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FDA Medical Officers Report Falling Standards Permit Dangerous Drug Approvals

Heavy Pressure from Industry and FDA Hierarchy Cited

WASHINGTON, D.C. -- Many Food and Drug Administration (FDA) medical officers say the safety and efficacy standards for approving new drugs have been lowered in the past few years, allowing many drugs to be approved which should not have been, according to a Public Citizen’s Health Research Group study released today.

The study, *FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals*, surveyed FDA medical officers -- physicians responsible for the primary reviews of New Drug Applications for drugs -- to determine their opinions about recent changes in the drug approval process.

“Our findings are shocking by any yardstick,” said Dr. Sidney M. Wolfe, Director of Public Citizen’s Health Research Group and co-author of the study. “Subtle and not-so-subtle pressure is being brought to bear on FDA physicians who dare to question a drug’s safety. Sometimes their safety objections are simply ignored or overruled.”

Nineteen medical officers identified 27 new drugs that they reviewed in the past three years and thought should not be approved but were approved anyway, and 17 medical officers described the current standards of FDA review for safety and efficacy as “lower” or “much lower” compared to those in existence prior to 1995.

The study, conducted in September and October 1998, followed the setting of two all-time FDA records. First, the largest number of new drugs was approved in any two-year period (92 in 1996 and 1997). Second, a record three new prescription drugs (all among the record-setting 92) were banned in a 12-month period because they were too dangerous to be allowed to stay on the market. For all three -- dexfenfluramine (Redux), mibefradil (Posicor) and bromfenac (Duract) -- data available prior to approval raised significant safety concerns and the drugs did not represent any significant advances over drugs already on the market.

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In the study released today, eight medical officers reported 14 instances in the past three years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved.

“These findings from FDA’s own reviewing physicians provide an alarming insight into the recent change in culture at the FDA, a change seriously jeopardizing the health of American patients by allowing drugs which would likely have been rejected in the past to get approved despite doubts about their safety or effectiveness,” said Dr. Peter Lurie, co-author of the report.

The study quotes the disturbing words of one medical officer who said: “In the last two years, I recommended that two drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards.”

In another case, a medical officer wrote that a high-ranking FDA official had said, “Everything is approvable. We can use the label creatively to lower the problems.”

The study also found that:

- Twelve medical officers identified 25 different new drugs that they reviewed in the past three years that in their opinion had been approved too fast.

- Nineteen medical officers stated that the pressure on them to approve a greater proportion of new drugs was “somewhat greater” or “much greater” compared to the period prior to 1995. The sources of this pressure were identified as the Office Director, Center Office, the pharmaceutical industry, the Congress and the medical officers’ own Division Directors.

“For FDA officials to ignore this information from its own medical officers is to continue on the current perilous course in which far too many me-too drugs are approved, despite questions about their safety or efficacy, only to be banned after enough people are injured or killed,” Wolfe and Lurie concluded.

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FDA Medical Officers Report
Lower Standards Permit Dangerous Drug Approvals

A Public Citizen’s Health Research Group Report

Peter Lurie, MD, MPH
Sidney M. Wolfe, MD

December 2, 1998
Summary

Background

In 1992, the U.S. Congress passed the Prescription Drug User Fee Act (PDUFA), which authorized drug companies to pay user fees to the FDA for the agency to hire more Medical Officers to review new drugs.

In 1997, the Congress reauthorized PDUFA and passed the Food and Drug Administration Modernization Act (FDAMA), which codified a number of practices that had become common in the agency: expanding the use of “accelerated approval” mechanisms for drugs for life-threatening conditions and using surrogate endpoints in clinical trials. It also included a number of mechanisms for speeding FDA review and changed the legal standard for new drug approval to a single clinical trial (instead of two).

In the past year, a record three drugs have been removed from the market due to serious safety problems: dexfenfluramine (Redux), mibefradil (Posicor) and bromfenac (Duract). For all three, data available prior to approval raised significant safety concerns.

Methods

In September 1998, we mailed a seven-page questionnaire to the home addresses of reviewing FDA Medical Officers. For those for whom no home address was available, we mailed the questionnaire to their address at the FDA. All Medical Officers were guaranteed anonymity.

Reminder mailings were sent to all Medical Officers in September and October 1998.

Results

Fifty-three out of 172 Medical Officers responded (31%).
Nineteen Medical Officers identified a total of 27 new drugs in the past three years that they reviewed that they thought should not have been approved but were approved.

Five Medical Officers identified a total of six new drugs that they reviewed in the past three years that they thought should have been approved but were not approved.

 Asked how they would compare the current standards of FDA review for safety and efficacy to those in existence prior to 1995, 17 Medical Officers described the current standards as “lower” or “much lower,” 13 described them as “about the same” and six described them as “higher.” None described the standards as “much higher.”

One Medical Officer stated: “My feeling after more than 20 years at FDA is that unless drugs can not be shown to ‘kill patients’ outright then they will be approved with revised labeling and box warning.”

Twelve Medical Officers identified 25 new drugs that they reviewed in the past three years that in their opinion had been approved too fast.

Thirty-four Medical Officers stated that the pressure on them to approve new drugs was “somewhat greater” or “much greater” compared to the period prior to 1995.

Nineteen Medical Officers stated that the pressure on them to approve a greater proportion of new drugs was “somewhat greater” or “much greater” compared to the period prior to 1995. Thirteen Medical Officers said that the pressure was “about the same.”

One Medical Officer stated: “We are in the midst now to approve everything but to describe drug weaknesses in the label. As one high ranking official said ‘Everything is approvable. We can use the labeling creatively to lower the problems.’”
Seventeen Medical Officers identified a total of 28 new drugs for which they were the primary reviewer in the past three years that had only been approved because post-marketing studies were required.

Eleven Medical Officers stated that, compared to the period prior to 1995, the frequency of drugs being approved that would not have been approved without requiring post-marketing studies was “somewhat more common” or “much more common.” Twenty Medical Officers said that this frequency was “about the same.”

Nine Medical Officers identified 19 new drugs that they had reviewed in the past three years that had been inappropriately shifted to the accelerated approval track.

Thirty-six Medical Officers reported that they “somewhat disapprove” or “strongly disapprove” of permitting drugs to receive accelerated approval solely on the basis of having a unique mechanism of action. Seven Medical Officers stated that they “somewhat approve” of this practice.

Nine Medical Officers reported a total of 23 inappropriate phone calls in the past three years regarding a drug they were reviewing, usually from the sponsor.

Eight Medical Officers reported 14 instances in the past three years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved.

Thirteen Medical Officers identified 18 occasions in the past three years when a supervisor, usually their Division Director, had asked the Medical Officer to change his or her opinion to agree with the supervisor’s, usually in a direction favoring approval.

One Medical Officer reported: “In the last 2 years, I recommended that two drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards
set up by the division, so they nullified the standards.”

Conclusions

Changes in FDA review and approval policies codified in FDAMA in the past several years appear to have led to a significant decline in the safety and efficacy standards for new drugs. Many drugs that have come on the market in the past three years have done so despite the opinion of the Medical Officer reviewing the drug that the drug should not have been approved.

Inappropriate pressure from Congress, the drug companies and senior FDA employees create an atmosphere in which the likelihood of drug approval is maximized. The pressure takes the form of inappropriate phone calls, pressure to withhold data or personal opinions unfavorable to a drug from FDA Advisory Committees, and pressure from supervisors to change their opinion in the direction of approving the drug.

Recommendations

Standards for drug approval should be strengthened, not weakened.

Sections of PDUFA and FDAMA that have led to the weakened drug approval standards should be revoked or modified.

Post-marketing studies need to be properly designed and actually performed, not used as a pretext for approval. Protocols for such studies should be developed prior to new drug approval.

The user fees authorized under PDUFA and FDAMA should also be used for post-marketing surveillance for adverse drug reactions.

Medical Officers must be better insulated from inappropriate pressure from the industry, the Congress and senior staff at the FDA.

