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FDA Working On New Ground Rules For "Adaptive" Clinical Trial Designs

By Paul Goldberg

FDA is trying to depart from exclusive reliance on frequentist statistics and is defining new ground rules for using "adaptive" clinical trial designs for drug approval, a top agency official said.

"The bottom line is this: We are open to new scientific advances in clinical trial design that enable us to learn more about how to safely guide clinical decisions," Scott Gottlieb, FDA deputy commissioner for medical and scientific affairs, said at a pharmaceutical industry conference July 10.

Adaptive designs allow scientists to alter trials on the basis of data that are being accumulated. In such trials, a finding of efficacy in a subset of patients can be a trigger for enrolling more patients who have these characteristics, and an unexpected toxicity can trigger a dose reduction or a discontinuation.

No new laws or regulations are needed for the agency to accept such trials. However, no sponsor would bet a multimillion-dollar development program on novel designs without an unambiguous declaration by the agency

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Professional Societies:

ASCO Picks Michigan Dean Allen Lichter As Executive Vice President And CEO

The American Society of Clinical Oncology said its board selected Allen Lichter, dean of the Medical School at the University of Michigan, as executive vice president and chief executive officer of the society.

Lichter, a radiation oncologist, served as ASCO president in 1998-99 and was chairman of the ASCO Foundation Board from 1999 to 2002. He plans to complete his term as medical school dean and begin his new position in late October.

"It is an understatement to say that ASCO's Board of Directors is thrilled to have Dr. Lichter join ASCO in this capacity," said Gabriel Hortobagyi, president of the society. "When we began our search nearly a year ago, we couldn't have imagined a more ideally-suited candidate for the position. Dr. Lichter is one of the most well-regarded oncologists in the world. He has served ASCO in numerous capacities over the years, and his personal commitment and dedication to the mission of the organization speaks for itself."

The board sought a candidate with extensive scientific knowledge,

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Five New Guidance Documents To Set Framework For Trials

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that such designs are henceforth welcome.

Gottlieb said the agency is preparing five guidance documents that would do just that:

—Sometime before January, the agency would complete work on a guidance for conducting trials that look at multiple endpoints in the same trial.

—Another document will offer advice on "enrichment designs," which increase the power of a trial to detect a treatment effect within subpopulations defined on the basis of biomarkers or clinical characteristics.

Three related guidances, which Gottlieb said would "take a little longer to draft," include a guidance on adaptive designs, a separate guidance on dealing with missing clinical trial data, and a long-awaited guidance on non-inferiority trial design. The latter document has been in the works since 2001.

Gottlieb's remarks at the conference sponsored by ExL Pharma are posted at http://www.fda.gov/oc/speeches/2006/trialdesign0710.html

The agency's efforts to spark innovation in the pharmaceutical industry is run through the "Critical Path" initiative, which seeks to produce new approaches to drug development.

"The whole concept of the Critical Path initiative was to try to think about areas where some of these new scientific tools could be incorporated into the regulatory process," Gottlieb said in an interview. "If we don't at least allow at least a pathway to think about how you would develop the science for qualifying and validating some of these approaches and tools, we are never going to enable them."

The Critical Path initiative is broken into two areas: development of clinical adaptive trial designs and validation—or, as the agency now says, "qualification"—of biomarkers in oncology and other areas of medicine.

"If you look at the Critical Path opportunities list, 50 percent of that opportunities list deals with biomarkers, and 50 percent of it deals with adaptive models," said Gottlieb, referring to a list of 76 projects that could be undertaken through the initiative. "I always say that the two biggest components of the Critical Path initiative are the development and the qualification of biomarkers and the validation of alternative clinical trial designs."

Though Critical Path has become the central element of FDA's public relations, the agency is attempting this initiative without any Congressional appropriations, and with the miniscule funding of $5.9 million, proposed in the President's budget for fiscal 2007.

Gottlieb said the agency is trying to obtain additional funds through user fees paid by the prescription drug industry.

