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FDA's Handling Of UFT Raises Questions About Agency's Isolation, Grasp Of Science

It would be difficult to argue that the oral drug UFT is a breakthrough in the treatment of advanced colorectal cancer. It may be a more convenient, less toxic version of intravenous 5-fluorouracil, the old workhorse of cancer care.

However, in its journey through the approval process at FDA, the drug has become an oncology landmark of another sort by bringing into question the agency's grasp of clinical medicine and its isolation from the mainstream of oncology.

"This case points to a disconnect between FDA's standards and the

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In Brief:

Reed To Leave NCI Next Year; Allegra Moves To Extramural Side; Ozer Heads Okla. Center

EDDIE REED, chief of the Medical Ovarian Cancer Section in the NCI Medicine Branch, Division of Clinical Sciences, was named director of the Mary Babb Randolph Cancer Center at West Virginia University. Reed will take the post vacated by **Fred Butcher**, founding director of the cancer center who resigned last year to become director of the Blanchette Rockefeller Neurosciences Institute. **George Spratto**, dean of the WVU School of Pharmacy, is interim director of the center until Reed joins the faculty early next year. Reed was awarded the U.S. Public Health Service Commendation Medal in 1993 for his work on the use of Taxol in ovarian cancer, and holds four patents for his work in developing cancer treatments and tests. He joined NCI in 1981. "Dr. Reed is known throughout the world for his innovative scientific work, and for the care he has given to patients at the NIH," said **Robert D'Alessandri**, dean of medicine and vice president for health sciences at WVU. "Our faculty are eager to begin working with him, and we expect that he will attract the very best physicians and researchers to the Mary Babb Randolph Cancer Center over the next decade." . . . **HOWARD OZER** was named director of the University of Oklahoma Cancer Center and Eason Professor of Hematology/Oncology and chief of the division of hematology/oncology. Ozer was director of MCP Hahnemann Cancer Center in Philadelphia for the past three years. . . . **CARMEN ALLEGRA**, chief of the NCI Medicine Branch, will take a new position of vice-deputy director of extramural science, working under Deputy Director for Extramural Science **Robert Wittes**. His job will be to develop

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Special Report:
FDA In Isolation

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FDA Isolated From Mainstream Oncology, Leading Experts Say

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needs of patients and the clinical oncology community," said Daniel Haller, a colon cancer expert at the University of Pennsylvania.

Disregarding a unanimous recommendation of an advisory panel, FDA withheld approval for UFT. But the problems in the agency's handling of UFT began long before the data were presented to the Oncologic Drugs Advisory Committee last September and persist to this day.

According to documents obtained by **The Cancer Letter**, in the process of reviewing the drug, FDA made multiple shifts in requirements for demonstrating the drug's safety and efficacy, made a series of fundamental mistakes in statistical interpretation of scientific data, and invoked an obscure regulation to demand clinical trials that, according to experts, would be useless, impractical, and unethical.

The implications of this controversy extend beyond UFT and two other applications for oral versions of 5-FU that have been tested in advanced colon cancer and are under FDA review. An examination of the agency's handling of the drug places a magnifying glass over criteria for evaluation of clinical trials that seek to demonstrate equivalence, or non-inferiority, of new drugs to established therapies.

Experts say such trials are becoming increasingly important, as scientists seek to refine existing therapies by reducing toxicity and enhancing convenience. In fact, UFT was developed to accomplish both of these goals.

"It becomes a dangerous exercise for the pharmaceutical industry to play 'guess-what-I-am-thinking' with FDA," said Haller, editor-designate of the Journal of Clinical Oncology. "You can hear this in every cooperative group; you can hear it in the pharmaceutical industry; you can hear it from people who are directly and indirectly involved." Haller was not involved in the development of the drug.

The schism between FDA and the rest of the oncology world is so profound that in the case of UFT, the agency did something that is almost unheard of: it disregarded the unanimous recommendation of its own advisory committee, which voted last September that the UFT/leucovorin treatment for advanced colorectal cancer was equivalent to 5-FU/LV, and should be approved.

Committee members contacted by **The Cancer Letter** said they are still searching for a plausible explanation for the agency's failure to approve the drug. After all, the 816-patient pivotal trial conducted by the drug's sponsor, Bristol-Myers Squibb, was the largest registration trial ever done in advanced colorectal cancer. Another study, a 380-patient confirmatory trial, was so consistent with the pivotal trial that committee members said the survival curves practically sat on top of each other. Most important, the statistical worst-case scenario for UFT—a 20-percent drop in survival—represented a few weeks of life, and was acceptable to experts who comprise ODAC.

"I walked out of that meeting with the expectation that the vote would result in approval," said Richard Schilsky, associate dean for clinical research at the University of Chicago and chairman of Cancer and Leukemia Group B, who at the time served as chairman of the advisory committee. "There was a technical, regulatory issue that remained to be resolved, which we expected to be resolved in negotiations between Bristol and FDA."

