports in a timely manner [47] and that required post-market studies are not monitored by FDA and are rarely completed.[39, 40]

3. The FDA should expect more from advisory committee members, and then be more responsive to their concerns.

The FDA should rely on the advisory committees for impressive expertise and sound advice. Their votes for or against approval should be discriminating and their recommendations about labeling and conditions of approval should be credible, useful, and enforceable. Based on the data in this study, the voting by some advisory committees does not appear to be sufficiently discriminating, and yet the few products that are not recommended for approval are often approved by the FDA anyway. The recommended conditions of approval are often not imposed. This suggests that the advisory committees are not providing advice that is being well-used by the FDA. However, the study results do not indicate whether the FDA is satisfied with the status quo, where advisory committee votes can be used to justify approval decisions, and members' concerns are frequently ignored.

Serving on FDA advisory committees is an honor and privilege. FDA should expect members to be well prepared at the meetings, and to have carefully reviewed the data and materials before the meeting. If it is necessary to provide more generous honoraria to ensure that, the FDA should do so. If scientific scrutiny is the goal, the FDA needs to do a better job of emphasizing the importance of careful review of data. The process needs to be changed so that committee members are encouraged to ask FDA staff for assistance in understanding data before or during an advisory committee meeting. If committee members lack the expertise to understand statistical analyses, training should be offered to help with that prior to the meetings. In addition, FDA should provide training or guidance regarding the limitations of conditions of approval, particularly those involving labeling and post-market surveillance and data collection and analysis.

A review of meeting transcripts makes it clear that many committees include members who are not fully participating. When it is obvious that certain panel members are not familiar with the materials that they were supposed to have reviewed, did not understand the essential findings, or are not fully engaged in the meeting presentations or discussions, the FDA should terminate their participation in that meeting or future committee meetings.

At the same time, the FDA should provide comprehensive, accurate information about the shortcomings of the research for the product under consideration and the questions raised by FDA scientists reviewing the data. The FDA written memorandum provided to advisory committee members should include a candid assessment of safety and effectiveness that accurately reflects the views of FDA scientists. These views should also be explicitly articulated as part of FDA's oral presentation at the meetings. If essential scientific issues are not raised during committee discussions, FDA scientists or officials at the meeting should raise them in the form of questions or reminders to committee members.

If implemented, these recommendations would result in more objective scientific scrutiny by advisory committee members, an atmosphere that emphasizes careful, research-based deliberation, and committee recommendations that truly provide credible, independent expertise and advice for the benefit of the American public.

FOOTNOTES

FDA Advisory Committees: Does Approval Mean Safety?

[1] Getting Outside Advice for 'Close Calls", January 1995 FDA Consumer special report. http://www.fda.gov/fdac/special/newdrug/advice.html Accessed August 14, 2006

[2] Advisory Committees: Critical to the FDA's Product Review Process, *FDA Consumer,* January-February 2004, FDA 04-1334C http://www.fda.gov/fdac/special/testtubetopatient/advisory.html

[3] Lurie P, Almeida CM, Stine N, Stine A.R. & Wolfe, S.M. Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings, *Journal of the American Medical Association*. 2006, 295: 1921-1928.

[4] Newburger, AE. Cosmetic Medical Devices and Their FDA Regulation, *Archives in Dermatology* 2006: *142*: 225-228.

[5] Sherman, LA. Looking Through a Window of the Food and Drug Administration: FDA's Advisory Committee System, *Preclinica*. Volume 2, No. 2 March/April 2004 http://www.preclinica.com/pdf/articles/sherman_2-2.pdf

[6] Cauchon D. FDA Advisers Tied To Industry. *USA Today*, September 25, 2000, pg 1A.

[7] FDA Inspection Report of Bausch & Lomb, Inc. Available at http://www.fda.gov/ora/frequent/483s/1032500_baushlomb/baush_lomb_483.pdf, accessed August 15, 2006

[8] FDA Arthritis Drug Advisory Committee Meeting Transcript, August 7, 1998, pg 231. Available at http://www.fda.gov/ohrms/dockets/ac/cder98t.htm, accessed November 29, 2005

[9] FDA Arthritis Drug Advisory Committee Meeting Transcript, March 5, 2003, pgs 417-418. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3930T2.pdf, accessed August 10, 2006

[10] FDA Consumer Information Sheet: Leflunomide (marketed as Arava), http://www.fda.gov/cder/consumerinfo/druginfo/Arava.HTM, accessed August 8, 2006

[11] FDA Arthritis Drug Advisory Committee Meeting Transcript, August 16, 2001, pgs 190-191. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3779t1.pdf, accessed August 14, 2006

[12] FDA Arthritis Drug Advisory Committee Meeting Transcript, April 11, 2000, pg 162-164 Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3608t1b.pdf, accessed August 16, 2006.