"We could very much benefit from more targeted resources specifically for this kind of scientific work," he said in an interview. "Hopefully, the money we would get in our budget and maybe money that will be set aside in the Prescription Drug User Fee Act we hope to have resources to do that. One of the things we are talking about with industry is that we are trying to set aside a small amount of resources for critical path work. I think the specific work that is most likely to get funded in the context of user fees is work on clinical trial design, because it's so cross-cutting to everyone on the industry that I think the industry recognizes that there is a benefit to enabling FDA to do some of that scientific work."

Acting FDA Commissioner Andrew von Eschenbach said the five guidances form the foundation for his agenda at the agency.

"The Critical Path initiative is committed to exploring modern technology-based approaches that embrace molecular biology as well as new bioinformatics and biostatistical models," von Eschenbach said in a statement to The Cancer Letter.

"An important part of this scientific work includes the development of adaptive clinical trial designs, and

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one of our first steps is going to be the development of five guidance documents that articulate these adaptive approaches.

"We will also be holding public meetings to discuss these approaches. Adaptive approaches have particular opportunity in application to cancer trials, and for this reason, these approaches were also an important part of the NCI Clinical Trials Working Group.

"I have witnessed first hand the development of the science around these adaptive approaches in urologic cancers in particular, working with Chris Logothetis [chairman of the M.D. Anderson Department of Genitourinary Medical Oncology], Don Berry, [chairman of the Department of Biostatistics], and others. It has become apparent that adaptive trial designs hold great potential for improving selection of the most effective interventions in the most efficient fashion.

"The key task now for FDA will be creating a regulatory framework that will enable well qualified adaptive approaches to be appropriately incorporated into registration trials where these trial designs present a distinct advantage," von Eschenbach said.

Qualification vs. Validation of Biomarkers

In recent public statements, FDA officials have referred to "qualification" of biomarkers, abandoning the word "validation," which was used in the past.

This change of terminology reflects the agency's current approach to the problem, Gottlieb said.

"The change did occur," Gottlieb confirmed. "[FDA Deputy Commissioner for Operations and head of the Critical Path initiative] Janet [Woodcock] has been talking about qualifying as opposed to validation. I am not sure exactly why people are using different language, but my sense is that it's not a binary process to determine whether a biomarker is clinically valid, and validation seems to imply that there is some kind of a binary event that needs to take place."

The term "validation" is routinely used in academia to refer to examination of biomarkers.

"That's something that I have written on a long time ago in a manner that probably serves as a roadblock for those who think that surrogate outcomes might be enough to act upon," said Ross Prentice, professor of biostatistics at Fred Hutchinson Cancer Research Center, who laid out the criteria for validation of biomarkers in a 1989 paper in the journal Statistics in Medicine. "I guess I am the one who put down some criteria that are pretty hard to achieve."

The Prentice criteria for establishing the effect of an intervention on the clinical efficacy endpoint were summarized in a paper in the January/February 2005 issue of Health Affairs by Thomas Fleming, chairman of the Department of Biostatistics at University of Washington:

"The biomarker must be correlated with the clinical endpoint; and the marker must fully capture the net effect of the intervention on the clinical efficacy endpoint." These two conditions must be met simultaneously.

Prentice said the new term, "qualification," suggests that FDA is considering something less stringent. "It's kind of a strange word," he said. "That's what you are probably going to need to get into if you are going to rely on one or more shorter-term outcomes and think that they are going to tell the story."

Gottlieb said the agency isn't loosening its standards.

"I don't think it was meant as something less rigorous," he said. "It was meant to imply that the process requires consensus-building in the scientific community, as opposed to a binary event. I don't think it was a conscious decision. I think it was just the way we have been talking about the process for validating them. The process isn't going to be one workshop or one study. It's going to be a series of scientific work that needs to evolve over time."

The agency is preparing a guidance document to address this issue, too, Gottlieb said.

"There is going to be another document that we are going to be developing, that Janet is working on, is about that question, how are you going to be qualifying or validating a biomarker for the purposes of regulatory approval," he said. "It's behind the guidance that we are working on to talk about how to develop a drug and a diagnostic within the same registration trial.