That technical, regulatory issue involved the contribution of uracil—the U in UFT—a naturally occurring substance that improves the absorption of FT, or tegafur, from the gastrointestinal tract and prevents the typical rapid breakdown of 5-FU formed from tegafur.

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Schilsky's expectation notwithstanding, months went by with no approval. Finally, last March, Bristol withdrew the application to avoid getting a "non-approvable" letter from the agency. The company has since resubmitted the application.

In the secretive environment of drug development, knowledge is the privilege of a small number of people who are bound by laws, traditions and confidentiality agreements to disclose as little as possible. To get the answers, one had to challenge FDA on science, demanding an explanation of its rationale for not approving the drug.

But who would mount such a challenge? Certainly not Bristol. While sponsors often grumble, they regard point-blank questioning of FDA as suicidal. Soon after the company withdrew its application for UFT, the staff of the House Committee on Commerce became interested in the controversy.

Relying on informal guidance from academic oncologists and clinical trials experts, the committee staff put together a series of questions designed to establish whether the agency's actions were based on mainstream science or a quirky homegrown doctrine.

The questions were conveyed to FDA Commissioner Jane Henney in a letter from Rep. Thomas Bliley (R-VA), chairman of the committee. **The Cancer Letter** obtained a copy of the agency's response to Bliley's questions.

After receiving the agency's response, Bliley attacked the quality of science at the agency. "An agency that proclaims itself science-based should not be practicing in junk science," Bliley said to **The Cancer Letter**. "Yet the FDA has ignored the recommendations of oncologists and its own panel of experts, to the detriment of cancer patients and their families."

The agency's response to Bliley is posted at http://www.cancerletter.com/newspage.html. Also posted is the April 21 issue of **The Cancer Letter**, which contains the Congressman's letter to the agency.

FDA Acknowledges Disregarding ODAC Vote

Why didn't the agency approve UFT?

"The central issue in this case involves determining whether or not UFT extends life to a similar extent as 5-FU/LV," the agency wrote in response to Bliley's questions.

"If there is no confidence that a new treatment prolongs life, greater convenience alone would not be a clinically sensible reason to recommend its use. [ODAC] has been repeatedly consulted on this matter and has consistently advised us that they consider evidence of a survival benefit critical when a new treatment is offered as an alternative to an existing treatment known to affect survival."

"An agency that proclaims itself science-based should not be practicing in junk science. Yet the FDA has ignored the recommendations of oncologists and its own panel of experts, to the detriment of cancer patients and their families."

Actually, at the Sept. 16, 1999, meeting, ODAC concluded that a combination of UFT and leucovorin is equivalent to what was then the standard of care, 5-FU/LV.

"It's not simply a matter of greater convenience not being sufficient for approval," said former committee chairman Schilsky. "We did not abandon survival as the gold standard for approval of drugs for the treatment of advanced colorectal cancer. We are talking about equivalence with respect to survival *and* greater convenience. The data supported the notion that—within the limit that we had been debating—the two drugs are equivalent."

The trials of UFT/LV were structured to demonstrate its equivalence with 5-FU/LV. In such trials, there is always a possibility that the new treatment would be statistically inferior to the standard of care.

In a potentially curable disease, like testicular cancer, clinicians would require a high level of confidence that the treatments are at least equivalent. However, in a disease like metastatic colorectal cancer, where therapy has a modest impact on survival, and where most patients die, a higher level of uncertainty can be accepted.

Thus, the committee voted that the worst-case scenario suggested in the UFT data, a potential 20-percent decrease in survival, would be acceptable.

Also, the committee noted that UFT/LV produces less leukopenia and neutropenia than 5-FU/LV, which could translate into better quality of life.

"The worst case scenario of a 20-percent inferiority really boils down to no more than a couple of weeks in this setting," Schilsky, a gastrointestinal cancer expert, said to **The Cancer Letter.** "Therefore, it's reasonable to sacrifice—potentially—a few weeks of survival in favor of a therapy that is more convenient and has a better toxicity profile, so patients who have a limited life expectancy can potentially enjoy that with a better quality of life."

By stating in the letter to Bliley that "the central issue in this case involves determining whether or not UFT extends life to a similar extent as 5-FU/LV," the agency admits that it chose to disregard ODAC's recommendation.

This is disturbing, said Schilsky.

"The members of ODAC are experienced clinicians and investigators," he said. "We are asked to devote a considerable time and effort with minimum compensation to advising the agency on these issues. There is a certain expectation that after we review all the documents and hear all the data presented, and deliberate, vote, and make a unanimous recommendation, that recommendation should be accepted, unless there is some compelling reason not to do so. In that case, the compelling reason should have been brought out during the committee's discussion."

