ing pockets of resistance to existing antimalarials and an increase in international travel by Americans.

But Halfan's review had at least one great similarity to Mivacron's evaluation. To expedite the review, FDA's reviewing division employed a division-of-labor approach to the NDA's clinical section. For Halfan, Lumpkin ordered that the NDA's 42 clinical studies, with an estimated 3,000 patients, be divided among no less than eight clinical reviewers.

Naturally, this division of labor created challenges for SmithKline's several-person regulatory staff assigned to the Halfan project, namely, fielding questions from a contingent of FDA reviewers. Still, the company instituted an "operational goal" of not allowing more than a one-day turn around for reviewer questions.

Positive forces

FDA and SmithKline officials agree that the effort was absolutely critical to maintaining the momentum of the review. At a July 1992 FDA advisory committee meeting, Lumpkin offered the following on Halfan's review: "I wanted to give a very sincere thanks to SmithKline for a very tremendous effort. We have been beating up on them on a daily basis with eight different medical reviewers, calling saying 'I need this data point, I need that data point, can you find this case report for me, can you translate this case record form.' And they have been extremely helpful in trying to fill in the various gaps in database that we felt needed to be filled in."

SmithKline officials concede, however, that meeting its goal with a larger clinical database would have been far more difficult. Indeed, Halfan's NDA was small compared to those for many drugs.

If FDA fulfills its user-fee promises, similar experiences will soon spread to more drugs and biologics. We in industry will be well served to do whatever it takes to become positive forces in these expedited reviews.

Scios Nova may purge Pergamid after FDA setback

WASHINGTON, D.C.—Pergamid, an agent being developed by Scios Nova (Mountain View, CA) for purging cancer cells from bone marrow, is not "approvable," decided the Food and Drug Administration (FDA, Bethesda, MD) and its Oncologic Drugs Advisory Committee last month. With Scios Nova officials now saying that they probably won't commercialize Pergamid, the drug's future is looking increasingly dismal, unless another corporate sponsor is found.

Last spring, Nova Pharmaceutical (Baltimore, MD), which that summer merged with Scios to form Scios Nova, filed a new drug application for Pergamid with FDA. The company was seeking approval to market the product as a bone-marrow treatment for patients with acute myelogenous leukemia (AML). As part of an aggressive approach to treating this malignancy, bone-marrow cells are removed from an AML patient, treated with Pergamid in an attempt to purge them of malignant cells, and then returned to the patient to restore crucial bone-marrow functions that combined chemotherapy and radiotherapy treatments have destroyed in the interim.

Treatment IND

Available clinical data on Pergamid shows that the agent was tested on some 234 AML patients between 1982 and 1989, when Nova took over its development. Since then, Pergamid has been used on an experimental basis under a treatment investigational new drug (IND) designation in a variety of bone-marrow-transplant procedures, including the purging protocol now being tested on many AML patients.

In large measure, the treatment IND and Pergamid's consequent wide use accounts for its regulatory troubles. Indeed, the FDA advisory committee concluded that Pergamid has not been properly tested in randomized clinical trials. Moreover, it added, the retrospective data assembled from Pergamid's on-going clinical protocols cannot be considered adequate for judging the drug's efficacy.

The situation is frustrating to experts in oncology, who see Pergamid's chances for success fading and a likelihood that current supplies will dry up. "Pergamid has been tacked onto a number of clinical protocols, and it has strong proponents who feel they should use it because it has a chance of working" due to its more clearly recognizable *in vitro* effects, says Bruce Cheson of the Clinical Investigations Branch at the National Cancer Institute (NCI, Bethesda, MD).

However, Cheson continues, since "investigators were and are unwilling to do the necessary clinical trials," conclusive data for determing whether Pergamid benefits patients are missing. Furthermore, Pergamid is relatively expensive and is "associated with a number of toxicities," he says. "You don't want to use it on everybody if there's no demonstrated benefit."

Lessons

With so much momentum against Pergamid, officials at Scios Nova are backing away from it. Although a full-scale clinical trial might vindicate Pergamid's use in AML patients, it would require a multicenter effort to accumulate the several hundred patients deemed necessary for evaluating efficacy, and the trial would likely take several years to complete. With there being only about 2,000 AML cases per year in the U.S., commercial incentives to develop it are dwindling.

These developments could also bode ill for other candidate bone-marrow-purging agents with treatment IND designations. "The same situation applies," NCI's Cheson says, adding that unless appropriate clinical trials are undertaken, "none of the purging agents will get anywhere. We should learn a lesson here. These products won't be accepted by FDA without sufficient data."

—Jeffrey L. Fox

In large measure, Pergamid's treatment IND and its consequent wide use account for its rejection by FDA.