[13] FDA Antiviral Drugs Advisory Committee Meeting Transcript, January 14 1998, pg 241. Available at http://www.fda.gov/ohrms/dockets/ac/cder98t.htm, accessed November 29, 2005

[14] FDA Antiviral Drugs Advisory Committee Meeting Transcript, July 27, 1999, pg 265. Available at http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3529t1c.pdf, accessed August 8, 2006

[15] FDA Antiviral Drugs Advisory Committee Meeting Transcript, February 27, 2001, pg166. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3731t1_02.pdf, accessed August 14, 2006

[16] FDA Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Transcript, March 17, 2003, pg 245. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3929T1.pdf, accessed August 8, 2006

[17] Letter from Suzanne Berkman, Regulatory Review Officer at the FDA, November 2, 2005. Available at http://www.wlf.org/upload/DDMwrnVitrase.pdf

[18] FDA Gastrointestinal Drugs Advisory Committee Meeting Transcript, June 27, 2000, pg 214. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3627t2c.pdf, accessed August 8, 2006

[19] FDA Gastrointestinal Drugs Advisory Committee Meeting Transcript, March 6, 2003, pg 243. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3928T1.pdf, accessed August 8, 2006

[20] FDA Pulmonary-Allergy Drug Products Advisory Committee Meeting Transcript, September 5, 2003, pg 216. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3976T1.pdf , accessed August 4, 2006

[21] FDA Reproductive Drugs Advisory Committee Meeting Transcript, April 10, 2000 pgs 193-194. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3602t1b.pdf, accessed August 8, 2006

[22] FDA Reproductive Drugs Advisory Committee Meeting Transcript, April 10, 2000, pgs 221-223. Available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3602t1c.pdf, accessed August 8, 2006

[23] FDA Ophthalmic Devices Panel Meeting Transcript, January 17, 2002, pg 31. Available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3833t1_01.pdf, accessed August 4, 2006

[24] FDA Ophthalmic Devices Panel Meeting Transcript, May 23, 2003, pg 255. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3953t1.doc, accessed August 4, 2006

[25] FDA Ophthalmic Devices Panel Meeting Transcript, October 3, 2003, pgs 428-430. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3991t1-05.pdf, accessed August 4, 2006

[26] FDA Ophthalmic Devices Panel Meeting Transcript, November 30, 2001, pgs 218-219. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3806t1_03_Afternoon_Session.pdf, accessed August 4, 2006

[27] FDA Ophthalmic Devices Panel Meeting Transcript, February 5, 2004, pg 351. Available at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/Pages%20from%204023t1-04.pdf, accessed August 4, 2006

[28] FDA Ophthalmic Devices Panel Meeting Transcript, February 13, 1998, pgs 169-170. Available at http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3379t2.pdf, accessed August 4, 2006

[29] FDA Radiological Devices Panel Meeting, December 2, 2002, page 278. Available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3918t1-03.pdf , accessed August 21, 2006

[30] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, January 29, 2001, pg 207. Available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3686t1_03.pdf, accessed August 8, 2006

[31] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 10, 2003, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3963t2.htm accessed August 8, 2006

[32] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 3, 2005, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4150t1.htm, accessed August 8, 2006

[33] FDA Immunology Devices Panel Meeting Transcript, July 15, 2005, page number not available. Available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4163t1.htm, accessed August 8, 2006

[34] FDA Microbiology Devices Panel Meeting Transcript, March 8, 2002, pgs 251-257. Available at http://www.fda.gov/ohrms/dockets/ac/02/Transcripts/3846t2_03.pdf, accessed August 4, 2006

[35] Shorto, R. "Contra-Contraception", *The New York Times*. May 7, 2006, Section 6; Column 1; Magazine; pg 48.

[36] FDA Obstetrics and Gynecology Devices Panel Meeting Transcript, June 3, 2004, pgs 331-332. Available at http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4046t1_04.pdf accessed August 17, 2006

[37] Letter from Donna-Bea Tillman, PhD, Director of Device Evaluation, FDA, to Robert Newman, InSightec – North America, October 22, 2004. Available at http://www.fda.gov/cdrh/pdf4/P040003a.pdf

[38] Letter from Daniel Schultz, MD, Director of the Office of Device Evaluation, FDA, to Paul Kramsky, eyeonics, inc, November 14, 2003. Available at http://www.fda.gov/ohrms/dockets/dailys/04/jan04/011304/04m-0012-aav0001-02-approval-order-vol1.pdf

[39] Brown SL, Bezabeh S, Duggirala HJ, Center for Devices and Radiological Health, Condition of Approval Studies As a Postmarket Tool for PMA Approved Cohort 1998-2000 Final Report, March 18, 2005

[40] Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies, *Federal Register*, Vol. 71, No. 42, March 3, 2006, page 10979.