University of Pennsylvania oncologist Haller said he was disappointed by the agency's statement that convenience should not be a factor that should be taken into account.

"That froze me," Haller said. "That says to doctors and patients that when given a choice of two drugs given by two different methodologies, they don't have the clinical ability to make the decision of which one to choose."

Paul Bunn, director of the University of Colorado Comprehensive Cancer Center who also served as chairman of ODAC, said that with better management, the explosion over UFT could have been avoided. "Many problems in life are due to misunderstandings, which are generally due to miscommunications," Bunn said.

"Obviously, there was poor communication between the agency and the committee; obviously, there were poor communications between the agency and the company," Bunn said. "Somebody should have been managing this, to make sure that bad things didn't happen."

"Obviously, there was poor communication between the agency and the committee; obviously, there were poor communications between the agency and the company. Somebody should have been managing this."

Was the agency acting within some alternative theoretical framework that contradicted the recommendation of its outside advisors? Was the technical question of the contribution of uracil indeed important, or was it invoked as a convenient smokescreen?

No Analytical Framework—Yet

In a response to Bliley, the agency said it has no alternative analytical framework to offer, but a "comprehensive guidance" is being developed by the agency's staff. The guidance is being drafted for those perplexed by design and analysis of trials that compare new therapies with the standards of care.

"FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research have formed a working group tasked with developing more specific and comprehensive guidance on design and analysis of active control trials," the FDA letter said.

Some outside observers question the feasibility of such guidelines. Others question the appropriateness and the wisdom of allowing an internal committee of FDA employees to wander out into the minefield of clinical trials methodology. However, all sides seem to agree that when the FDA working group confronts the task of writing guidelines for non-inferiority trials, it will have its hands full.

The agency is trying to avert the following hypothetical scenario:

Let's say a cancer therapy, Drug A, was

approved sometime in the late 1970's on the basis of its ability to shrink tumors. No data exist on its effect on survival or quality of life.

Though Drug A may not be better than placebo, because of oncologists' eagerness to offer something—anything—to their desperate patients, the drug becomes the "standard of care."

Years later, a drug company conducts a clinical trial designed to compare Drug B, a new drug, to Drug A.

When you perform non-inferiority trial, you have to accept that the experimental therapy, in the worst-case scenario, could be less efficacious than the standard of care. If regulators misjudge the clinical relevance of the worst-case scenario and approve Drug B, they could be approving a therapy that is less effective than the standard of care, which, in turn, may be no better than placebo.

There is no evidence that this has occurred in oncology, but that's a concern.

Describing this methodological challenge in the letter to Bliley, the agency appears to offer a glimpse of the analytical framework that has influenced its decision to disregard the ODAC recommendation and kill UFT:

"Interpretation of non-inferiority trials is scientifically difficult, and providing generally applicable guidance on design and analysis of such trials will be a difficult task. These trials… must be designed to show that the standard therapy (control) has some effectiveness, and that the new treatment is equivalent to, or not worse than, the standard therapy.

"If one cannot reasonably define the effect of a control in a study…, it is not possible to interpret an equivalence study. Defining the effect of the control is more problematic where the effect of the control is relatively small (e.g., increases survival by 2-3 months). A risk in any given study population is that the control had no effect, and that a new treatment that was indistinguishable from control might have no effect as well."

Using Historical Controls

In its analysis of the UFT data, FDA made several departures from accepted standards of data analysis, clinical trials experts said.

The standards accepted by clinical trialists are straightforward: to produce convincing data, one needs to define the trials prospectively and randomize patients to the arms of the study.

Data drawn from other studies can be useful, but are always trumped by results obtained from studies using concurrent controls. Yet, the agency's analysis of UFT hinges on statistical adjustment of data obtained from the literature.

"If the true effect of the 5-FU/LV regimen is less than 2.68 months, then the UFT regimen may be a placebo or worse than a placebo in its effect on median survival time," Robert White, the FDA reviewer, concluded.

Here is what the agency did:

■ To ascertain the effectiveness of the control regimen, the agency went through the medical literature and produced a list of eight studies and a meta-analysis comparing 5-FU/LV with 5-FU as a single agent. The 5-FU/LV regimens have not been compared with placebo, and 5-FU has not been shown to extend survival. The effect of 5-FU/LV on median survival fell into the range from zero to 4.3 months.

That accomplished, the agency adjusted the results of the eight trials and the meta-analysis to reflect the worst-case scenario for the potential loss of survival from UFT. "If the true effect of the 5-FU/LV regimen is less than 2.68 months, then the UFT regimen may be a placebo or worse than a placebo in its effect on median survival time," Robert White, the FDA reviewer, concluded at the ODAC meeting last September.

■ The agency also made a comparison of the control arms of the two trials presented by Bristol.