"I would say it's at least a year away."

Choose One: (a) Frequentist, (b) Bayesian, (c) Both

The agency's plans to issue a guidance on clinical trials design is less daunting than its venture into validation of biomarkers.

"We can't do biomarker qualification here at FDA; we don't have the research capacity," Gottlieb said in an interview. "But we do have the research capacity to do clinical trial modeling, because it's largely a computational exercise, and we do sit on a repository of data that enables us to do that kind of research."

Some of the same scientists who are skeptical about reliance on biomarkers for drug approval are less skeptical about reliance on biomarkers to "enrich" clinical trials with populations that may be likely to benefit.

"I am more supportive of that, if they are saying that you can have a trial with a clinical outcome like breast cancer or prostate cancer, and you are going to use the short-term outcomes like sample changes in a whole array of proteins following intervention to try to strengthen the analysis concerning breast cancer," Prentice said. "That's a novel idea, not very well developed, but one that might have potential to somewhat shorten or reduce the size of the hard-endpoint clinical trial."

The guidances Gottlieb described would constitute a departure from a strictly frequentist approach that the agency's drug regulators have used for as long as there has been drug regulations. (The agency's Center for Devices and Radiological Health has been using the Bayesian approach for almost a decade.)

Here, debates reflect a schism that has divided statisticians for a century, since the advent of the frequentist approach. The difference is fundamental:

A frequentist pretends to know nothing about what a drug might do in a population of patients and often structures experiments to disprove the initial hypothesis.

"One of the great things about frequentist trials is that they are dumb," said M.D. Anderson biostatistician Berry. "That means that any idiot can run them. They are highly scientific, rigorous, and there is not much that you can do make the thing go wrong. Adaptive design is a whole new ball game. If you don't know what you are doing, you can do some very bad things and damage the integrity of the trial, and of the whole process."

Berry is a leading champion of the Bayesian approach to biostatistics and the architect of a clinical trial design that combines the Bayesian and frequentist approaches.

Unlike a frequentist, who fears contaminating studies with prior knowledge, a Bayesian doesn't hide from prior knowledge, and changes course if necessary. This flexibility can have a high price, frequentists say. A Bayesian trial—and, for that matter, an adaptive trial—has to be protected from bias of the sponsors and investigators.

If the trial's protocol is insufficiently detailed, the whole endeavor degenerates into an out-of-control exploration of the universe.

"I don't think there is much to be added by bringing in your hunches and beliefs at an early stage," said Prentice. "I tend to think we should design studies with good quality and let the data speak for themselves for research purposes. The Bayesian approach does it in the other order. You make your assumption and hunches on all the key quantities that you are trying to estimate at the beginning, and you let the data modify those."

While all Bayesian trials are adaptive, not all adaptive trials are Bayesian. Berry's trial design incorporates prior knowledge at the outset, uses the data that accumulates in the trial to update the knowledge, and evaluates the resulting design using the frequentist approach.

"In the trials that I design for companies and for my home institution, everything is done prospectively," Berry said. "The DSMB then becomes an automaton guided by the protocol and their charter. You write down prospectively everything you are going to do, depending on the results that are obtained. It's a lot of work. It takes a lot of people putting their heads together, saying, 'This is what I would do if such-and-such happens, and the such-and-such is potentially every possible kind of data that accrues in the trial."

Berry, who consults with pharmaceutical companies and serves on an advisory committee to the FDA Center for Devices, said the guidances on adaptive design will ultimately benefit patients. "I strongly believe that we can build scientifically rigorous trials that deliver better medicine to the heroic patients who participate in clinical trials and thereby help in the future treatment of patients with the same disease," Berry said.

Protecting Independence of DSMBs

The guidances will have to design a method of protecting the integrity of adaptive trials from the sponsors' influence.