[41] Dembner, Alice. "US keeps limits on implants". *Boston Globe*, January 9, 2004, http://www.boston.com/news/nation/articles/2004/01/09/us_keeps_limits_on_implants/

[42] "Comment on Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings", http://www.fda.gov/oc/advisory/analysis.html

[43] McComas, KA and Sherman LA, "Conflicts of Interest and FDA Advisory Committee Meetings: A Study of Public Attitudes and Opinions" http://www.fda.gov/oc/advisory/acstudy0904/JIFSANresearch.html

[44] Union of Concerned Scientists FDA Survey: Essay Responses. Available at http://www.ucsusa.org/scientific_integrity/interference/fda-scientists-survey-summary.html,
accessed on August 18, 2006.

[45] Berenson, A. and Harris, G. "10 Voters on Panel Backing Pain Pills Had Industry Ties". *The New York Times*, February 25, 2005, http://www.nytimes.com/2005/02/25/politics/25fda.html?ei=5088&en=ad0fd8db4df113e0&ex=1267074000&adxnnl=0&partner=rssnyt&adxnnlx=1155745825-kF+05zqs05ShxqiF5cqJDA&pagewanted=all&position=

[46] See, for example CDER/CBER Risk Management Public Workshop, April 9-11, 2003, http://www.fda.gov/cder/meeting/riskManagement.htm, accessed August 19, 2006

[47] FDA Presentation to Consumer Groups, Washington D.C., on May 23, 2006

APPENDIX A

Center for Devices and Radiological Health Advisory Panel Process [1]

When considering new medical devices for market approval, the Food and Drug Administration (FDA) refers to an outside panel of experts, or an advisory committee, to review the safety and effectiveness of the product(s). The pre-market application (PMA) of the product, which outlines the product's description, intended use, and any clinical research on its safety, is reviewed during a public meeting. Then the advisory panel must submit a final report to the FDA that includes the committee's recommendation and the basis for such recommendation on the PMA.

Within 180 days of the date of filing of the PMA, the FDA will complete its review of the PMA and of the advisory committee's report and recommendation, and then the FDA submits its final decision. When none of the reasons that would deny its approval apply, the PMA receives an approval order. The FDA's approval announcement and summary of the product's safety and effectiveness are then made available to the public on its Web site, and any adverse effects of the device on human health are listed.

The FDA might instead issue an "approvable" letter to the applicant, which describes the information that the FDA requires to be provided or the conditions that the applicant is required to meet in order to obtain approval. The "Conditions of Approval" are the standard post-approval conditions imposed by the FDA and are applicable to all original PMAs and PMA supplements. For example, the applicant may have to agree to a post-approval study, restrictions on prescription use, or restrictions on the training of individuals who may use the device before approval. In general, as a condition of approval, the applicant agrees to abide by advertising and final printed labeling requirements and to submit adverse event reports, annual reports, and PMA supplements for changes. The applicant has three choices when met with an approvable letter: to amend the PMA as requested; to consider the decision as a denial of the PMA and to request administrative review; or to withdraw the PMA entirely.

In the event that a PMA does not meet FDA standards, the FDA will administer a "not-approvable" letter to the applicant that describes the deficiencies in the application. In many cases, the FDA is unable to reach an "approvable" decision due to a lack of significant information in the application. This decision informs the applicant what can be improved or changed to make the PMA approvable. Upon receiving the not-approvable letter, the applicant can choose one of the three actions mentioned earlier: to amend the PMA, to request administrative review, or to withdraw it.

Finally, the FDA may issue an order denying approval of a PMA after sending an approvable or not-approvable letter to the applicant. Such a decision is based on several factors. The PMA will not be approved if the application contains a false statement of material fact or if the labeling of the device does not comply with FDA requirements. Also, the PMA will be denied if an essential non-clinical laboratory study was not conducted in compliance with FDA regulations, or also if the safety and rights of human subjects were not adequately protected during testing. Where practical, the denial order also will identify measures required to place the PMA in approvable form, and its contents are made available to the public on the FDA's Web site.