The trials were different in design. The pivotal trial was designed to detect equivalence, with survival as a primary endpoint. The trial enrolled 816 patients, mostly in the US, and used the four-week 5-FU/LV regimen as a control. The confirmatory trial was designed to detect superiority, with time to progression as the primary endpoint. That trial enrolled 380 patients, mostly in Europe, and used a five-week

infusion regimen.

This led the agency to hypothesize that the survival curves in the two studies appear identical only because the regimen used in the second study was not as intensive as in the first.

ODAC members were not impressed.

Looking at the cross-study comparison, Kathleen Lamborn, a biostatistician at the University of California at San Francisco, who served as a voting consultant to the committee, said detected nothing but statistical noise.

"It looks to me like it's just the luck of the draw," Lamborn said at the ODAC meeting last September.

Committee member Derek Raghavan, head of medical oncology at the University of Southern California, was similarly unimpressed.

"You can do any amount of statistical mumbo-jumbo to hypothesize what might happen on a Tuesday at 3 o'clock, but the reality is, these are identical curves, and there is no evidence on the table to suggest that there is a real difference," Raghavan said at the meeting.

"The FDA approach will deny some patients the advantage of an improved quality of life in their last few weeks of life. If that's not scientific nonsense, what is?"

A closer look at FDA's analysis of the data raises questions about the competence of the agency's statistical analysis and its understanding of the treatment for advanced colorectal cancer, scientists say.

Cross-study comparisons are occasionally performed on cocktail napkins at meetings of clinical trials cooperative groups, but are uncommon in formal situations.

"They've gone off the deep end there," said John Crowley, director of the Southwest Oncology Group Statistical Center. "Using historical controls to draw that kind of a conclusion is something we have been fighting against for 15 years, and are still fighting.

"That's completely discredited," Crowley said.

The agency's error is fundamental, clinical trialists agree. "To take an arm out of one trial and compare it to a separate arm from another trial is subject to many different kinds of biases," said Paul Catalano, associate professor of biostatistics at Dana-Farber Cancer Institute and a biostatistician for the Eastern Cooperative Oncology Group. "I would certainly discourage my students from doing it."

"Doing a meta-analysis in your head of two different studies is even weaker than doing a formal meta-analysis of two different studies," said Richard Goldberg, chairman of gastrointestinal oncology programs at Mayo Clinic and North Central Cancer Treatment Group.

Now, let's consider the alleged differences between the two control arms:

The median survival on the four-week regimen in the pivotal trial was 13.4 months, compared to 10.3 months on the five-week regimen in the confirmatory trial.

To evaluate this argument fully, it may be useful to set aside the issues of methodology and enter the agency's analytical paradigm, which in this case entails borrowing the cocktail napkin for a minute.

Can this difference mean something?

"It's the same result," Goldberg said.

Median survival with the Mayo regimen varies from 10 to 14 months. "Everything in between is consistent with random variation," Goldberg said. "What they found is well within the confidence intervals for the median survival determinations observed across studies employing the regimen. In clinical trials, we avoid such confusion by using concurrent controls instead of historical controls."

Is there a difference in survival between 5-FU/LV regimens?

"The results in both advanced disease and adjuvant studies have shown that there is essentially identical activity in all major 5-FU/LV regimens," Goldberg said. "The toxicity profile differs somewhat. The choice of regimens is a matter of convenience and investigator comfort."

The agency's data analysis technique cannot be regarded as a one-time aberration.

Originally presented by medical reviewer White, the historical comparison and the cross-study comparison were subsequently cited in the agency's letter to Bristol. That letter, dated March 23, was signed by Robert Justice, who was then the deputy director of the Oncology Drug Products Division.

Richard Pazdur, the division director, was the principal investigator on the UFT pivotal trial before he joined the agency, and hence was recused from handling the New Drug Application. Pazdur declined a request for an interview.

"A cross-study comparison of survival on the two regimens suggests that survival on [the modified Mayo regimen arm] may be inferior to that on [the Mayo regimen]," Justice wrote in a letter to Bristol.

Later, the cross-study comparison was cited in the agency's letter to Bliley. Though signed by Melinda Plaisier, the agency's associate commissioner for legislation, the drafting of that letter involved scientific, policy, legal, and legislative affairs officials at the agency.

In the letter to Bliley, the agency acknowledged that "cross-study comparisons should be interpreted with caution."

Nonetheless, the agency said it regards the differences in median survival on the two control arms as "adding some credibility to the concern that the differences in survival observed with the standard and modified Mayo Clinic regimens could be due to the less intensive treatment in [the confirmatory study.]"

Ironically, the agency's repeated references to the four-week infusion regimen as the Mayo Clinic regimen are incorrect, Haller said. "The original Mayo Clinic regimen is administered every four weeks for the first two cycles, then every five weeks thereafter," he said.

"If this is the methodology that's going to be used to determine what agent is to be approved, why are we doing randomized prospective clinical trials?" wonders Norman Wolmark, chairman of the National Surgical Adjuvant Breast and Bowel Project.