"Adaptive designs are an upfront, prospectively planned trials where the adaptations are, for the most part thought out in advance, and these are not after-the-fact adaptations that are trying to salvage a study that does not go the way you think it should have done," said Robert O'Neill, director of the Office of Biostatistics at the Office of Translational Sciences at the FDA Center for Drug Evaluation and Research.

Gottlieb said the guidance would likely urge that adaptive trials be directed by independent panels.

"There is a sense internally here that it's going to be done by a group that's independent of the sponsor," he said. "We have a model for that—the DSMBs. Right now, they make binary decisions, whether to allow a trial to go forward or not.

"You are talking about pre-specified criteria. You are talking about the ability to adapt a trial based on things that you have pre-specified before the trial has even begun.

"There would be agreement upfront on what

characteristics you'd be able to adapt on," Gottlieb said.

The data and safety boards running these trials would likely a different status than current DSMBs, O'Neill said in an interview.

"I believe there is a lot of controversy as well as the need to settle what is going to be the operational way of carrying out an adaptive design so that you do so in a way that the sponsor does not have an over-influence in these decisions," O'Neill said. "On the other hand, if you talk to some sponsors, they would like to be at the table in making some of those adaptive decisions.

"That is where we are. That is the controversy with these designs. It's one of the questions that is going to have to take some public exploration and discussion."

Though development of methodology for adaptive trials is a work in progress, "eight to 10 pharmaceutical firms are actively pursuing this and dealing with us on this matter," O'Neill said.

On Nov. 13 and 14, FDA and PhRMA will hold a jointly sponsored workshop to sort through the issues of adaptive design.

Whether they are Bayesian, frequentist, or a combination of the two, adaptive trials would likely foster greater reliance on randomization earlier in the drug development process.

"Any trial that is not randomized, frankly, has a problem in its own right," O'Neill said. "This is not a problem of needing more randomization. Randomization is a core, basic principle for all of these trials."

Berry agrees. "Randomization is a basic and critical component of clinical trials, but randomization can be adaptive and not necessarily balanced equally among various treatment arms," he said.

Adaptive Designs Useful In Early Stage Trials

In early-stage trials, adaptive trials can help select a patient population and a drug dose, O'Neill said.

"I think everybody feels that there is lots to be gained in the early learning phases, phase I and phase II," he said. "You are talking about designs that may be are helping you determine the optimal conditions under which a product and/or a patient entrance criteria should be decided on for further study, maybe in a phase III confirmatory trial."

"In the context of phase I (dose-finding) studies, I think the current thinking is that adaptive designs can be efficient in leading us to the optimum dose, when compared with the more traditional, static, dose-finding designs," said Colin Begg, chairman of the Department of Epidemiology and Biostatistics and acting chief of the Biostatistics Service at Memorial Sloan-Kettering Cancer Center.

Using an adaptive phase II trial, Bayer Pharmaceuticals selected a target population for its drug Nexavar (sorafenib). The study used a randomized discontinuation trial design, an enrichment design that was first proposed in 1975 and used in many therapeutic areas.

In the trial, all patients received the drug for an initial run-in period, followed by random assignment of potential responders to either the study drug or placebo.

According to a paper published June 1 in the Journal of Clinical Oncology, "this design creates a controlled trial without upfront randomization, and decreases the heterogeneity of the randomly assigned population, resulting in increased statistical power with smaller patient numbers."

The trial was performed to assess sorafenib in patients with metastatic solid tumors who maintain stable disease after a 12-week run-in period.

"The original protocol focused on patients with metastatic colorectal carcinoma, based on the putative importance of Raf/MEK/ERK signaling in this tumor type," the paper states. "However, the broad eligibility criteria of the protocol also enabled enrollment of patients with other malignancies. Early signs of antitumor activity in patients with [renal cell carcinoma] and low numbers of patients with CRC achieving the criteria for randomization after the 12-week run-in period led to a refocus of this study toward patients with RCC…"

"I am all for adaptive designs, particularly for phase I and II," said Mark Ratain, Leon O. Jacobson Professor of Medicine at the University of Chicago, the lead author of the paper. "For phase III, it is a bit problematic, as the purpose of phase III is to confirm prior findings (and to some extent, convince skeptics)."