[1] Information from CDRH Device Advice for Industry website. Available at http://www.fda.gov/cdrh/devadvice/pma/review_process.html Accessed August 16, 2006

APPENDIX B

Center for Drug Evaluation and Research Advisory Committee Process

ACTION ON COMMITTEE RECOMMENDATIONS [1]

Advisory committees provide recommendations to the Agency on matters brought before them for consideration, but final decisions on such matters are made by the Agency. Section 505(n)(8) of the Act directs the FDA official responsible for the matter to notify affected persons of the Agency's decisions on advisory committee recommendations within 90 calendar days of the committee recommendation. As used in this guidance with respect to the clinical investigation of a drug or the approval for marketing of a drug, the FDA official responsible for the matter (i.e., the primary Agency decision maker) is the individual (generally a Division Director or Office Director) who has the authority to approve the application (see CDER MAPP 4634.1, CBER SOP 8405). To maintain consistency with FDA disclosure of information regulations (e.g., 21CFR Part 20 and §§ 312.130 and 314.430), "affected persons" with respect to advisory committee recommendations means the sponsors of clinical investigations and/or applicants for FDA approval of drug products on which an advisory committee has provided advice.

To implement this provision, the primary Agency decision maker should, within 90 calendar days of the committee recommendation, review the committee's recommendation and notify the affected persons of the status of FDA's decision on the matter. If no decision has been reached within this time frame, the primary Agency decision maker should notify the affected persons and indicate the reasons for no decision. The rationale for decisions and reasons for no decisions should be documented.

[1] Copied verbatim from Guidance for Industry, Advisory Committees: Implementing Section 120 of the Food and Drug Administration Modernization Act of 1997. October 1998

Drug Panels Votes Summary, 1998-2005

	Entire Panel						Votes by individual panel members		
Panel	Total panel votes on APPROVAL of NDA's	Total Panel Votes For APPROVAL of Drug	# of Unanimous votes	Panel votes for APPROVAL that were unanimous	% of Panel Votes for APPROVAL	% of ALL votes that were unanimous for APPROVAL	Total votes by panel members	Total votes for APPROVAL	% of all panel votes for APPROVAL
Antiviral Drugs	18	15	12	11	83%	61%	215	172	80%
Arthritis Drugs	9	9	8	8	100%	89%	83	81	98%
Dermatologic and Ophthalmic Drugs	8	5	2	2	63%	25%	69	40	58%
Gastrointestinal Drugs	6	4	2	2	67%	33%	62	43	69%
Pulmonary and Allergy Drugs	5	3	2	2	60%	40%	58	40	69%
Reproductive Health Drugs	4	2	1	0	50%	0%	40	20	50%
TOTAL	50	38	27	25	76%	50%	527	396	75%

Antiviral Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	10	11
Meeting Date	1/14/98	5/5/98	5/6/98	10/6/98	11/2/98	2/24/99	7/27/99	1/10/01	2/27/01	10/3/01	10/4/01
Product	CellCept	Priftin	Cryptaz	Epivir-HBV	Ziagen	Relenza	Rapamune	Cancidas	Valganciclovir	Viread	Vfend
Sponsor	Syntex	Hoechst Marion Roussel	Unimed	Glaxo Wellcome	Glaxo Wellcome	Glaxo Wellcome	Wyeth-Ayerst	Merck	Syntex	Gilead Sciences	Pfizer
Unanimous ?	Yes	No	No	Yes	No (7-2)	No	Yes	Yes	No	Yes	Yes
Approval? (Y-N-A)*	Yes (9-0)	Yes (10-1)	No (1-8)	Yes (6-0)	Yes (7-2)	No (4-13)	Yes (11-0)	Yes (8-0)	Yes (11-1)	Yes (12-0-2)	Yes (10-0)
TOTAL											
	Total	# Unanimous	% Unanimous								
Voting Sessions	18	12	67%								
For Approval	15	11	73%								
For Non-approval	3	1	33%								

*Votes are represented by (Yes-No-Abstain)
All votes FOR approval are counted as "yes"
All votes AGAINST approval are counted as "no"

**Abstentions are not counted

12	13	14	15	16	17	18
3/19/02	8/6/02	11/14/02	5/13/03	5/14/03	3/11/05	5/19/05
Pleconaril	Adefovir dipivoxil	Pagasays/ Copegus	Reyataz	Valtrex	Entecavir	Tipranavir
ViroPharma	Gilead Sciences	Hoffman-LaRoche	Bristol-Myers Squibb	GlaxoSmith Kline	Bristol-Myers Squibb	Boehringer Ingelheim
Yes	Yes	Yes	Yes	Yes	YES	No
No (0-15)	Yes (15-0)	Yes (12-0)	Yes (15-0)	Yes (13-0)	Yes (18-0)	Yes (10-3)
				TOTAL VOTES**	FOR Approval	%
				215	172	80%