The Inspector General of the Department of Health and Human Services or the General Accounting Office should conduct an investigation into whether current FDA practices have lowered the standards for new drug approval.
Background

After years of criticism from the drug industry that the drug approval process was too slow, the U.S. Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992. The Act authorized drug companies to pay user fees to the FDA for the agency to hire more Medical Officers to speed up the review of new drugs. One result of this has been that larger numbers of drugs are now being approved. Whereas in 1995 28 new drugs were approved, similar to the numbers in previous years, in 1996 the number of new drugs approved had risen to 53; 39 new drugs were approved in 1997. However, these fees cannot be used to hire more people to monitor for adverse drug reactions, even as larger numbers of new drugs come on the market.

At the end of 1997, the Congress reauthorized PDUFA and passed the Food and Drug Administration Modernization Act (FDAMA), which permitted drug approval based on a single clinical trial (instead of two), codified and expanded the use of “accelerated approval” mechanisms for drugs for life-threatening conditions, and established the use of surrogate endpoints in clinical trials. It also included a number of mechanisms for speeding FDA review.

While much of this has been good news for the industry, it is becoming increasingly clear that patients are paying the price. In the past year, a record three new drugs have been removed from the market due to serious safety problems: dexfenfluramine (Redux), mibebradil (Posicor) and bromfenac (Duract). For all three, data available prior to approval indicated potential safety problems. Industry profits handsomely from this stream of new drugs, most of which offer no therapeutic benefit over already approved drugs and which may have less expensive generic counterparts.

When a New Drug Application (NDA) is submitted to the FDA, it is usually assigned a single Medical Officer, a physician responsible for coordinating the reviews of the drug by other FDA employees, including chemists, toxicologists, pharmacologists and statisticians. The Medical Officer reviews the clinical trials in detail and makes a recommendation as to whether the submitted data support approval of the drug. No FDA employee is more familiar with the entirety of the NDA than the Medical Officer who reviews the application. When the new drug is sufficiently advanced in the review process, the data are usually presented to an
Advisory Committee, a panel of outside experts who advise the agency and whose recommendation the agency usually follows.

The opinions of Medical Officers on the recent changes in the review process are thus of great importance, but are seldom heard. One Medical Officer felt obligated to write a letter to the Washington Post on August 24, 1998 in order to voice his concerns about the new drug approval process. He was then asked to resign for having written the letter, but that request was later withdrawn. We undertook this survey in order to determine the opinions of those most intimately familiar with the impact of changes in the FDA review process, the Medical Officers.

Methods

In late July 1998, we obtained a list from the agency of all 216 Medical Officers in FDA’s Center for Drug Evaluation and Research (CDER). We eliminated 22 Medical Officers who are the Directors or Deputy Directors in CDER or who direct the reviewing Divisions (Attachment 1). An additional 21 Medical Officers were excluded because they are in the Office of Scientific Investigation, which investigates potential improprieties in clinical trials, or are responsible for such agency functions as statistics, epidemiology or surveillance. These Medical Officers do not review NDAs. One Medical Officer was known to have left the agency. This left a total of 172 potential respondents.

In order to maintain the confidentiality of respondents as much as possible, we searched phone books and the Internet for home mailing addresses for the Medical Officers in the metropolitan Washington, DC area. We identified home addresses for 108 (63%) of the Medical Officers and used mailing addresses at the FDA for the remaining 65 Medical Officers.

Each Medical Officer received a cover letter explaining the purpose of the study (Attachment 2). We designed a seven-page questionnaire (Attachment 3) for the Medical Officers to complete and return to us by mail. The survey explored seven general areas: 1. Whether there was pressure on the Medical Officers to approve drugs more rapidly; 2. Whether there was pressure on the Medical Officers to approve a greater proportion of new drugs; 3. Whether drugs were being inappropriately shifted into the “accelerated approval” track; 4. Whether studies were obtaining FDA approval only because post-marketing studies were required;
5. Whether FDA standards for safety and efficacy had been lowered; 6. Whether inappropriate internal or external pressure was being placed upon Medical Officers to approve drugs; and 7. Whether drugs they had reviewed had been inappropriately approved or disapproved in the last three years. The questionnaire did not ask for the names of specific drugs, as this would have compromised the Medical Officers’ confidentiality, but they were invited to provide their reviewing division if they so chose. A series of questions on the use of placebos in clinical trials were not used as the Medical Officers’ responses indicated that those specific questions were not sufficiently clear.

We mailed the questionnaires to the Medical Officers on three occasions in September and October 1998. Because the Medical Officers were not asked for their names, we were unable to distinguish between those who had and had not responded, so all received three mailings. However a code on the return address envelope allowed us to determine to which mailing the Medical Officer was responding and whether the questionnaire had been mailed to his or her home address or to the FDA.

Responses were entered into Foxpro for analysis. If the respondent indicated that a drug they were reviewing fell into a particular category but failed to mention the number of such drugs, we assumed that only one drug fell into that category for that reviewer, as “one” was the most common response to these questions. Due to the large number (and sometimes great length) of responses received to qualitative questions, only representative comments are included in full in the text; all comments are included in Attachment 4.

Results

Sixty-five percent of the responses received were from the first mailing, 27% from the second and 8% from the third, for a total of 53 responses (31% response rate). The response rate for those receiving the questionnaire at home was 28% and for those receiving it at their FDA office was 35%. Twenty-five Medical Officers voluntarily provided their reviewing division; the respondents were drawn from a minimum of 11 of the FDA’s 15 reviewing divisions.

*Lowered FDA Standards for New Drug Approval*
Nineteen Medical Officers identified a total of 27 new drugs that they had reviewed in the past three years that they thought should not have been approved but were approved (Figure 1). Due to possible under-reporting, this is a minimum estimate of the number of drug approvals that the Medical Officers consider inappropriate. Fifteen Medical Officers indicated that they had reviewed one drug that had been inappropriately approved; three mentioned two drugs; and one said that six drugs he or she had reviewed had been inappropriately approved. In marked contrast, five Medical Officers identified only six drugs that they thought should have been approved, but were not.

The Medical Officers were asked how they thought the standards of safety and efficacy now in existence compare with those existing prior to January 1995 (Figure 2). Seventeen of 36 Medical Officers (47% of those responding) described the current standards as “lower” or “much lower,” 13 (36%) described them as “about the same” and six (17%) described them as “higher.” None described the standards as “much higher.” (The smaller number of Medical Officers responding to this question was presumably due to some Medical Officers only having been hired in 1995 or later.) Of the 17 Medical Officers who stated that a drug they had reviewed should not have been approved, 11 (65%) stated that current FDA standards were “lower” or “much lower.”

The following are representative of the Medical Officers’ comments on the issue of standards for FDA new drug approval (see also Attachment 4):

“We are shifting the burden of proof on safety onto ourselves. Instead of asking the drug companies to prove the drug safe, we are trying to prove the drug dangerous. If we cannot show that the drug is dangerous, then it is assumed safe.”

“We are told that approvability is our goal with ‘problems’ to be addressed in labeling.”

“Efficacy criteria should include clearly evident benefits. Obvious example is Redux: little efficacy for weight loss; no evidence for health benefits; high degree of questionable safety in areas of pulmonary hypertension and neuropathology.”

“I am very much concerned about lower standards for safety, in particular, the size of safety data base required prior to marketing. I am very much concerned that there now appears to be support for a single study to demonstrate efficacy. I believe this ‘mutual confirmation’ [by two studies] greatly reduces the possibility that an inaccurate conclusion or inference of efficacy will be made.”
"The standards are good if it comes to simply identifying a problem or determining how well a drug works. However, implementation is a problem. So often, we identify a problem pre-approval, and it is simply inserted into the label with everything else the practitioner has no time to read."

"Efficacy standards are definitely lower. Safety review standards are higher, but then when there is found to be a safety problem we approve the drug. There is no more a judgement of benefit to risk ratio, as there was for so many years."

"The agency is allowing a lot of ‘me-too’ drugs on the market some of which are less safe or less efficacious than existing drugs already approved and marketed in that drug class."

"These are value judgements. Each case is open to many considerations and criticism depending on one’s perspective. In general, the FDA standards are the same as in other jurisdictions."