Later Stage Use Triggers Concerns

Another variety of adaptive trials allows a seamless transition from phase II to phase III, either using phase II data as a trigger, or incorporating the data from one phase to another.

O'Neill said seamless transition trials are "of interest to the industry," and are being explored.

"We are concerned about where that would be most appropriate," O'Neill said. "It's not a solution for everybody's problems… There is a lot of risk in that design, because it requires that you have to have thought through all your planning parameters very

early on, without real data in hand, because you haven't completed any phase II data to give you that real data to plan your phase III."

Begg said adaptive designs for phase III trials have been discussed over then past 30 years, failing to gain broad acceptance.

"In these designs more patients are allocated to the treatment that seems to be doing 'better,'" Begg said to The Cancer Letter. "The problem with this approach is that it does not reduce the expected duration of the trial (contrary to what some advocates claim), and it raises thorny ethical problems, i.e., how do you explain to a patient that you will flip a coin and with 80 percent chance he/she will receive the treatment you think might be better? This implies you know what is better, undermining the equipoise that is needed to justify randomization."

Reliance on biomarkers to select patients could be problematic, too, Begg said.

"By limiting trial eligibility (adaptively) to these patients we might identify a population in which the impact of the treatment is much greater, the statistical power is much greater, and the necessary sample size is much smaller," Begg said. "This is one of the promises of the genomics revolution, and if it comes true then maybe we really can speed up the approval process. But the predictive markers need to be found, and these may well be drug-specific.

"I am not aware of any new statistical designs that have been built on this concept, but I may simply be ignorant, and I look forward to the upcoming FDA guidance documents to educate us on what might be done," Begg said.

M.D. Anderson's Berry said scientists have difficulty pinpointing the subsets that could be used to "enrich" a phase III trial.

"It's difficult inferentially," Berry said. "This is an area that's a bugaboo for pharmaceutical companies.

"You run a trial and you see that you had a marginal impact overall, but the benefit was exclusively in a subset of the population. You then run another trial focusing just on that subset, that process almost always leads to negative studies.

"It's because people don't appreciate the randomness in the process, the multiple subsets that you can look at—and some of them are going to show benefit just by chance," Berry said.

"No Free Lunch"

"Clearly the FDA is under pressure, and they want to be seen to be responsive," said Begg. "However, I have the feeling that there is no free lunch.

"To demonstrate convincingly that a drug works you need to evaluate it in a randomized trial with endpoints of genuine clinical significance. This requires lots of patients. If you narrow the focus to smaller groups of patients defined on some biochemical or genomic basis, then the patients are even harder to come by, and so the trials will take longer (all other things being equal).

"This strategy can only work if predictive tests are indeed highly predictive of which patients are likely to respond. Whether or not this will happen is speculative.

"The idea that 'adaptive' statistical designs represent the cavalry coming to save us is not realistic."

Whatever the outcomes, the planning process would benefit drug development, O'Neill said.

"This is all for the better, because it's putting more of a premium on up-front prospective planning and thinking through, in advance, how things might play out," he said. "And that's a big step forward in terms of clinical trial planning and drug development, tying it all together in a more integrated way."

Professional Societies:

Lichter To Join ASCO As EVP, CEO, In October

(Continued from page 1)

experience in clinical research and patient care, dedication to teaching, effective organizational leadership, and strong performance in running a non-profit organization.

"I am very honored to have been chosen for the position," Lichter said. "This represents a once-in-a-lifetime opportunity to dovetail my personal, lifelong goals of improving the care and treatment of patients with that of an organization dedicated to the same mission."

Lichter replaces Charles Balch, who returned to oncology practice last fall. Joseph Bailes has served as the society's interim EVP and CEO during the search process. Bailes will continue in the interim position through the fall.

Lichter has held many prominent positions in ASCO. He served on ASCO's Board of Directors from 1992-1995. He is a member of the ASCO Foundation Board and chairman of ASCO's Ethics Committee.

