Letters

FDA: Guidelines Chiseled in Stone

On 10 June, the Food and Drug Administration told the pharmaceutical industry that it intends to draw up detailed "guidelines" for the future clinical study of 25 classes of drugs. FDA invited industry's scientists to help.

Since then, the number of classes of drugs has grown to 29 (antianginal, anticholinergic, anabolic, anticonvulsant, and so forth) and guidelines are being drafted for publication by the end of 1970. Are clinical investigators aware of these plans? Lack of comment in the medical or scientific press leads me to believe they are not. They should be, as should all clinicians and bioscientists in related fields.

The drug industry is divided—nothing new about that. Those in favor of guidelines believe in them, or may really need them, or hope guidelines will prevent FDA's "recommending" last-minute studies.

Those opposed (I'm one) are not so much opposed as they are afraid the guidelines will become rigid checklists—"cookbooks" with the force of law, even if irrelevant scientifically. I'm afraid that resources will frequently be wasted on studies done to satisfy an obsolete guideline, done at the expense of work *more* relevant to safety and efficacy. Meanwhile, though, my company's scientists are serving on FDA-industry guideline committees. They're trying to write guidelines that will focus on the *questions* that should be asked about a new compound, not on every specific test to answer them.

FDA itself has been reluctant in the past to set clinical guidelines, probably realizing that guidelines can build impressive piles of unimpressive data, can even provide *false* assurance of safety and efficacy, while robbing investigators of judgment and deadening innovation in drug invention and development. But FDA's past reluctance doesn't reassure me now. Neither does this sentence in its model guideline (for antilipemics): "Some of the more esoteric tests above are optional under certain conditions. . . ." FDA's history repeatedly shows it cannot allow such options without fear of second-guessing and criticism. It is so much safer, easier, to ask the sponsoring drug company to do studies than it is to make a needed exception.

Who can blame FDA? The other day in Washington, I heard what can happen to FDA people who decide a guideline is obsolete. At a congressional hearing, they were asked sharply how this can happen in a country of law and order? How dared they waive a guideline? Shouldn't those who did so be disciplined? FDA answered, no, they should be *commended* for using their best scientific judgment. A brave answer. But all "guidelines" became a little more rigid that day.

I believe that those at FDA who must one day administer the guidelines for the clinical study of all of this nation's new drug products should be supported by panels of outside scientists when exceptions to the guidelines are indicated. Not that advisory groups are the answer to everything, nor can they ever remove from FDA its regulatory responsibility for proof of safety and efficacy. But their recommendations, openly arrived at after consulting both the sponsoring company's scientists and the FDA's, should provide the support FDA will need in dealing with studies of the truly innovative compounds I think are coming from drug research in the next few years.

Elements of this suggestion have been a part of several proposals from observers, friends, and critics of FDA over the past few years. So the suggestion is certainly not novel with me; but I think it deserves public airing and commentary—before guidelines and the way they are administered become chiseled in stone.

ROBERT L. DEAN
Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101

Tektite: Expectations and Costs

With only limited resources to apply to an infinity of problems it seems imperative that value judgments be made in allocation of funds for research. The Tektite 1 program ("Tektite 1, man-in-the-sea project: Marine science program," 8 May, p. 659) cost $2.5 million according to Navy estimates. It was justified on the basis of technological development, biomedical and behavioral investigations, and marine science. Previously, shallow-water manned habitats have been utilized by Cousteau, Link, Perry, and MacInnis and in British, German, and Russian programs. For Tektite 1 the unlimited working time which was claimed as an advantage is misleading. It is possible with present technology to spend 6 to 8 hours per day at 50 feet and return to the surface with no time lost in decompression. The Tektite 1 divers averaged just over 2 hours per day in the water. Once inside the habitat there is no advantage and many disadvantages over a surface facility.

No serious biomedical problems have been encountered in other shallow-water habitats and there was no reason to expect any in Tektite 1. In fact there were none. The main justification seems to have been behavioral studies of an "isolated" group under the "stress" of a "hostile" environment.

John E. Randall previously spent several years studying the same area of St. John, supported by grants totaling about $60,000. He worked from a shore base with an outboard skiff and scuba. He published over 30 papers on the biology and systematics of marine life which were the result of his investigations. In terms of man-hours, his project was far smaller than Tektite 1—only three people were involved. As a marine biologist extensively employing diving in research, I am very much aware of the tremendous advantage of in situ studies, but I fail to see that the results of Tektite 1 justified such an expensive program.

WALTER A. STARCK, II
R.F.D. 1, Box 194, Fort Pierce, Florida 33450

Starck is quite correct in saying that value judgments must be made with regard to awarding funds for research. In addition to program reviews by the Office of Naval Research, Department of the Interior, and General Electric, NASA awarded two independent small

study contracts to determine possible gains in knowledge of crew behavior from such a program prior to becoming a participant in Tektite.