"I don't think that the FDA standards have been lowered. If any change has occurred, it has been in the direction of demanding higher standards of safety and efficacy."

"In some aspects the safety review is improving due to electronic submissions and investment in software to review safety data submitted electronically."

"I believe the training given reviewers now is far better than previously and that staffing has also improved."

**More Rapid Drug Approvals**

Twelve Medical Officers identified 25 new drugs that they reviewed in the past three years that they believed had been approved too fast (Figure 3). Eight Medical Officers identified one such drug, two mentioned four drugs and one Medical Officer apiece specified three and six drugs.

Thirty-four of 38 Medical Officers responding (89%) stated that the pressure on them to approve new drugs was “somewhat greater” or “much greater” compared to the period prior to 1995 (Figure 4). None answered “somewhat less” or “much less.” (Again, the smaller number of Medical Officers responding was presumably due to some Medical Officers only having been hired in 1995 or later.) Asked to identify the source of the pressure to approve drugs more rapidly from a list of yes-no options, 26 (68%) identified the Center for Drug Evaluation and Research Office, 19 (50%) the Congress, 18 (47%) the pharmaceutical industry, 14 (37%) the Office Director, 13 (34%) the Division Director and 11 (29%) the Team Leader. (Because some Medical Officers identified more than one source of pressure, the
percentages exceed 100%.)

The Medical Officers were also asked about pressure on other Medical Officers to approve new drugs more rapidly (Figure 5). Thirty-five of 38 Medical Officers responding (92%) described the pressure on other Medical Officers to approve new drugs more rapidly as “much greater” or “somewhat greater,” two (5%) described this pressure as “about the same” and one (3%) described it as “somewhat less.”

The Medical Officers also offered comments on the issue of the speed of new drug approvals, including the following (see also Attachment 4):

“Rapid approval often means insufficient time to examine carefully original data, accepting ‘on faith’ validity of randomization, screening, use and misuses of inclusion and exclusion criteria. There is insufficient time to discuss outlying observations.”

“The official times allowed for the review process keep getting shorter and shorter. The recently passed ‘FDA Modernization Act’ is making things a lot worse.”

“Medical Officers don’t approve NDA’s. We simply recommend for or against approval. Office Directors make the final decision.”

“[Deputy Center Director for Review Management Murray] Lumpkin and [Director of the Center for Drug Evaluation and Research Janet] Woodcock are mainly interested in counts of approvals, time to approval and not quality.”

“FDA approvals of drugs at a fast speed are without question more risky than before (slow approvals) but faster approvals have had a positive public health impact on the treatment of life-threatening diseases (AIDS and cancer).”

“In my division the accelerated approvals were justified and resulted in a measurable health benefit.”

“Long overdue. I do not believe that the decreased approval time has necessarily compromised safety. The system was too open-ended previously.”

“Improved computer support, information technology, communication technology and better staffing have greatly enhanced the speed at which we can work and review applications in less time today than prior to 1995.”

Approving a greater proportion of drugs
Nineteen of 33 Medical Officers responding (58%) stated that the pressure on them to approve a greater proportion of new drugs was “somewhat greater” or “much greater” compared to the period prior to 1995 (Figure 6). Thirteen (39%) said that the pressure was “about the same” and one (3%) described the pressure as “somewhat less.” The sources of this pressure were identified from a series of yes-no options. Thirteen Medical Officers each identified the Office Director and the Center Office (39% each), 10 (30%) the pharmaceutical industry, nine (27%) the Congress, eight (24%) the Division Director and six (18%) the Team Leader.

The Medical Officers described similar pressures upon their colleagues (Figure 7). Twenty of 32 Medical Officers responding (63%) described the pressure upon other Medical Officers as “much greater” or “somewhat greater” than in the period prior to 1995, with the remaining 12 describing that pressure as “about the same.”

The following were among the Medical Officers’ comments on the issue of approving a greater proportion of new drugs (see also Attachment 4):

“We are in the midst now to approve everything but to describe drug weaknesses in the label. As one high ranking official said ‘Everything is approvable. We can use the labeling creatively to lower the problems.’”

“Pressure to approve comes largely from the Office and Center level. Decisions should be left with the Division -- that is where the expertise is.”

“Borderline drugs are being approved with the correct labeling and rectifying many deficiencies (safety) of products.”

“What are the options; everything must now be ‘approved’ or approvable.”

“In the last two years, I recommended that two drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards.”

“I personally do not use or prescribe new drugs/vaccines unless they have been on the market 2-3 years in U.S. (Though I don't work with cancer, AIDS, etc.).”

“Not all drugs that are reviewed more quickly are approved; one can also reach a decision not to recommend approval more quickly than in former years.”
“If we are approving a greater proportion of NDAs it would be the result of improved communication and collaboration during the pre-NDA process.”

“The public (clinicians and patients) are served better when there are more options for treatment. The risk/benefit ratio should be recognized by all in order to take full advantage of more drug availability.”

Relying on Post-marketing Studies for Approval

Seventeen Medical Officers identified a total of 28 new drugs in the past three years for which they were the primary reviewer that in their opinion had only been approved because post-marketing studies were required (Figure 3). Ten Medical Officers identified one drug, five identified two drugs and one each identified three and five drugs.

Eleven of the 32 Medical Officers (34%) responding stated that, compared to the period prior to 1995, the frequency of drugs being approved that would not have been approved without requiring post-marketing studies was “somewhat more common” or “much more common” (Figure 8). Twenty Medical Officers (63%) described this frequency as “about the same” and one (3%) described it as “somewhat less common.”

The Medical Officers’ comments on the issue of relying on post-marketing studies for approval included the following (see also Attachment 4):

“We don’t trust that the companies will carry out Phase IV studies with due diligence, either before or after PDUFA.”

“Post-marketing studies are frequently not completed. FDA has no power to ensure such commitments. Drugs have been marketed before post-marketing protocols have been reviewed. I can think of only one such study that was designed properly and is being conducted reliably--metformin.”

“Good idea but no way to enforce Phase IV studies. If sponsors don’t do them correctly what recourse does FDA have? It’s tough to pull a drug.”

“The agency forfeits its most powerful weapon -- withholding approval. Essentially all Phase IV studies which are required are for safety reasons. If a problem is identified, the agency negotiates
with the company for labeling changes. Withdrawal is extremely unlikely even if its problem is very serious."

"Post-marketing surveillance done by the sponsors is inadequate as is post-marketing surveillance at FDA -- this is one area of the agency that could really be improved."

"There are no teeth in post-marketing agreements."

"I think that all drugs should have a large randomized safety study at approval focusing on death and serious events occurrence. If properly designed, the cost would be reduced and not too great."

"Post-marketing is often necessary to examine aspects of a drug that seems safe and effective and should become available for use but may have not had adequate testing. All drugs can have more serious events that may not be revealed in clinical trials."

"I have not seen drugs approved based on Phase IV commitments."

**Inappropriate Use of the "Accelerated Approval" Category**

Nine Medical Officers identified 19 new drugs that they had reviewed in the past three years that in their opinion had been inappropriately shifted to the accelerated approval track (Figure 3). Five Medical Officers identified a single drug that had been inappropriately shifted to the accelerated approval track, one identified two drugs, two identified three drugs and one identified six drugs.

Thirty-six of 50 Medical Officers (72%) reported that they "somewhat disapprove" or "strongly disapprove" of permitting drugs to receive accelerated approval strictly on the basis of having a unique mechanism of action (Figure 9). Seven (14%) each stated that they "neither approve nor disapprove" or "somewhat approve."

The Medical Officers made the following additional comments on the issue of shifting drugs to the accelerated approval track (see also Attachment 4):

"Some drugs need to be in the accelerated approval category, although this should not be based on a unique mechanism of action."

"The industry is more and more aggressive to get their NDA designated for 'priority review.' We have to fend off those inappropriate ones with considerable resources."

"This is a formula for disaster. The patient doesn't benefit. A prime example is Fosamax touted
as a ‘gold standard’ yet of questionable value. Another is tamoxifen for ‘prevention’ of breast cancer, but not yet fully available. Still another--Viagra.”