"This approach will discourage the pharmaceutical industry from developing novel agents in oncology," Wolmark said. "What will happen with the array of new agents, small molecules that are going to work in subsets of patients?"

NSABP is a testing UFT as an adjuvant treatment for colorectal cancer.

Howard Ozer, director of the University of Oklahoma Cancer Center and Eason Professor of Hematology/Oncology, said the agency's analysis of UFT is an example of "scientific nonsense." Ozer coined that term two years ago, as a description for the arguments of Stanislaw Burzynski, a Houston-based practitioner of alternative medicine who has a history of run-ins with FDA (**The Cancer Letter**, Oct. 30, 1998).

"It appears as though the FDA physicians have forgotten—or have never known—what it's like to treat these kinds of patients on a daily basis," Ozer said. "The FDA approach will deny some patients the advantage of an improved quality of life in their last few weeks of life.

"If that's not scientific nonsense, what is?"

Profound Questions?

The agency's reliance on historical controls is spreading.

To keep UFT afloat, Bristol recently reanalyzed its data. Drawing on historical data, the company recently superimposed a 5-FU arm onto the data from its randomized trial of UFT/LV vs. 5-FU/LV.

Yet, after all the statistical manipulations, the agency does not seem to have a clear perspective on UFT. Even Robert Temple, Director of the FDA Office of Drug Evaluation I and the architect of the agency's approach to active control trials, was perplexed by the significance of the data.

Last December, at an ODAC meeting, Temple reflected on the problems of interpreting the UFT data:

"We recently reviewed fluorouracil results, and the improved survival varies from half a month to three months or four months," said Temple said, referring to 5-FU/LV data. "What does that mean in any given trial? Was this one where the effect was half-a-month, in which case the equivalence trial was uninformative, or was it three or four months, in which case the equivalence trial might be informative?

"And there isn't any way to know," Temple said.

Clinical trialists say that by asking this question two months after ODAC made its recommendation on UFT, Temple is stepping over the boundary where biostatisticians usually bow out, leaving it to clinicians to pass the final judgment on a therapy:

■ "Although there may be no way to know the precise contribution of LV to 5-FU in these trials, the survival for 5-FU/LV in the pivotal trial is well within the range of what we have come to expect for this regimen, and the UFT results are no different," said former ODAC chairman Schilsky.

■ "All of the issues that FDA is raising are reasonable scientific issues," said Craig Henderson, adjunct professor of medicine at the University of California, San Francisco, also a former ODAC chairman. "But I believe that in some cases they can be quite rigid, and lose touch with patient care issues.

The question of where the lower limit should be needs to be resolved by doctors and patients. It's not the government's decision."

■ "If you don't have an observation-only arm in the trial, how are you going to get a handle on how much better the standard is than observation?" said Crowley.

"You have to go back to randomized trials of standard vs. observation, and do something with them. Average them. Weighted-average them. Bayesian them. Take a worst-case scenario. You have to do something. That's what [Temple] is struggling with, and that's a legitimate research question," Crowley said.

"The clinical judgment comes in when you try to decide how much less than the standard therapy are you going to tolerate. Does it have to be 90 percent, or 80 percent? The reasonable thing to do in this case is to rely on the collective wisdom of ODAC."

■ "There is never going to be a universally acceptable statistical solution to this, because of the inherent difficulty of taking non-concurrent controls and combining them with the data from randomized trials," said ECOG and Dana-Farber statistician Catalano. "Once the studies have been executed, and they have been analyzed, and they have passed statistical muster, and the results are available for scientifically valid interpretation, can an statisticians help in that process? Yes. But ultimately the clinicians are the ones who are going to decide."

■ "ODAC has the wisdom to perceive how beneficial UFT can be in the real world, and for Dr. Temple to suggest that somehow they've missed the statistical point is absurd," said the University of Oklahoma Cancer Center Director Ozer.

■ "When you are talking about equivalence trials, you are really talking about something similar to a null-hypothesis study," Haller said. "The problem with null-hypothesis studies is that proof of equivalence with no possibility of error in either direction requires a huge sample size. Should we be spending our clinical trials resources on such studies?"

From Vision To Policy?

Like it or not, FDA officials are working on developing their methodology for interpretation of active control trials.

"Methods for determining the non-inferiority margin are evolving, and BMS has suggested alternative methods for determining the margin here," the agency said in the letter to Bliley.

"At this time, the [internal working] group is surveying and evaluating current practices to identify best practices and areas of apparent inconsistency prior to beginning to draft a guidance," the letter said. "This guidance will be made available in draft for public comment at an appropriate point in its development."

"The issue is not so much whether we need their guidance; we are supposed to be guiding them. The committee is supposed to be advisory to FDA; not the other way around. The committee has the expertise to make judgments based upon looking at the data."