Arthritis Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	
Meeting Date	08/07/98	09/16/98	12/01/98	04/20/99	07/12/00	08/16/01	03/05/03	06/25/03	09/06/05	
Product	Arava	Enbrel	Celebrex	Vioxx	Remicade	Kineret	Arava	Enbrel	Abatacept	
Sponsor	Hoechst Marion Roussell	Immunex	Searle	Merck	Centocor	Amgen	Aventis	Amgen	Bristol-Meyers Squibb	
Unanimous?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	
Approval? (Y-N-A)*	Yes (10-0) (for two indications)	Yes (17-0)	Yes (9-0)	Yes (8-0)	Yes (8-0)	Yes (6-2-1)	Yes (10-0)	Yes (6-0)	Yes (7-0)	
TOTAL										
	Total	# unanimous	% unanimous					TOTAL VOTES**	FOR Approval**	% Approval
Voting Sessions	9	8	89%					69	67	97%
For Approval	9	8	89%							
For Non-approval	0	0	0%							
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"										
**Abstentions are not counted										

Dermatologic and Ophthalmic Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6	7	8	
Meeting Date	07/21/99	11/04/99	05/23/02	03/17/03	09/09/03	09/10/03	07/12/04	08/27/04	
Product	Cyclosporine	Loprox	Amevive	Vitrase	Raptiva	Methyl Aminole-vulinate	Tazoral	Macugen	
Manufacturer	Allergan	Hoescht Marion Roussel	Biogen	ISTA Pharm.	Genentech	PhotoCure ASA	Allergan	Eyetech	
Unanimous?	No	No	No	No	Yes	No	No	Yes	
Approval? (Y-N-A)*	No (1-5-1)	Yes (9-3)	Yes (8-2-1)	Yes (7-5)†	Yes (11-0)	No (2-9)	No (3-8-4)	Yes (8-0)	
							TOTAL VOTES**	FOR Approval**	% Approval
TOTAL							69	40	58%
	Total	# unanimous	% unanimous						
Voting Sessions	8	2	25%						
For Approval	5	2	40%						
For Non-approval	3	0	0%						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"									
**Abstentions are not counted									
† Earlier question: Has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage? NO (4-8) # committee members vote to approve, although they did not believe there was evidence of efficacy (Chew, Feman, Steidl)									

Gastrointestinal Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	6			
Meeting Date	05/28/98	11/16/99	06/26/00	04/23/02	06/25/03	07/14/04			
Product	Avakine	Lotronex	Zelmac	Lotronex	Serostim	Zelnorm			
Sponsor	Centocor	Glaxo Wellcome	Novartis	GlaxoSmith Kline	Serono	Novartis			
Unanimous?	Yes	Yes	No	No	No	No			
Approval? (Y-N-A)*	Yes (9-0)	Yes (6-0)	No (1-6)	Yes (14-4)	No (3-6)	Yes (10-3)			
						TOTAL VOTES**	FOR Approval**	% Approval	
						62	43	69%	
TOTAL									
	Total	# Unanimous	% Unanimous						
Voting Sessions	6	2	33%						
For Approval	4	2	50%						
For Non-approval	2	0	0%						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"									
**Abstentions are not counted									

Pulmonary and Allergy Drugs Advisory Committee Votes, 1998-2005

	1	2	3	4	5	
Meeting Date	11/23/99	09/06/02	05/15/03	09/05/03	06/06/05	
Product	Advair Diskus	Spiriva	Xolair	Ariflo	Pulminiq	
Sponsor	Glaxo Wellcome	Boehringer-Ingelheim	Genetech	GlaxoSmithKline	Chiron Corp	
Unanimous?	Yes	No	Yes	No	No	
Approval? (Y-N-A)*	Yes (10-0)	Yes (8-3)	Yes (11-0)	No (3-7)	Tie vote (8-8)	
				TOTAL VOTES**	FOR Approval**	% Approval
TOTAL				58	40	69%
	Total	# Unanimous		% Unanimous		
Voting Sessions	5	2		40%		
For Approval	3	2		67%		
For Non-approval	1	0		n/a		
Tie approval vote	1	n/a		n/a		
†Voting Committee consultant June 6, 2005 meeting						

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"

**Abstentions are not counted

Reproductive Health Drugs Advisory Committee Votes, 1998-2005

	1	2		3			
Meeting Date	04/20/98	04/10/00		12/02/04			
Product	Antocin	Uprima		Intrinsa			
Sponsor	RW Johnson	Tab Holdings		Procter & Gamble			
Unanimous?	No	No	No	Yes			
Approval? (Y-N-A)*	No (1-10-1)	Yes (10-2)	Yes (10-2)	No (0-16)			
Notes	Show of hands	(for 2 mg dose)	(for 4 mg dose)		**Votes by Individual Panel Members**		
					TOTAL VOTES**	FOR Approval**	% Approval
TOTAL					40	20	50%
	Total	# unanimous	%				
Voting Sessions	4	1	25%				
For Approval	2	0	0%				
For Non-approval	2	1	50%				
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no"							
**For Individual Member Votes, only roll call votes are counted and abstentions are not counted							