“It is particularly in the case of drugs with new mechanisms of action that unanticipated safety problems are likely to occur. These are drugs that should not be subjected to accelerated approval.”

“I think it is abused by companies for marketing reasons, when the benefit to public health (or some small subset) will be minimal at best.”

“Should be reserved for life-threatening or incapacitating conditions for which there are no other treatments.”

“Drugs for serious pain or other critical conditions that have ‘unique mechanisms’ and treat conditions for which no adequate therapy is presently available deserve accelerated status.”

“Accelerated approval regulations are very carefully written and appropriate balance provided for population needs and demonstrating safety and efficacy. It is the application of the [regulations] that will be the true test.”

“This has been one of the most recent successes of the FDA. I lived through the days when AIDS activists criticized us for being paternalistic and not allowing them (AIDS patients) to have access to new drugs. Patients were willing to take risks and we were in their way. Accelerated approval brought to them many new drugs that have increased survival time.”

**Inappropriate Pressure on Medical Officers**

Nine Medical Officers reported a total of 23 inappropriate phone calls in the past three years regarding a new drug they were reviewing (Figure 10). Four Medical Officers reported one phone call, one reported two, three reported four and one reported five inappropriate phone calls, usually from the sponsor. Only one inappropriate visit (by a sponsor) was reported during that period.

The Medical Officers made the following additional comments on the issue of inappropriate phone calls and visits (see also Attachment 4):

“My feeling after more than 20 years at FDA is that unless drugs can not be shown to ‘kill patients’ outright then they will be approved with revised labeling and box warning.”

“Supervisors and administrators--from Congress re: myotropin [a drug for amyotrophic lateral sclerosis].”
“I heard of one Medical Officer who is said to have quit because of pressure from Capitol Hill about a controversial drug.”

“Fortunately, there has been none, and I would be very resistant should any be made.”

“I am not aware of any inappropriate external pressure on FDA Medical Officers. In my eight years of FDA experience I have never been confronted with inappropriate external pressure. This is one of the issues I treasure the most about being a Medical Officer: My decisions are strictly scientific. They are based on data. I have not had political or economical pressures of any kind.”

“I haven't heard of a single such case in my division.”

Eight Medical Officers reported 14 instances in the past three years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved (Figure 10). Five Medical Officers reported one such occurrence, one reported two occurrences, and one person each reported three and four occurrences.

The following were among the comments offered by the Medical Officers on the issue of withholding opinions or data from FDA Advisory Committees (see also Attachment 4):

“There is a Center effort or at least a discussion to prevent the Divisions from offering opinions.”

“The Advisory Committee (or anybody) don't pay much attention to what the primary reviewers say.”

“I was ‘guilty’ of expressing my opinions before the Advisory Committee of our Division and several others for whom I wrote consultative reviews before 1995. I have not been asked to present reviews since.”

“A Medical Officer must be forceful on safety concerns.”

“The default appears to be ‘yes’ [to approval]; the hurdle to disapprove a drug is much higher than approving a drug.”

“The Advisory Committees are increasingly pro-approval in recent years.”

“It depends if management has been ‘for’ or ‘against’ drug approval. In my case they were supportive of my comments since there were problems with drug efficacy.”
"I find the agency and its supervisory staff to be quite willing to discuss issues with Medical Officers, even if their views differ. The exchanges I have had have been most informative—both ways. At some times I have made my point; other times I learned something that caused me to change my views."

"In retrospect, I think the ‘instruction’ ... was appropriate and contributed to the scientific quality of my presentation."

"Never [been told to not present data or own opinion at an Advisory Committee meeting]. It would be against our policy and procedures to do so."

Thirteen Medical Officers identified 18 occasions in the past three years when a supervisor, usually their Division Director, asked the Medical Officer to change his or her opinion to agree with the supervisor’s (Figure 10). Nine Medical Officers reported that this had happened once, three reported it had happened twice and one person reported three such episodes. Nine of the 13 Medical Officers indicated the direction in which they had been asked to change their opinion, and seven of these were in the direction of approval.

Medical Officers who said that a drug that they had reviewed had been inappropriately approved were almost twice as likely to describe at least one form of pressure described in this section compared to Medical Officers who did not think a drug they had reviewed had been inappropriately approved (Relative Risk for inappropriate pressure = 1.84; 95% confidence interval: 1.02-3.31).

The Medical Officers’ remarks on the issue of being pressured by supervisors included the following (see also Attachment 4):

"Superiors will try to get reviewers to change his/her mind so that they will not need to take the heat if something goes wrong. They have the option to override and should be willing to do so in writing."

"My office director told me that he was going to overrule me because the sponsor (Wyeth-Ayerst) would just go over our heads to Capitol Hill. He felt it was best to approve the drug for an indication not studied and have the sponsors do a Phase IV post-marketing trial in support of the indication. I reminded him that this sponsor had failed to honor other Phase IVS. He went ahead and approved the drug."
“Our superiors don’t put pressure on us. They just ignore our opinion and write their own memo.”

“I feel free to express and argue my views and position, even thought I do not always persuade.”

“My interactions with supervisors have been marked by disagreements about different issues that we discuss and even argue about but I have not felt that they were pressuring me one way or another. Half the time I was right, half the time I was wrong. The free discussion of the issues led us most of the time to make the right decisions or decisions that if wrong, didn’t have a major public health impact. Most of the decisions are reached by consensus.”

Conclusions

Changes in the FDA review and approval process in the past several years appear to have led to a significant decline in the safety and efficacy standards for new drugs. Many drugs that have come on the market in the past three years have done so despite the opinion of the Medical Officer reviewing the drug that the drug should not have been approved. Said one Medical Officer: “My feeling after more than 20 years at FDA is that unless drugs can not be shown to ‘kill patients’ outright then they will be approved with revised labeling and box warning.”

These findings should raise a red flag that the very integrity of the drug approval process in the United States, long an example to the rest of the world, is being seriously eroded. It is inexcusable to, in effect, override the opinion of the person most familiar with a drug’s safety and efficacy data in many cases and approve the drug.

Top FDA officials have asserted that the reductions in reviewing time that date back to the early 1990s have not resulted in the lowering of safety and efficacy standards. Yet the opinions of many Medical Officers testify otherwise. Seventeen Medical Officers responding to our survey believe that the standards for safety and efficacy have been lowered, with only six believing they have been raised. One Medical Officer put it this way: “[Deputy Center Director for Review Management Murray] Lumpkin and [Director of the Center for Drug Evaluation and Research Janet] Woodcock are mainly interested in counts of approvals, time to approval and not quality.” Because about half of the Medical Officers did not state their Division (in order to protect confidentiality, we had emphasized that providing such data was optional), we cannot speculate as to whether standards or practices may vary between or within Divisions.
Senior officials at the FDA have also asserted that the shortening of review times is the result of improved efficiency, in part due to electronic NDA submissions, and some Medical Officers echoed that assertion. While this may have some credence, the responding Medical Officers identified 25 new drugs that they said had been approved too rapidly in the past three years and the vast majority of those responding described greater pressure to approve drugs more rapidly. In these circumstances, it is no surprise that unsafe new drugs seem increasingly to be slipping through the FDA safety net.

The study also demonstrates that inappropriate pressure from Congress, the drug companies and senior FDA officials create an atmosphere in which the likelihood of drug approval is maximized. The pressure takes the form of inappropriate phone calls, pressure to withhold data or personal opinions unfavorable to the drug from FDA Advisory Committees, and pressure from supervisors on Medical Officers to change their opinion in the direction of approving the drug. One Medical Officer reported that another Medical Officer had resigned “because of pressure from Capitol Hill about a controversial drug.” While some FDA employees reported that they had not experienced these kinds of pressures, the only acceptable number of inappropriate phone calls or instructions to withhold data from Advisory Committees is zero. Together, these forms of coercion threaten to undermine the scientific credibility of FDA reviews and to reduce the public’s trust in the agency.