The letter appears to suggest that in some cases, three-arm trials testing new treatments simultaneously against active control and no treatment would be appropriate. "[Trials] must be designed to show that the standard therapy has some effectiveness and that the new treatment is equivalent to, or no worse than, the standard therapy," the letter states.

If the agency is suggesting such trials, it will soon learn that trials that randomize patients to best supportive care in diseases where other treatments exist cannot be done in the U.S., said ODAC member George Sledge, an oncologist at the University of Indiana.

"We certainly need to challenge old dogmas, but if you ask, 'Are you going to get physicians to use no-treatment control arms when they have been using a regimen they consider active?' the answer is 'No, it will not fly,'" Sledge said to **The Cancer Letter**. "The study simply will not be accomplished."

Such trials have been done outside the U.S., in countries where patients have few treatment options. "In the U.S., where you have a highly mobile population and multiple sources of care, it's simply impossible to force people into those sorts of trials," Sledge said.

As the process of codifying knowledge on

active control trials continues to move forward at FDA, many observers wonder who would be the grateful beneficiary of all that work.

Schilsky said ODAC doesn't need the guidance.

"I think the issue is not so much whether we need their guidance; we are supposed to be guiding them," Schilsky said. "The committee is supposed to be advisory to FDA; not the other way around. There may be regulatory issues where the committee wants clarification from FDA in the course of their deliberations, but the committee has the level of expertise that is sufficient to be able to make judgments based upon looking at the data without being guided by the agency."

ODAC member Sledge said the guidance could be useful if it clarifies the agency's requirements.

"If you are a cooperative group or a company, and you are going to devote years and resources to answer a particular clinical problem, not knowing at the end of the day whether it's going to be shot down, based upon what's basically a definitional question, you need to know that before you head into it," Sledge said. "Otherwise, we waste a huge amount of resources, and I don't mean just financial resources. If you are conducting a multi-hundred-patient clinical trial, those represent patients who could equally well take part in trials of other interesting drugs."

Observers warn that efforts to develop comprehensive standards for active control studies can turn into an open-ended endeavor. Developing such standards in-house would not be too different from developing a guideline on the meaning of life and putting it out for comment, observers said.

ODAC member Richard Simon, chief of the National Cancer Institute's Biometric Research Branch and an expert in the evaluation of active control trials, said that while the standards could be useful, the agency should avoid drafting these standards in isolation.

"It may be useful to have guidelines for the design and conduct of active control trials in order to clarify the situations where such designs are appropriate, to foster appropriate analyses and to provide guidance to FDA staff in review of applications," Simon said.

"Such guidelines are best developed by a joint committee of FDA staff and external clinical and biostatistical scientists," he said. "Internal development by FDA staff alone does not provide an adequate context to ensure that the proposals are based on peer reviewed clinical trials methodology."

The risk is obvious, said Peter Boyle, director of the division of epidemiology and biostatistics at the Milan-based European Institute of Oncology.

"It's such an important issue that you need to have all the best advice in the beginning. If you don't have real methodological experts involved from the outset, you risk making a mistake, and then the whole thing could be trashed once you bring it out."

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On The Uracil Question

An examination of the agency's letters to Bliley and Bristol points to the growing importance of "fixed combination" regulations.

The rule was developed in the late 1960's, to evaluate the drugs that were approved before 1962, when Congress amended the Food, Drugs and Cosmetics Act to require that drugs demonstrate efficacy.

Many of these legacy treatments from the time when only safety data were required were improbable combinations that had no scientific justification. By demanding that sponsors demonstrate the contribution of each of the ingredients to the effectiveness of the treatment, the agency sought to weed out combinations whose only purpose was to provide a basis for a patent or an unsubstantiated claim.

Before UFT, the regulation had not been applied in oncology. In the case of UFT, the rule was applied twice: to the combination of uracil and tegafur, which are part of the same pill, and to oral leucovorin, which Bristol wanted to market in the same package with UFT.

The law does not specify the kind of proof the

agency should demand. "Under the 'fixed combination' rule, the way to demonstrate the role of each component in the combination is not specified, and would depend on the role of the component," the agency said in the letter to Bliley.

In the case of UFT, FDA asked for the highest level of proof possible, demanding that the sponsor conduct randomized trials to demonstrate the contribution of uracil to UFT.

"Even if UFT/LV and 5-FU/LV were both effective, there must be a contribution of uracil to the effect of UFT/LV," the agency wrote in the letter to the company. "The design of [the two studies] does not permit a direct assessment of the contribution of uracil to the UFT/LV regimen."

Had FDA been so inclined, it could have waived the requirement altogether, by declaring that the therapy constitutes an "important therapeutic advance."

ODAC, too, could have made a recommendation on avoiding the uracil issue, but apparently failed to recognize that opportunity. Asked whether UFT constituted an "important therapeutic advance" in the treatment of advanced colorectal cancer, the committee said No. After all, UFT is just another form of 5-FU, the committee said.