Devices Panels Votes Summary, 1998-2005

	Votes by Panel						Votes by Individual Panel Members		
Panel	Total panel votes on PMA's	Total Panel Votes For APPROVAL* of Device	# of Unanimous votes	Panel votes for APPROVAL* that were unanimous	% of Panel Votes for APPROVAL	% of ALL votes that were unanimous for APPROVAL	Total votes by panel members**	Total votes for APPROVAL	% of all panel votes for APPROVAL
Immunology Devices	4	3	3	3	75%	75%	29	24	83%
Microbiology Devices	3	2	2	1	67%	33%	21	12	57%
Obstetrics And Gynecology Devices	9	7	5	5	78%	56%	87	66	76%
Ophthalmic Devices	16	14	10	9	88%	56%	157	129	82%
Radiological Devices	7	6	6	6	86%	86%	45	41	91%
TOTAL	39	32	26	24	82%	62%	339	272	80%
* for approval & approval with conditions									
** does not count abstentions									

Immunology Devices Panel Votes, 1998-2005

	1	2	3	4			
Meeting Date	2/2/98	9/4/98	11/9/98	7/15/05			
Product	Free PSA Assay	HercepTest	FISH HER-2/neu gene	AlzheimAlert NTP Test			
Manufacturer	Hybritech	DAKO	Vysis	Nymox			
Motion	A + C	A + C	A + C	Not approvable			
Unanimous	Yes	Yes	Yes	No			
Approved? (Y – N – A)*	Yes (7-0)	Yes (6-0)	Yes (9-0)	No (2-5)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL					29	24	83%
	Total	#Unanimous	%Unanimous				
Voting Sessions	4	3	75%				
For Approval	0	0	--				
For Non-Approval	1	0	--				
For Approval + Conditions	3	3	100%				
†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval							
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no." When there are no abstentions, votes are counted (Y-N).							
**Abstentions are not counted							
A + C refers to Approval with Conditions							

Microbiology Devices Panel Votes, 1998-2005

	1	2	3			
Meeting Date	10/12/01	11/11/01	3/8/02			
Product	QuantiFERON-TB	Endotoxin Activity Assay	Supplement to HPV			
Manufacturer	Cellestis Limited	Sepsis, Inc.	Digene Corp.			
Motion □	A + C	Not Approvable	A + C			
Unanimous?	Yes	Yes	No			
Approved? (Y-N-A)*	Yes (6-0)	No (0-7)	Yes (6-2)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL				**21**	**12**	**57%**
	Total	# unanimous	% unanimous			
Voting Sessions	3	2	67%			
For Approval	0	0	--			
For Non-approval	1	1	100%			
For Approval + Conditions	2	1	50%			
†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval						
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)						
**Abstentions are not counted						
□A + C refers to Approval with Conditions						

Obstetrics and Gynecological Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	
Meeting Date	10/20/98	1/24/00	1/29/01	4/22/02	7/22/02	6/10/03	6/3/04	5/17/05	6/23/05	
Product	Vesta Dub Treatment System	Nellcor N-400	First Option Uterine Cryoblation Therapy System	STANs21 Fetal Heart Monitor	Essure Micro-Insert Device	Microwave Endometrial Ablation System	ExAblate 2000	LUMA Cervical Imaging System	STANs31 Fetal Heart Monitor	
Manufacturer	Valley Lab, Inc	Nellcor Perinatal	CryoGen	Neoventa	Conceptus, Inc	Microsulsis	InSightec	MediSpectra	Neoventa	
Motion □	A+C	A+C	A+C	NA	A+C	A+C	A+C	NA	A+C	
Unanimous	Yes	No	Yes	No	Yes	Yes	No	No	Yes	
Approved? (Y-N-A)*	Yes (6-0)	Yes (10-1)	Yes (9-0)	No (5-6)	Yes** (8-0-1)	Yes (9-0)	Yes (8-5)	No (2-9)	Yes (9-0)	
TOTAL								TOTAL VOTES**	For Approval**	% Approval
								87	66	76%
	Total	# Unanimous	% Unanimous							
Voting Sessions	9	5	56%							
For Approval	0	0								
For Non-approval	2	0	0%							
For Approval + Conditions	7	5	71%							
†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval										
*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)										
**Abstentions are not counted										
□A + C refers to Approval with Conditions										