The Navy, as lead agency for Tektite 1 along with NASA, bore the major cost of the $2.5-million program which included extensive biomedical and behavioral investigations as well as marine scientific studies. We are well aware of the shallow-water programs mentioned by Starck and have been in direct contact with many of them. Although each of these efforts has involved shallow-water habitats, none have utilized the gas mixture used in Tektite 1 (92 percent nitrogen, 8 percent oxygen) and none have conducted comprehensive biomedical studies to determine the effects on humans living under these conditions over extended periods. Even though "there was no reason to expect" any serious biomedical problems, Starck must realize the value of substantiating such expectations.

The human behavioral studies are considered by many to be some of the most sophisticated ever conducted under field conditions. Similar studies in the past have almost invariably been conducted in a laboratory situation where the work and the hazards were artificial. It is essential to study human behavior in the real world where tasks and risks are real if we are to understand such behavior and to properly select crews for future space or undersea missions.

From a marine science standpoint I cannot agree with Starck that "once inside the habitat there is no advantage and many disadvantages over a surface facility." For too long we have been drawing conclusions about the marine environment based on short excursions from the surface. By living at a depth of 50 feet it is possible for a diver using conventional diving gear to work down to a depth of 70 feet with no time lost in decompression. The extremely short time spent in the water during Tektite 1 was due to a commitment to the behavioral and biomedical programs and the unavailability of closed-cycle rebreather units. In Tektite 2 scientists are averaging 5 to 6 hours per day, and several have put in over 10 hours in a single day. So far 21 aquanauts have utilized the GE closed-cycle rebreather system. It is their unanimous opinion that the use of such systems coupled with ocean-floor habitation will greatly expand their capability to study marine life in situ.

Those scientists who have conducted research in Tektite 1 and 2 and are qualified to evaluate the advantages and disadvantages of living in a habitat (as opposed to returning to the surface after each dive), agree that living in the ocean is decidedly more advantageous than returning to the surface after each dive. Since it is recognized that scientists can obtain certain kinds of data only by venturing into the ocean, either by diving from the surface or living there, the economics of each method must be considered. The stated costs of Tektite 1 and 2 are not a measure of the cost of conducting marine research from a habitat because they include the costs of the biomedical and behavioral programs as well as capital equipment.

The 100-foot, two-man habitat program in Tektite 2 should further open up areas of the continental shelves. It allows divers breathing nitrogen and oxygen to reach depths of 170 feet with a duration of 5 hours while living in a habitat located 100 feet under the water. Thus far in Tektite 2, new decompression tables have been developed for 100-foot nitrogen saturation dives in a 14-day, six-man chamber dive has been successfully completed at a depth of 100 feet.

The Department of the Interior's interest in Tektite 1 was to evaluate this method of collecting data relevant to the conservation and development of continental shelf resources. Interior has assumed the lead agency role for Tektite 2 and intends to continue to explore the oceans using whatever tools are necessary to collect the data.

JAMES W. MILLER
Tektite 2, Room 5122,
Department of the Interior,
Washington, D.C. 20240

Our Free Enterprise System

The intemperate language and specious arguments of Henry G. Manne are a strange companion to his boast of pioneering the development of a scientific approach to the study of American corporations (Letters, 24 July). Nothing in Luther J. Carter's report on Campaign GM (24 April, p. 452; and 29 May, p. 1077) merits such abusive terms as "foolish," "vacuous moralizing," "unhelpful cliches," and "illiterate simplicities." I also doubt that any of the named and unnamed villains of Manne's letter are "absurdly prejudiced and uninformed" about economics, unless his own and as yet unpublished new science of economics will replace completely the existing stock of knowledge of that subject. Much less can I see where Berle, Means, and Nadar conspired to bring about a "nonmarket, nonprivate property system." What they, and all other "intellectuals" for whom Manne has utter scorn, are trying to do is much less ambitious: not, as he maliciously charges, to turn General Motors into public property, but rather to have *all* property used in accordance with the principles of best public interest. This aim is not so terribly revolutionary since the arrangement under which it could be realized is known as competition.

Manne's problem is that his emotional fervor about our "free enterprise system" blinds him completely to the only valid criterion by which that system (or any other economic system) is to be measured—social welfare, including all noneconomic consequences of economic activity. The traditional defense of free market system has been that it operates at full capacity, lowest cost, with all economic needs best satisfied and all costs fully compensated. Instead of trying to invent new science, Manne might try to rediscover some of the old ones, like those of Adam Smith and Alfred Marshall. He may then discover that some of his despicable and ignorant enemies are in effect his allies.

ZARKO G. BILBIJA
Department of Economics,
Florida State University,
Tallahassee 32306

It was a pleasure to read Manne's comments on Carter's articles concerning the Campaign GM project. Although it is tiring to observe the continued, but unhelpful, pronouncements of the "anti-GM" groups, it is all too seldom that those of us in the business community bother to reply to these attacks on the basis of our free enterprise system.

Before embarking upon the "vacuous moralizing," as so aptly termed by Manne, I would suggest that Carter and others of his persuasion weigh carefully the status of life in the United States—the product of free private enterprise—and on the other hand, the status of life in Red China and the Soviet Union—the products of central governmental economic control.

WILLIAM M. BOYER
Fiberfil, Evansville, Indiana 47717