"The committee took that question at face value with respect to does this represent a therapeutic advance, meaning, does it clearly show improved efficacy?" Schilsky said. "Had the question been asked in a different way, or had the committee considered the issue of therapeutic index, as opposed to just outright improvement in efficacy, the question might have been answered differently.

"I personally would have voted in favor of the question of it being a therapeutic advance," Schilsky said (**The Cancer Letter**, April 21).

Former ODAC chairman Bunn said committee members should never be blindsided by the agency's questions.

"When I was the chair, [FDA staff] always gave the questions to me well in advance, so we could discuss them and change them," said Bunn. "Points that have not been previously discussed, yet suddenly appear at a committee meeting, are going to cause problems. And that's what happened here."

Of course, even with 20/20 hindsight, the committee's vote probably wouldn't have made a difference.

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Even the agency's principal question to the committee about the drug's approval contained an ominous caveat. "If the FDA concludes that the contribution of uracil to the UFT capsule is adequately shown, is this NDA approvable?"

Fixed Combination: The Meaning

Did BMS know about the fixed combination rule before walking into the buzz saw at ODAC? Are clinical trials designed to answer the uracil question feasible—and ethical? Most important, what is the significance of the agency's decision to apply the fixed combination regulation in oncology?

"If they are saying that the contribution of each element in a combination therapy has to be demonstrated in a clinical venue, they are saying that in any combination therapy, you are going to have to isolate each component and test it individually," said Mace Rothenberg, the Ingram Associate Professor of Cancer Research at the Vanderbilt Ingram Cancer Center. "That bodes poorly for cancer vaccines, and dendritic cell therapy, and gene therapy, and noncytotoxic therapy. What they are saying is that we are now putting a complete halt to the development of all novel therapies that require more than one component."

In the body, the tegafur component of UFT is converted to 5-FU. Meanwhile, uracil, a pyrimidine that is naturally present in ribonucleic acid, competes with 5-FU at the level of the important catabolic enzyme dihydropyrimidine dehydrogenase (DPD),

slowing down the breakdown of 5-FU.

"The reason we don't think that [uracil's] contribution needs to be further assessed now is because of the clear past experience with tegafur alone," said Bristol clinical oncologist Steven Benner at the ODAC meeting last September.

"Tegafur, given as an oral regimen, produced survivals that appear worse than what we achieve now with 5-FU/LV or with UFT/LV in metastatic colorectal cancer, [and] was associated with significant toxicities, so much so that the development of tegafur as an oral drug was abandoned in the U.S."

In individuals who have DPD deficiency, the level of uracil can be 100 times higher than the level they receive in UFT. Yet, under normal circumstances, these people suffer no ill effects.

The company's case for the safety of UFT included 15 years worth of adverse events reporting and other safety data from Japan, where UFT is used for a variety of indications, and several volumes of pharmacology data that were given to the agency but not presented to ODAC. The agency's assessment of these data was not discussed in the letters to Bliley and BMS.

Clinicians contacted by **The Cancer Letter** say they accept the argument that the role of uracil in UFT does not need to be proven with precision.

"There is no one, absolutely no one of the face of the Earth who is experienced in this area who would tell you that (1) uracil is a toxic agent, and (2) that in this setting it does not contribute to the uptake and the activity of tegafur," said Rothenberg. "The ability of increased uracil concentrations to inhibit the DPD, and for that inhibition to be able to increase the half-life and potency of 5-FU is well established."

Yet, according to FDA, the safety of uracil is uncertain. "Unfortunately, theories about roles of components are not always borne out, and unexpected consequences, even of naturally occurring substances, have been described," the agency said in the letter to Bliley. "The contribution and value of uracil is thus a matter of clinical importance."

In the letter to Bristol, the agency noted that "available data do not exclude an adverse effect of uracil on the safety of tegafur."

The claim that data "do not exclude" harm from uracil merits consideration. Data are observational. They cannot "exclude."

"Can you exclude the possibility that someone's nose might fall off during treatment?" asked Rothenberg rhetorically. "No. It may not have been seen in the 20,000 people treated, but it *could* happen."

"Can you exclude the possibility that someone's nose might fall off during treatment?" asked Rothenberg rhetorically. "No. It may not have been seen in the 20,000 people treated, but it *could* happen."

Prospective In Reverse

Despite requiring sponsors to design studies prospectively, in the case of UFT, the agency did not lead by example.

According to the letter to Bliley, Bristol had no reason to be surprised when the fixed combination rule was invoked.

In 1991, the agency advised Taiho Pharmaceuticals, the drug's sponsor at the time, to conduct a three-arm study to answer the uracil question.