Ophthalmic Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7	8	9	10
Meeting Date	2/13/98	2/13/98	7/22/99	7/22/99	7/23/99	7/23/99	7/20/01	11/30/01	1/17/02	1/18/02
Product	PMA Scanning laser	Lasik	Thermal keratoplasty	Lasik	IOL	Lasik	Soft Contacts	Keratoplasty	Capsular Tension Ring	CRT Submission
Manufacturer	Autonomous Technologies	Kremer Excimer Laser	Sunrise Technologies	CRS Clinical	Bausch & Lomb	Summit Tech	Ciba Vision	Refractic	Morcher	Paragon Vision
Motion □	A+C	NA	NA	A+C	A+C	A+C	A+C	A+C	A+C	A+C
Unanimous (Y-N-A)*	Yes	No	Yes	Yes	Yes	Yes	Yes	N	No	Yes
Approved?	Yes (6-0)	No (2-4)	No (0-12)	Yes (9-0-2)	Yes (12-0)	Yes (9-0-1)	Yes (10-0)	Yes (9-1)	Yes (8-1-1)	Yes (11-0)
Total										
	Total votes	# Unanimous		% Unanimous						
Voting Sessions	16	10		63%						
For Approval	0	0		0%						
For Non-approval	2	1		50%						
For Approval + Conditions	14	9		64%						

†When a motion is for non-approval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)

**Abstentions are not counted

□ A + C refers to Approval with Conditions

11	12	13	14	15	16
1/18/02	8/1/02	5/23/03	10/3/03	2/5/04	2/6/04
Quadra Lens	Custom-Cornea Myopic L.	CrystaLens	Implantable Contact Lens	ARTISAN Myopia Lens	Supplement 5 for CK System
Paragon Vision	Alcon's Refractive	C&C Vision	STAAR Surgical	OPHTEC USA	Refractec
A+C	A+C	A+C	A+C	A+C	A+C
No	Yes	Yes	No	No	Yes
Yes (10-1)	Yes (9-0)	Yes (7-0)	Yes (8-3)	Yes (7-6)**	Yes (12-0)
			TOTAL VOTES**	FOR Approval**	% Approval
			157	129	82%

Radiological Devices Panel Votes, 1998-2005

	1	2	3	4	5	6	7			
Meeting Date	5/11/1998	8/18/1998	8/18/1998	11/6/2000	3/5/2001	12/2/2002	2/3/2004			
Product	ImageChecker For Mammograms	Caries Detector	trans-spectral impedance scanner	SIR-Spheres	Chest Radiographs	Breast thermal imagery	Image Checker For Lung Nodules			
Manufacturer	R2 Tech. Inc.	Logicon RDA	TransScan	Sirtex Medical, Ltd	Deus Tech.	Computerized Thermal Imaging	R2 Tech. Inc.			
Motion □	A+C	A	A+C	A+C	A+C	NA	A+C			
Unanimous?	Yes	Yes	Yes	Yes	Yes	No	Yes			
Approved? (Y-N-A)*	Yes (6-0)	Yes (8-0)	Yes (6-0)	Yes (6-0)	Yes (5-0)	No (3-4)	Yes (7-0-1)	TOTAL VOTES**	FOR Approval	% Approval
TOTAL								45	41	91%
	Total	# unanimous		% unanimous						
Voting Sessions	7	6		86%						
For Approval	1	1		100%						
For Non-approval	1	0		0%						
For Approval + Conditions	5	5		100%						

†When a motion is for nonapproval, votes FOR the motion are considered votes AGAINST approval, and votes AGAINST the motion are considered FOR approval

*Votes here are represented by (Y-N-A) or (Yes-No-Abstain) all votes FOR approval are counted as a "yes" and all votes AGAINST approval are counted as "no". When there are no abstentions, votes are counted (Y-N)

**Abstentions are not counted

□A + C refers to Approval with Conditions.

APPENDIX E

FDA Advisory Committees: Does Approval Mean Safety?

General and Plastic Surgery Advisory Panel

Of all the FDA advisory panels, the General and Plastic Surgery panel has been one of the most active and certainly the most controversial. From 1998 through 2005, the panel considered 17 applications for approval, but the 6 applications for breast implants received more attention than all the other medical device advisory panel meetings combined.

The General and Plastic Surgery Advisory Panel was not randomly selected to be part of the study that is the basis of this report. In light of the controversy about the panel's implant decisions, however, a separate analysis was conducted to see how the panel's voting patterns and panel members' comments compared to those of the randomly selected advisory panels in the study.