Three additional areas of concern were identified by the Medical Officers. The first is the apparently growing use of the label to address safety concerns and facilitate approval, instead of denying approval. One Medical Officer quoted a high-ranking FDA official as saying “Everything is approvable. We can use the label creatively to lower the problems.” This represents a complete abdication of responsibility by the agency, particularly because it is well known that few physicians actually read the label. Second, at least some drugs have received approval by deferring unresolved questions to a post-marketing study to be done by the drug company. But, as the Medical Officers made clear, these studies are often of poor quality or not carried out at all. The result is drugs coming onto the market with unresolved questions, usually safety issues. Finally, it is clear that many Medical Officers feel that their opinions are being overlooked, even though they are most familiar with the data on the particular drugs they are reviewing. As one Medical Officer put it, “The Advisory Committee (or anybody) don’t pay much attention to what the primary reviewers say.” Said another: “In the last two years, I recommended that two drugs not be approved. They were both approved without consulting me. This
never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards.”

The main criticism likely to be leveled against this report is that the respondents were more likely to be critical of FDA than non-respondents. But, it is also conceivable that Medical Officers wishing to support the agency would have been particularly motivated to respond. There is, of course, no way to be certain whether those responding were more or less likely to be critical of the FDA. The response rate of 31% is quite good, considering the perceived potential for reprisal in this situation (one Medical Officer declined to provide his or her Division “for fear of retaliatory measures”) and the difficulties in establishing Medical Officer addresses. In any event, the absolute numbers of Medical Officers expressing dissatisfaction with current FDA drug approval processes is extremely worrisome.

Even if one believes that non-response could bias the results, this criticism does not apply to questions seeking numbers of particular events (e.g., the number of drugs that have been approved despite the Medical Officer’s opposition, those that were approved too fast, those that were approved only because post-marketing studies were required and those inappropriately shifted to the accelerated approval track). We did not ask the Medical Officers for the names of specific drugs, as this would have compromised their confidentiality. However, we believe that there is little, if any, overlap between the drugs mentioned. While “split reviews” in which more than one Medical Officer reviews an NDA do occur, our understanding from phone calls to FDA employees and our own experience over the years suggests that this is not common. With 53 Medical Officers responding from at least 11 of the FDA’s 15 reviewing divisions, substantial overlap among the respondents between drugs is unlikely. For these questions, the limited number of responses more likely leads to an undercount of an already serious number of events. Similarly, the numbers of episodes in which the Medical Officer experienced inappropriate pressure are probably minimum estimates. In addition, the Medical Officers may not have been able to recall all events in the past three years and not all Medical Officers had been hired at the FDA for the full three years, resulting in further underestimates of the actual number of events.

Recommendations

- Standards for drug approval should be strengthened, not weakened. For
example, the practice of using the labeling to permit drugs that would otherwise not be approved to come to market must be ended.

- Sections of PDUFA and FDAMA that have led to the weakened drug approval standards should be revoked or modified.

- Post-marketing studies need to be properly designed and actually performed, not used as a pretext for approval. Protocols for such studies should be developed prior to new drug approval by the FDA.

- The user fees authorized under PDUFA and FDAMA should also be used for post-marketing surveillance for adverse drug reactions.

- Medical Officers must be better insulated from inappropriate pressure from the industry, the Congress and senior staff at the FDA.

- The Inspector General of the Department of Health and Human Services or the General Accounting Office should conduct an investigation into whether current FDA practices have lowered the standards for new drug approval.
Figure 1: New Drugs They Reviewed in the Past 3 Years Whose Status FDA Medical Officers Think Was Wrongly Decided

Number of Drugs

Should have been disapproved but were approved: 27
Should have been approved but were disapproved: 6
Figure 2: FDA Medical Officers' Opinions on Review Standards for Safety and Efficacy Compared to 3 Years Ago
Figure 3: FDA Medical Officers' Descriptions of Problems in New Drug Approval Process in the Past 3 Years

- Approved too fast
- Approved only because of post-marketing studies
- Inappropriately shifted to accelerated track

Number of Drugs
Figure 4: FDA Medical Officers' Descriptions of Pressure on Them to Approve New Drugs More Rapidly Compared to 3 Years Ago
Figure 5: FDA Medical Officers' Descriptions of Pressure on Other Medical Officers to Approve New Drugs More Rapidly Compared to 3 Years Ago
Figure 6: FDA Medical Officers' Descriptions of Pressure on Them to Approve a Greater Proportion of New Drugs Compared to 3 Years Ago

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Medical Officers</th>
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<tbody>
<tr>
<td>Much greater</td>
<td>9</td>
</tr>
<tr>
<td>Somewhat greater</td>
<td>10</td>
</tr>
<tr>
<td>About the same</td>
<td>13</td>
</tr>
<tr>
<td>Somewhat less</td>
<td>1</td>
</tr>
<tr>
<td>Much less</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 7: FDA Medical Officers' Descriptions of Pressure on Other Medical Officers to Approve a Greater Proportion of New Drugs Compared to 3 Years Ago

![Bar chart showing the number of medical officers' descriptions of pressure on other medical officers to approve a greater proportion of new drugs compared to 3 years ago. The chart has three categories: Much greater, Somewhat greater, About the same. The numbers for each category are: Much greater = 10, Somewhat greater = 10, About the same = 12.}]
Figure 8: FDA Medical Officers' Descriptions of Frequency of New Drugs that Would Not Have Been Approved Without Post-marketing Studies Compared to 3 Years Ago
Figure 9: FDA Medical Officers' Opinions About Whether New Drugs Should Receive Accelerated Approval Strictly on the Basis of a Unique Mechanism of Action
Figure 10: Inappropriate Pressure on FDA Medical Officers in the Past 3 Years

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<thead>
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<th>Category</th>
<th>Number of Episodes</th>
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<td>Inappropriate phone calls</td>
<td>23</td>
</tr>
<tr>
<td>Inappropriate visits</td>
<td>1</td>
</tr>
<tr>
<td>Instructed not to present data or own opinion to Advisory Committee</td>
<td>14</td>
</tr>
<tr>
<td>Asked to change opinion to agree with supervisor</td>
<td>18</td>
</tr>
</tbody>
</table>
September 8, 1998

Dear Medical Officer:

We are writing to ask no more than 15 minutes of your time to fill out a questionnaire asking you about recent developments in FDA's drug approval process.

The question of whether changes in the FDA drug approval process may have led to lapses in public protection has been raised. We believe that, as a non-supervisory FDA medical officer whose job it is to review New Drug Applications, you are best placed to assess the impact of these changes.

This questionnaire focuses on five mechanisms by which the FDA approval process could have become less stringent: 1. More rapid approval of drugs; 2. Approval of a greater proportion of drugs reviewed; 3. Deferral of safety concerns to postmarketing studies; 4. Assignment of drugs to the accelerated approval track based primarily on a unique mechanism of action; and 5. Lowering the standard for safety or efficacy.

When possible, we have mailed the questionnaire to home addresses, in order to minimize any discomfort you may feel from receiving the questionnaire at work. The respondents to this survey are not being asked to identify themselves, but, if you feel comfortable, please fill in your reviewing division (such as Cardio-Renal Drug Products) at the end of the survey; this may permit us to assess whether there are differences in responses between divisions.
This survey will allow us to assess the views of medical officers, the group in the best position to understand the impact of these new policies and procedures. Please respond by September 21 and mail back this questionnaire in the enclosed stamped envelope. A copy of the results will be sent to all recipients of the survey.

Thank you in advance.

Sincerely,

Peter Lurie, MD, MPH
Medical Researcher

Sidney M. Wolfe, MD
Director
Medical Officer Survey
The FDA Drug Approval Process

In all questions in this questionnaire, we are referring to New Molecular Entities, not all drug approvals.

I. Approving Drugs More Quickly?

In 1992, Congress approved the Prescription Drug User Fee Act (PDUFA), which, among other things, allowed for the pharmaceutical industry to pay a user fee to the FDA for the purpose of expediting review of NDAs. These provisions took some time to implement.

If you began working at the FDA in January 1995 or later, please go to Question I.4.

