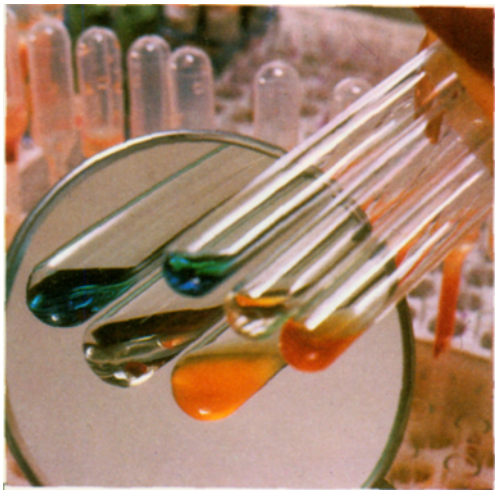
FDA REVIEW OF NEW INDICATIONS IS LENGTHY, COSTLY PROCESS

Just what is involved in changing package insert labeling to include a new indication for drug use? The manufacturer must obtain approval for the new indication from the FDA by submitting a supplement to the existing new drug application (NDA). The supplement must provide data from "two well-controlled, randomized trials," according to Aleta Sindelar, Consumer Safety Officer, Division of Oncology and Radiology of the FDA's Center for Drugs and Research. Sindelar explains that the FDA "does not impose any restrictions on the number of patients that must be enrolled in those trials, but the response for the indication must be evident." Only the original NDA applicant may submit a supplement to an approved application. "If that party does not choose to pursue this course of action, the labeling accepted by the FDA at the time of NDA approval must remain unchanged," says Thomas Holohan, M.D., Medicine Staff, Office of Health Affairs of the FDA.



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Clinical Trials

Pharmaceutical representatives say that, on average, it takes two to three years to complete the necessary clinical trials and, they contend, three years is an "optimistic forecast" when it comes to chemotherapy agents, because of the scarcity of eligible patients to enroll in drug trials. Moreover, it can be difficult to persuade cancer patients and their families to agree to a chemotherapy drug trial that, to date, shows no certain clinical or theoretical improvement in disease when other agents of proven efficacy are already available to them.

In a number of cases, existing clinical literature supports the efficacy of existing drugs for unlabeled indications and such uses already are considered to meet sound standards of medical practice. However, existing studies usually do not meet what the FDA considers to be the "essential characteristics" of an "adequate and well-controlled study." Such data can be submitted as substantiation for the validity of new indications, pharmaceutical representatives say, but not as proof of their efficacy. As a result, drug manufacturers frequently must underwrite the cost of new trials because the FDA has much stricter requirements in such areas as duration of treatment periods, the age of sample groups, differences in controls, etc. In addition, if a promising new indication is completely outside the bailiwick of current applications for an existing drug (for instance, the treatment of AIDS patients with an anti-viral drug) not only may previous clinical trials have to be completely redone, but new toxicological studies, taking six months to two years to complete, may be required before clinical trials can begin. In such cases, a supplemental application can be as time-consuming and costly as the original NDA.

FDA Review

What about the timeframe required for FDA review of supplemental applications? According to the code of federal regulations (21CFR, Part 314, Subpart C), the FDA has 60 days to determine whether a supplemental application is "sufficiently complete to permit a substantive review." If it is, the filing date falls on the 60th day after receipt of the application. Then the FDA has 180 days to review the application and send the sponsor an approval letter, an approvable letter, or a not-approvable letter. If the FDA refuses to file an application, the applicant has 30 days to request a conference. If an application is filed over protest, the filing date is 60 days after the date the applicant requested a conference. If the application is incomplete in any way, or if there are scientific or medical disputes about the way in which the clinical studies were conducted, further timetables are established for end-of-review conferences, other meetings, the filing of amendments (45 days for FDA review), and hearings (the applicant has 30 days to file a request for a hearing, the FDA has 30 days to decide if the applicant is eligible for an opportunity for a hearing; the applicant then has 60 days to submit additional data and information to justify a hearing if it initially is denied, and, if approved, the FDA has 90 days to actually begin the hearing).

The Cost

Pharmaceutical representatives say that the research and development costs for obtaining FDA approval for new indications can range from $500,000 to $5 million, depending on the time and effort required to complete preclinical and clinical studies (animal trials, autopsies, clinical investigators' fees, etc). They also say that it is more costly to obtain approval for chemotherapy indications, because of the paucity of drugs and the limited number of patients who are eligible to participate in clinical trials. According to one firm's business manager for new hospital products, "if you had an antineoplastic agent that was being used for testicular cancers, and you wanted to expand its use to breast cancers, it could easily cost $5 million to satisfy FDA approval requirements."

There is no way to tell approximately how many new chemotherapy indications are approved annually, because supplements are filed for a number of reasons, i.e., new dosage forms, dosage regimens, a change in the route of administration, the population for which the drug is prescribed (geriatric, adult, pediatric) and even a change in tablet scoring requires the submission of a supplemental appplication, because, Sindelar of the FDA explains, it "changes the manufacturing of the tablet." ■