The voting patterns for the General and Plastic Surgery Advisory Panel show less consensus than most of the device advisory panels in the study. Only 41% of the 17 voting sessions were unanimous, and only 46% of the panel's approval recommendations were unanimous. In contrast, most of the device panels in the study were unanimous every time they voted for approval. Nevertheless, the percentage of votes recommending approval on the General and Plastic Surgery Advisory Panel are typical for the device advisory panels. Of the 17 general and plastic surgery medical devices reviewed by the panel, 14 (82%) were recommended for approval, almost always with conditions. Of the total of 144 General and Plastic Surgery Advisory Panel votes cast over the eight years of the study, 115 (80%) were for approval. Both those statistics are exactly identical to the average of the five device panels that were randomly selected and analyzed in the study.

It is notable that of the three products that the panel recommended against approving between 1998 and 2005, two were breast implants.

The breast implant advisory panel meetings, held in 2000, 2003, and 2005, attracted enormous media attention, featuring public comments by plastic surgeons and patients praising the implants, other patients describing debilitating pain and physical deformity from leaking implants, and numerous scientists and physicians testifying for and against approval. The panel meetings differed from most other device panel meetings in a fundamental way: although the companies involved were asking that their product be approved by the FDA for the first time, the companies had been selling the implants in the United States for many years.[1] As a result, there were many women who had implants for decades who testified about the risks and benefits of the devices.

For those attending the meetings, panel members' comments and votes seemed strangely contradictory. For example, in their review of silicone breast implants in 2003, panel members consistently and strongly criticized the lack of long-term safety data, the lack of information about the causes and consequences of implant rupture, and the "lack of obligation that the sponsor felt to pursue a better product," after which the panel recommended the implants for approval.[2]

At the 2-day meeting on saline breast implants in 2000, saline implants made by McGhan (now Inamed) and Mentor were recommended for approval with numerous conditions, despite strongly worded criticisms about the very high complication rates and the lack of long-term safety data. Saline implants made by another company, PIP, were rejected unanimously because the panel members concluded that the research studies were inferior to those of the other two companies.

At the 2-day meeting for Inamed silicone gel breast implants in 2003, the criticisms of the lack of long-term safety data were nearly unanimous and the implants seemed destined for rejection when the company saved the day by proposing a compromise with numerous unusually stringent conditions of approval. The vote was closer than is typical for FDA advisory committees, 9-6, with most approval votes coming from plastic surgeons and other surgeons, at least one of whom received a waiver from the FDA to allow him to participate despite having received a grant from Inamed.

In 2005, the FDA held a 3-day meeting to review Inamed and Mentor silicone gel breast implants. This was the first time the advisory panel recommended against approval for Inamed breast implants, voting 5-4 that the implants were non-approvable because of the high rupture rate and the failure to collect more than 3 years of longitudinal data. The next day, however, the same panel recommended approval for Mentor silicone gel breast implants, 7-2, although the company had provided only 2 years of longitudinal data on implant rupture and leakage, compared to Inamed's 3 years of rupture data.

The approval of Mentor after the disapproval for Inamed received considerable media attention, and there was speculation about the apparent contradiction between criticizing Inamed for their 3-year rupture study and being satisfied with a 2-year rupture study from Mentor. Although there were other differences in the data provided by the two companies, the basic contradiction remained. In the context of the study findings presented in this report, however, the disconnect between the panel members' explicit concerns and the unanimous and lopsided votes in favor of approval are not surprising. In fact, the pattern is very similar to other device panel deliberations. Moreover, a review of the 1998-2005 votes of the 11 advisory committees in the study in addition to the General and Plastic Surgery panel, indicates that *none of these drug or device advisory ever voted against approval for two products in a row in the same year, let alone the same week*. To reject two products two days in a row would have been completely inconsistent with the approval-oriented voting patterns repeatedly demonstrated in the study. This helps explain the vote in favor of Mentor implants the day after rejecting Inamed's application for a very similar product with similar research studies.

In light of the overwhelming trend toward approval among FDA medical device advisory panels and the reluctance to reject more than one product per year, the large number of panel members who expressed strong concerns and then voted for approval can be seen as typical rather than unusual. In fact, the breast implant applications received more votes against approval than the vast majority of medical devices reviewed by all six device advisory panels we studied.

[1] The FDA did not have the authority to regulate breast implants until 1976. Since breast implants were sold since the early 1960's, they were "grandfathered" and could still be sold after 1976. PMAs were first required for silicone gel breast implants in 1991, but although the implants did not obtain FDA approval, they were allowed to be sold under restricted conditions after that. Saline breast implants went through the PMA process in 1999-2000.

[2] This quote is from bioethicist Nancy Dubler, October 14, 2003 FDA meeting transcript, page 495; however, similar quotes regarding the lack of safety data are available in the FDA meeting transcripts for the implant advisory meetings in 2000, 2003, and 2005.

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