1. Compared to the period prior to January 1995, how would you describe the pressure on you to approve NDAs rapidly? (Circle most appropriate answer)

   a. Much greater
   b. Somewhat greater
   c. About the same
   d. Somewhat less
   e. Much less

2. If you answered a or b to question 1, where do you think the pressure to approve NDAs more rapidly is coming from (circle all that apply)?

   a. Team leader
   b. Division director
   c. Office director
   d. Center office
   e. Pharmaceutical industry
   f. Congress
   g. Other (i) Who? __________

3. Compared to the period prior to January 1995, how would you describe the pressure on other FDA medical officers to approve NDAs rapidly?

   a. Much greater
   b. Somewhat greater
   c. About the same
   d. Somewhat less
   e. Much less

4. In your opinion, in the past three years, how many drugs that you were reviewing, if any, were approved too fast? _____
5. My additional comments on the issue of the speed of FDA drug approvals are:

II. Approving a Greater Proportion of NDAs?

*If you began working at the FDA in January 1995 or later, please go to Question II.4.*

1. Compared to the period prior to January 1995, how would you describe the pressure *on you* to approve a greater proportion of NDAs you review?

   a. Much greater
   b. Somewhat greater
   c. About the same
   d. Somewhat less
   e. Much less

2. If you answered a or b to question 1, where do you think the pressure to approve more NDAs is coming from (circle all that apply)?

   a. Team leader
   b. Division director
   c. Office director
   d. Center office
   e. Pharmaceutical industry
   f. Congress
   g. Other (i) Who?

3. Compared to the period prior to January 1995, how would you describe the pressure *on other FDA medical officers* to approve a greater proportion of NDAs they review?

   a. Much greater
   b. Somewhat greater
   c. About the same
   d. Somewhat less
   e. Much less

4. My additional comments on the issue of approving a greater proportion of NDAs are:
III.  Relying on Post-Marketing Studies?

The FDA has at times required post-marketing studies such as phase IV studies as a condition for approval, especially if there is a concern about the safety of the drug.

If you began working at the FDA in January 1995 or later, please go to Question III.2.

1. Compared to the period prior to January 1995, how would you describe the frequency of drugs that would not have been approved without requiring post-marketing studies?
   a. Much more common
   b. Somewhat more common
   c. About the same
   d. Somewhat less common
   e. Much less common

2. In your opinion, in the past three years, how many drugs that you were reviewing, if any, were only approved because post-marketing studies were required? 
   
3. My additional comments on the issue of the reliance on post-marketing studies are:

IV.  Shifting Drugs Into the “Accelerated Approval” Category?

The Prescription Drug User Fee Act (PDUFA) also required drugs for life-threatening conditions to be shifted to an "accelerated approval" category. Some drugs have been reviewed under this accelerated approval mechanism simply on the basis of a unique mechanism of action, even though the drugs did not treat a life-threatening condition.

1. Do you approve of permitting drugs to receive accelerated approval strictly on the basis of a unique mechanism of action?
   a. Strongly approve
b. Somewhat approve  
c. Neither approve nor disapprove  
d. Somewhat disapprove  
e. Strongly disapprove  

2. In your opinion, in the past three years, how many drugs that you were reviewing, if any, were inappropriately shifted to the accelerated approval track? ____  

3. My additional comments on the issue of shifting drugs into the accelerated approval category are:  

V. Lowered Standards of Review for Safety and Efficacy?  
FDA approval standards could be lowered either by one or more of the four mechanisms identified above (Sections I-IV above) and/or by a lowering of the standards for safety and efficacy.  

*If you began working at the FDA in January 1995 or later, please go to Question V.2.*  

1. Compared to the period prior to January 1995, how would you describe the current standards of review for safety and efficacy that exist in practice?  
   
a. Much lower  
b. Lower  
c. About the same  
d. Higher  
e. Much higher  

2. My additional comments on whether existing FDA standards of safety or efficacy are adequate:  

VI. Summary Questions  
1. In the past three years, have you received pressure in the form of inappropriate
phone calls with regard to a drug you were reviewing?

a. Yes  (i) How many times? ____________
      (ii) From whom (circle all that apply)?
      a. Sponsor
      b. Members of congress
      c. Congressional staff
      d. Other (i) Who? ____________

b. No

2. In the past three years, have you received pressure in the form of inappropriate visits to your office with regard to a drug you were reviewing?

a. Yes  (i) How many times? ____________
      (ii) From whom (circle all that apply)?
      a. Sponsor
      b. Members of congress
      c. Congressional staff
      d. Other (i) Who? ____________

b. No

3. My additional comments on the issue of inappropriate external pressure on FDA medical officers are:

4. In the past three years, have you been instructed, prior to an FDA Advisory Committee meeting on a drug that you reviewed, not to present data or your own opinion when the data or opinion might have reduced the likelihood of the drug receiving Advisory Committee support?
a. Yes  
   (i) How many times? ________
   (ii) By whom (circle all that apply)?
   a. Team leader
   b. Division director
   c. Office director
   d. Center office
   e. Other (i) Who? ________

b. No

5. My additional comments on the issue of medical officers' ability to express their own views are:

6. In the past three years, has there been any drug for which you were the reviewing Medical Officer that you think should not have been approved but was approved?

a. Yes (i) How many drugs? _____
b. No

7. In the past three years, has there been any drug for which you were the reviewing Medical Officer that you think should have been approved but was not approved?

a. Yes (i) How many drugs? _____
b. No

8. Has your supervisor asked you to change your opinion to agree with his or hers in the past three years?

a. Yes  (i) How many times?_____
   (ii) Which supervisor?
   a. Team leader
   b. Division director
   c. Office director
   d. Center office
   e. Other (i) Who? ________

6
(iii) In which direction were you asked to change your opinion?
   a. In favor of approval
   b. In favor of disapproval
   c. Neither in favor of approval nor disapproval

b. No

9. My additional comments on the issue of pressure from supervisors are:

10. How do you feel about the use of placebos in clinical trials designed to lead to FDA approval which are for serious conditions for which effective treatment exists?
    a. Strongly approve
    b. Somewhat approve
    c. Neither approve nor disapprove
    d. Somewhat disapprove
    e. Strongly disapprove

11. In the past three years, for how many drugs for the treatment of serious conditions for which effective treatment exists and for which you were the reviewing Medical Officer have placebos been used? ______

12. How many times in the past three years, if any, have you complained to a supervisor about this use of placebo controls? ______

13. My additional comments on the issue of the use of placebo controls are:

We greatly appreciate the time you have taken to fill out this survey. Please feel free to attach additional information.
If you wish, please indicate which reviewing division you are in:

Date: _________________________________

Please return the completed questionnaire in the enclosed stamped envelope.
We will send you a copy of the results of the survey as soon as they are available.
Comments by FDA Medical Officers

Whether Existing FDA Standards of Safety or Efficacy are Adequate

The evidence document lays out lower standards.

The time period required for these reviews is currently generally adequate but should not be shortened.

We are shifting the burden of proof on safety onto ourselves. Instead of asking the drug companies to prove the drug safe, we are trying to prove the drug dangerous. If we cannot show that the drug is dangerous, then it is assumed safe.

Again, we are told that approvability is our goal with "problems" to be addressed in labeling.

Efficacy criteria should include clearly evident benefits. Obvious example is Redux: little efficacy for weight loss; no evidence for health benefits; high degree of questionable safety in areas of pulmonary hypertension and neuropathology.

Only minimal demonstration of efficacy (statistical) seems necessary.

There may be examples of both lower and higher standards.

Scrutiny of applications not as thorough as prior.

I think existing standards are adequate, at least in my division (Office of Drug Evaluation, Division of Dermatologic and Dental Drug Products).

I have been strongly impressed with the very high standards exercised and met by the agency of safety and efficacy of new drugs. There is consistent effort within the agency to strengthen, clarify and make more uniformly consistent across divisions.

Accelerated approval may be a real trojan horse.

Yes.

I am very much concerned about lower standards for safety, in particular, the size of safety data base required prior to marketing. I am very much concerned that there now appears to be support for a single study to demonstrate efficacy. I believe this "mutual confirmation" [by two studies]
greatly reduces the possibility that an inaccurate conclusion or inference of efficacy will be made.