"In our initial meeting with Taiho on Sept. 11, 1991, FDA indicated that the contribution of [uracil] was a serious issue," the agency said. "FDA suggested that a third arm, FT/LV, be added to the phase III study."

The letter fails to state that at a later meeting, the agency agreed to a phase III development plan that didn't include the third arm.

Sources said the agency changed its mind about the third arm after Taiho submitted the data that drew on extensive experience with tegafur and uracil. This included preclinical data, pharmacokinetics, and clinical data on UFT and its tegafur component.

At the ODAC session last September, FDA officials did not contradict the sponsors' statement that the phase III trials were developed in cooperation with the agency.

"Throughout the entire development of UFT and leucovorin, a series of meetings were held involving the sponsor and FDA," Renzo Canetta, head of oncologic drugs development at Bristol, said at the ODAC meeting. "As a result of these meetings, the registration plan was developed with a stated goal to demonstrate equivalence and efficacy, as measured

by survival, in comparison with the standard of care of intravenous 5-FU/LV."

Yet, after the trials were completed, the agency returned to its original view that the role of uracil should be described. Justifying a demand for randomized trials, the agency cited five small European phase II studies that tested tegafur as a single agent.

"Tegafur administered orally on a prolonged daily schedule (especially in combination with leucovorin) has been reported to have clinically significant activity with acceptable safety in advanced colorectal and other cancers," the agency said in the letter to BMS.

One of the studies was conducted in advanced colorectal cancer; the rest were breast cancer studies. All the studies cited by the agency were published since 1994, the year Bristol and the agency agreed on the phase III plan for UFT.

The suggestion that Bristol look into using tegafur alone is rich in subtext: while UFT is protected by a current patent, uracil and tegafur are not. A suggestion that the company study a substance it doesn't own is equivalent to saying, "Go do something nice for the generics."

"If companies are going to be asked to conduct further trials based on sketchy information that emerges after their pivotal trials begin, clinical testing will become interminable," said attorney Grace Powers Monaco, a patient advocate and a former ODAC member. "I know it's a difficult concept to grasp, but companies seek a return on their investment, and patients and physicians need to have access to products that will make their quality of life easier, particularly in hard-to-treat cancers."

But, like it or not, the agency has spoken:

"[A] randomized controlled clinical trial designed to assess the contribution of uracil to the safety and effectiveness of tegafur appears to be feasible and necessary," the agency said in its letter to Bristol.

Feasible? Necessary?

■ Youcef Rustum, an expert in flouropyrimedines, a class of drugs that includes 5-FU and UFT, said the role of uracil should be addressed in pharmacological studies, not clinical trials.

"A randomized clinical trial is not going to be decisive," said Rustum, senior vice president, scientific affairs, at Roswell Park Cancer Institute, who served as a consultant to Taiho. "It would require a large number of patients, and the end result may not justify the time, and effort, and expense."

■ "[Fixed combination] is a real issue that's being overdone here," said former ODAC chairman Bunn. "FDA could have gotten away from it. If they had talked with the committee, most likely, the committee would have said, 'Don't change your policy.' Ordinarily, in a combination you do want to know the contribution of each component. But here you are never going to find it out. It's safe the way it is, and there is a theoretical reason why it probably does contribute."

■ "The agency is in the Dark Ages; they are counting the angels on the head of a pin," said Robert Comis, chairman of Eastern Cooperative Oncology Group. "None of us would randomize our patients to a three-armed study with two inactive drugs, i.e. tegafur and uracil, versus an obviously active agent for the sake of pharmacology and an inane regulation. The [survival] curves are on top of each other.

"The agency should just take the advice of their experts, approve the drug, and allow the doctors and their patients to decide," Comis said.

In Brief:

Sandra Swain Is Acting Chief Of NCI's Medicine Branch

(Continued from page 1)

an implementation plan for applying discoveries in NCI's prime areas of scientific emphasis, particularly the "Extraordinary Opportunities" of the Bypass Budget, to cancer treatment, detection, and prevention, according to a memo Wittes wrote to Institute staff. Allegra's initial emphasis will be in prostate and gastrointestinal cancers. **Sandra Swain** was named acting chief of the Medicine Branch. . . . **FIRST ANNUAL** Advances in Cancer Prevention Lecture, sponsored by the NCI Division of Cancer Prevention, is scheduled for Aug. 3, at 3 p.m. in Lister Hill Auditorium, NIH. The inaugural speaker is **Bernard Levin**, vice president, Division of Cancer Prevention, University of Texas M. D. Anderson Cancer Center. Levin's presentation, "Cancer Prevention: What is the Future?" is open to the public and registration is not required. Persons requiring assistance or accommodations should call 301-496-8640. . . . **FEDERATION OF AMERICAN** Societies for Experimental Biology report finds NIH support for equipment and instrumentation is insufficient and should be increased. For a copy of the report, see: http://www.faseb.org/opar/instrument/report.html.

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