Previously, he served as chairman of the Public Issues Committee, Special Awards Selection Committee,

and co-chairman of the Fellows Task Force. He has also served on the Scientific Program Committee, the Nominating Committee, and the Audit and Finance Committee. He also was a member of the editorial board of the Journal of Clinical Oncology.

"Having worked with ASCO's Board of Directors as well as the ASCO staff over the years, I am eager to start my new position as EVP so I can provide strategic leadership on the important work of the society and help fully realize the Board of Directors' vision and ASCO's mission to prevent cancer and improve the treatment, care, and survival of people living with cancer," Lichter said.

Lichter was a professor of the Department of Radiation Oncology at the University of Michigan between 1984 and 1997, and in 1993 he was named the first Isadore Lampe Professor of Radiation Oncology, an endowed chair. Prior to 1984, he was director of the Radiation Therapy Section of the NCI Radiation Oncology Branch.

While at the NCI, he conducted one of the pivotal trials that found the use of lumpectomy and radiation therapy to be as effective as the traditional treatment of mastectomy. Lichter is also known for his research in three-dimensional treatment planning and conformal dose delivery of radiation therapy.

Lichter received his bachelor's (1968) and medical (1972) degrees from the University of Michigan. He trained in radiation oncology at University of California, San Francisco, before joining the faculty at Johns Hopkins University, and later NCI.

Cancer Advocacy:

Cancer Declaration Urges Commitment To Prevention

A "World Cancer Declaration" released July 12 during the International Union Against Cancer (UICC) World Cancer Congress in Washington, D.C., called for making cancer prevention a higher priority in the public and private sectors.

Estimates indicate that cancer deaths worldwide could reach 10 million by 2020 and a majority of those deaths will occur in developing nations, which are least prepared to handle the burden, the declaration said.

The declaration outlines actions that groups need to implement during the next two to three years:

—Create new opportunities to consistently deliver a set of compelling messages that can be tailored to different country settings and to traditional and non-traditional partners.

—Establish more national cancer control plans, along with the budgets for implementing them.

—Develop an international plan for organizing human papillomavirus vaccination programs in low- and middle-income countries with high cervical cancer rates.

—Integrate the Hepatitis B vaccine with other routine infant vaccination programs in countries, particularly those with high rates of liver cancer.

—Increase the number of countries with viable and adequately funded cancer surveillance systems, including cancer registries that collect and analyze data about cancer trends.

—Implement the effective strategies identified in the World Health Organization Framework Convention on Tobacco Control.

—Adopt and implement evidence-based guidelines for cancer early detection and treatment.

—Make pain relief and palliative care an essential service.

—Empower people living with cancer and those touched by cancer to fully participate in community, regional, and country cancer control efforts.

"The world cancer community's vision is to have a world where cancer is no longer a major threat for future generations," said Franco Cavalli, UICC president. "A world where what we know about cancer, our resources for diagnosing and treating patients who have it, and most importantly our ability to prevent it, are equal in every region of the globe."

The global burden of cancer is not only increasing, but is shifting from developed to developing nations according to "The Cancer Atlas," released this week by UICC, ACS, and the Centers for Disease Control and Prevention. Also released this week was the second edition of "The Tobacco Atlas." The publications are available for purchase at www.cancer.org/bookstore.

Funding Opportunities:

Lustgarten Foundation Offers One-Year Research Grants

Lustgarten Foundation for Pancreatic Cancer Research is providing one-year grants of up to $100,000.00 for research on adnocarcinoma of the pancreas.

Priority will be given to grants focusing on the following areas: Screening for the early detection of pancreatic cancer. Screening can include the study of biospecimens and/or imaging. Novel therapies in pancreatic cancer. Novel technologies for pancreatic cancer genetics.

Applications will be accepted from individual investigators as well as collaborating investigators, with funding beginning in January. Letter of Intent Receipt Date: July 31. Application Receipt Date: Aug. 18. Full text: www.lustgarten.org. Inquiries: 516-803-2304.

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