No, drugs without documented safety and efficacy should not be approved.

Do not believe standards are low.

In some aspects the safety review is improving due to electronic submissions and investment in software to review safety data submitted electronically.

I believe the training given reviewers now is far better than previously and that staffing has also improved.

The standards are good if it comes to simply identifying a problem or determining how well a drug works. However, implementation is a problem. So often, we identify a problem pre-approval, and it is simply inserted into the label with everything else the practitioner has no time to read. At the very least, there needs to be an improvement in the way the agency communicates its review of the drug to the medical community. Maybe the Medical Officer involved should write an “executive summary” of their review of the NDA, which could be published in a high profile journal. At least that way practitioners can get their information from someone more objective than a drug company rep. and get an idea of what is important and what is not (e.g., the 10-day restriction on Duract prescribing).

Our standards remain appropriate to the risk and benefit equations specific to the severity of the disease and the availability of alternative treatments.

Efficacy standards are definitely lower. Safety review standards are higher, but then when there is found to be a safety problem we approve the drug. There is no more a judgement of benefit to risk ratio, as there was for so many years.

I don't think that the FDA standards have been lowered. If any change has occurred, it has been in the direction of demanding higher standards of safety and efficacy.

Again, post-marketing surveillance could be beefed up. The case of Duract exemplifies the outside pressure on the agency to approve.

Higher standards have created additional work requirements which now must be completed in less time than previously. Higher standards are a result of increased sophistication in analyzing safety and efficacy data.

Although my own division has maintained its standards there is more pressure to cut corners than before.
Many investigators appear to be investigating outside their clinical expertise and have no real training in research and the conduct of clinical trials. Follow-up on adverse events is impaired because of lack of clinical knowledge or lack of primary responsibility for patients. The phenomenon of too few patients per investigator does not permit individual investigators to link the drug with particular problems.

The agency is allowing a lot of "me-too" drugs on the market some of which are less safe or less efficacious than existing drugs already approved and marketed in that drug class.

These are value judgements. Each case is open to many considerations and criticism depending on one’s perspective. In general, the FDA standards are the same as in other jurisdictions.

**Speed of FDA New Drug Approvals**

I think the time lines to make a decision are good but there should be little pressure to approve; user fees creating more pressure than many acknowledge; the "law" does not say that a new drug has to offer a substantial improvement over older one.

I have been at the agency for only a year which is too short a period to make any additional comments.

Speed is not the problem, see below.

Less stress on safety and more stress on "post-marketing" data even in situations where efficacy not there in NDA data.

Rapid approval often means insufficient time to examine carefully original data, accepting "on faith" validity of randomization, screening, use and misuses of inclusion and exclusion criteria. There is insufficient time to discuss outlying observations with other relevant discipline.

I know of other applications that were [approved rapidly]; 2 were approved later and withdrawn from market.

Due to the large volume of NDA data, primary review was done by a few medical reviewers (split review by indication, efficacy, safety, etc.) to speed up [review]. There is a sense of total overview. Secondary reviewer's summary may have the best viewpoint.

I have been at FDA 10 months and therefore have limited experience on drug approval.
Although I started work as a medical reviewing officer in June 1995, I had previously worked as a consultant to pharmaceutical companies for 11 years and as an officer for two companies five years before that. Pressure to make a decision not approve.

The official times allowed for the review process keep getting shorter and shorter. The recently passed "FDA Modernization Act" is making things a lot worse.

Issue is not rapid "approval" but rapid review.

In my division the accelerated approvals were justified and resulted in a measurable health benefit --antivirals -- HIV protease inhibitors.

Long overdue. I do not believe that the decreased approval time has necessarily compromised safety. The system was too open-ended previously.

My greatest concern is with rapid approval of over-the-counter switches, because external exposure suddenly increases rapidly and incorrect dosing (too long, too much) also increases. (Seldane almost went over-the-counter a few years ago, it is now known to interact with many other medications and cause torsades [a heart arrhythmia] ... there are other examples pulled back "just in time.")

Improved computer support, information technology, communication technology and better staffing have greatly enhanced the speed at which we can work and review applications in less time today than prior to 1995.

FDA approvals of drugs at a fast speed are without question more risky than before (slow approvals) but faster approvals have had a positive public health impact on the treatment of life-threatening diseases (AIDS and cancer).

Standards for animal studies are being stretched or disregarded. Companies sometimes attempting to go straight to Phase III from I.

The FDA review process is still too slow given the vast resources of the agency.

Medical Officers don't approve NDAs. We simply recommend for or against approval. Office directors make the final decision.

Computer-assisted NDAs require too much time to learn how to use and can be set up in such a way to hide data. The center is not interested in addressing these issues. It is difficult to put an [Investigational New Drug (IND)] on hold and to make sponsors live up to IND agreements proposed.
Approving a Greater Proportion of New Drugs

They need to be approved strictly on the basis of their (individual) merits.

We are in the midst now to approve everything but to describe drug weaknesses in the label. As one high ranking official said "Everything is approvable. We can use the labeling creatively to lower the problems."

Pressure to approve comes largely from the office and center level. Decisions should be left with the division -- that is where the expertise is.

The idea of PDUFA was to accelerate review. I would hope reviewers do not feel they have to approve anything they wouldn’t want to.

Borderline drugs are being approved with the correct labeling and rectifying many deficiencies (safety) of products.

Lesser split data review by medical reviewers though it may take little longer time.

Not all drugs that are reviewed more quickly are approved; one can also reach a decision not to recommend approval more quickly than in former years.

We hear rumors about pressure from Congress and higher administration but nothing concrete.

No pressure to approve or not approve.

There was an issue in our division but almost all of the discussion I've heard regarding this is from outside our division.

What are the options; everything must now be "approved" or approvable.

If we are approving a greater proportion of NDAS it would be the result of improved communication and collaboration during the pre-NDA process.

In the last two years, I recommended that two drugs not be approved. They were both approved without consulting me. This never happened before. In one case, the drug did not meet the standards set up by the division, so they nullified the standards.
The public (clinicians and patients) are served better when there are more options for treatment. The risk/benefit ratio should be recognized by all in order to take full advantage of more drug availability.

I personally do not use or prescribe new drugs/vaccines unless they have been on the market 2-3 years in U.S. (Though I don't work with cancer, AIDS, etc.).

Some feel that all problems can be avoided by having them listed in the label.

I do not believe there is a pressure to approve a greater proportion of applications than before.

Reliance on Post-marketing Studies

I think that all drugs should have a large randomized safety study at approval focusing on death and serious events occurrence. If properly designed, the cost would be reduced and not too great.

These studies are in many instances essential; in the case of many diseases the exposure base can never be adequate prior to approval (Phases I-III).

We don't trust that the companies will carry out Phase IV [post-marketing] studies with due diligence, either before or after PDUFA.

Potentially dangerous scenario.

Post-marketing studies are frequently not completed. FDA has no power to ensure such commitments. Drugs have been marketed before post-marketing protocols have been reviewed. I can think of only one such study that was designed properly and is being conducted reliably--metformin.

Good idea but no way to enforce Phase IV studies. If sponsors don't do them correctly what recourse does FDA have? It's tough to pull a drug.

Post-marketing is often necessary to examine aspects of a drug that seems safe and effective and should become available for use but may have not had adequate testing. All drugs can have more serious events that may not be revealed in clinical trials.

Companies do not always do the post-marketing studies. They agreed to do them poorly or very slowly--and there is neither incentive for the company nor regulatory power by the agency to improve or accelerate the study, making "reliance" problematic.

I have not seen drugs approved based on Phase IV commitments.
More drugs are being approved without requiring post-marketing studies.

Because they are a requirement for drugs under accelerated approval regulation.

I don't believe any drug should be approved on post-marketing studies; they should supplement approval but I would never recommend a drug for approval if there were any questions whether safety was unknown (which is to say a drug must be safe but that there are no criteria identified).

The agency forfeits its most powerful weapon -- withholding approval. Essentially all Phase IV studies which are required are for safety reasons. If a problem is identified, the agency negotiates with the company for labeling changes. Withdrawal is extremely unlikely even if its problem is very serious.

Question above poorly worded. It is much more common to have Phase IV studies now.

No clinical trial is sufficient enough to learn the safety profile of a drug. Post-marketing studies are (and have always been) essential to learn the true safety of a drug. Post-marketing studies are more common now and this may be one of the reasons we are learning more about safety than ever before.

Post-marketing surveillance done by the sponsors is inadequate as is post-marketing surveillance at FDA -- this is one area of the agency that could really be improved.

Post-marketing studies should be required of all chronic therapies.

There are no teeth in post-marketing agreements.

FDA has been more vigilant and more demanding than before. This may account for Phase IV studies being more common.

**Shifting New Drugs Into the Accelerated Approval Category**

Some drugs need to be in the accelerated approval category, although this should not be based on a unique mechanism of action.

The industry is more and more aggressive to get their NDA designated for "priority review." We have to fend off those inappropriate ones with considerable resources.

Our division has been strict with this.
This is a formula for disaster. The patient doesn't benefit. A prime example is Fosamax touted as a "gold standard" yet of questionable value. Another is tamoxifen for "prevention" of breast cancer, but not yet fully available. Still another--Viagra.

Lack of consistent wording to pull off the market drugs when sponsors do not do what they should or commit to do.

Drugs for serious pain or other critical conditions that have "unique mechanisms" and treat conditions for which no adequate therapy is presently available deserve accelerated status.

The drug which I reviewed [was accelerated approval]; it was not approved secondary to safety after Advisory Committee by company request.

This should be done very judiciously, based on the public need for the medication, as medically assessed--not on motives based on political, economic profit or newness for its own sake.

It is particularly in the case of drugs with new mechanisms of action that unanticipated safety problems are likely to occur. These are drugs that should not be subjected to accelerated approval.

Tricky issue, could be a real problem.

Accelerated approval regulations are very carefully written and appropriate balance provided for population needs and demonstrating safety and efficacy. It is the application of the [regulations] that will be the true test.

Why to assign a priority status to the drug which does not work.

I can't really answer this. I believe accelerated approval was long overdue and supply forced use with surrogate markers long accepted by physicians anyway.

I think it is abused by companies for marketing reasons, when the benefit to public health (or some small subset) will be minimal at best.

The person who wrote these questions betrays a profound misunderstanding of the regulations under sub-part h, and of the review process.

This has been one of the most recent successes of the FDA. I lived through the days when AIDS activists criticized us for being paternalistic and not allowing them (AIDS patients) to have access to new drugs. Patients were willing to take risks and we were in their way. Accelerated approval brought to them many new drugs that have increased survival time.
Should be reserved for life-threatening or incapacitating conditions for which there are no other treatments.

Appropriate in some cases.

**Inappropriate External Pressure on FDA Medical Officers**

I have experienced no pressure of this nature.

Thank God, I have not seen any.

My feeling after more than 20 years at FDA is that unless drugs can not be shown to "kill patients" outright then they will be approved with revised labeling and box warning.

Fortunately, there has been none, and I would be very resistant should any be made.

Haven't experienced it.

This is not new!

If anything the mandate to approve drugs is more internal. I dislike images recently projected of the agency hand-in-hand with drug companies helping to bring "safe and effective" drugs to the consumer. That is not our role.

Primary reviewers are organizationally insulated from inappropriate external contacts. We are not authorized to receive calls or visits not scheduled by project management staff and [Consumer Safety Officers]. Meetings must take place in presence of [the Consumer Safety Officer] who records information.

I am not aware of any inappropriate external pressure on FDA Medical Officers. In my eight years of FDA experience I have never been confronted with inappropriate external pressure. This is one of the issues I treasure the most about being a Medical Officer: My decisions are strictly scientific. They are based on data. I have not had political or economical pressures of any kind.

Supervisors and administrators--from Congress re: myotropin [a drug for amyotrophic lateral sclerosis].

Personally, I feel somewhat shielded from external pressures. However, internal pressures have increased significantly.

I haven't heard of a single such case in my division.
I heard of one Medical Officer who is said to have quit because of pressure from Capitol Hill about a controversial drug.

Probably rare.

**FDA Medical Officers’ Ability to Express Their Own Views at FDA Advisory Committee Meetings**

There is a Center effort or at least a discussion to prevent the divisions from offering opinions.

These views are respected in my experience.

The Advisory Committee (or anybody) don't pay much attention to what the primary reviewers say.

On the whole respected. However, we are limited in our ability to ask "politically incorrect" questions of the Advisory Committee.

I was "guilty" of expressing my opinions before the Advisory Committee of our Division and several others for whom I wrote consultative reviews before 1995. I have not been asked to present reviews since.

A Medical Officer must be forceful on safety concerns.

The default appears to be "yes" [to approve]; the hurdle to disapprove a drug is much higher than approving a drug.

I find the agency and its supervisory staff to be quite willing to discuss issues with Medical Officers, even if their views differ. The exchanges I have had have been most informative--both ways. At some times I have made my point; other times I learned something that caused me to change my views.

We can [express our own opinions] and I do.

It is important to balance presentation of data with "influence" in Advisory Committee settings.

For final NDA decision, MD's views disregarded at least openly.

Opinion is not usually presented either positive or negative.
In retrospect, I think the "instruction" [not to present particular data or one's own opinion] was appropriate and contributed to the scientific quality of my presentation.

I don't think we are censored, but our opinions aren't always taken seriously however.

Never [been told to not present data or own opinion at an Advisory Committee meeting]. It would be against our policy and procedures to do so.

A lot of freedom to do this. I feel my opinions and views are respected and always taken in consideration. (I don't always win, which is OK.)

They are free to express, but can easily be over-ridden re: Duract.

The Advisory Committees are increasingly pro-approval in recent years.

It depends if management has been "for" or "against" drug approval. In my case they were supportive of my comments since there were problems with drug efficacy.

Adequate in general.

Pressure on FDA Medical Officers from Supervisors to Change Their Opinions

I have been under no pressure from supervisors.

Our superiors don't put pressure on us. They just ignore our opinion and write their own memo.

I did not change my review and asked them to write above me, which they did.

User fees provide stress to whole agency “to be a partner” with drug company for approval. Case report forms need to be reviewed more carefully.

I feel free to express and argue my views and position, even thought I do not always persuade.

Not in this division.

In general, I have not found this to be a problem.

Medical Officers are under no pressure in my discipline to conform. If supervisory opinion differs, the Medical Officer review stands and the team leader/division director writes a separate document.
My opinion was simply ignored/overruled.

As a team leader supervisor and reviewer I often influenced those who were under my direction yet never in a way that did not reflect my true beliefs and always with the understanding that their opinion was paramount.

My supervisor is helpful and supportive of good work.

Hurry and finish the review.

You are not pressured to change your mind, you just don't receive the positive reinforcement which goes along with an "approval" (a laudatory e-mail from the director, for example).

My interactions with supervisors have been marked by disagreements about different issues that we discuss and even argue about but I have not felt that they were pressuring me one way or another. Half the time I was right, half the time I was wrong. The free discussion of the issues led us most of the time to make the right decisions or decisions that if wrong, didn’t have a major public health impact. Most of the decisions are reached by consensus.

Supervisors are not allowed to order a reviewer to change his or her recommendations.

Superiors will try to get reviewers to change his/her mind so that they will not need to take the heat if something goes wrong. They have the option to override and should be willing to do so in writing.

My office director told me that he was going to overrule me because the sponsor (Wyeth-Ayerst) would just go over our heads to Capitol Hill. He felt it was best to approve the drug for an indication not studied and have the sponsors do a Phase IV post-marketing trial in support of the indication. I reminded him that this sponsor had failed to honor other Phase IVS. He went ahead and approved the drug.

Supervisors may express their opinion and sometimes convince the primary reviewer. Supervisors should never ask the primary reviewer to change his opinion. If they still disagree, both opinions should be on record.