The Food and Drug Administration and the Backward Motion Toward the Source

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IN HIS UNACCOUNTABLY NEGLECTED POEM, "West-Running Brook," Robert Frost describes the reverse spume thrown up when swiftly running water strikes a boulder. From this mundane observation, he produces a remarkable insight:

> It is this backward motion toward the source,
> Against the stream, that most we see ourselves in,
> The tribute of the current to the source.

This "backward motion toward the source" captures much of the essence of public health activities. They seek to reach back toward—in order to eliminate—the source of health-threatening conditions, rather than concentrating on their unfortunate post-facto results. This special kind of backward motion has surely characterized the 180 years of the Public Health Service and—with increasing intensity—the shorter course of the Food and Drug Administration.

Indeed, FDA's ability to master the public health problems it faces now and will face in the future can be gauged by the extent to which it is able to marshal the statutory and research resources necessary for extending its reach further backward.

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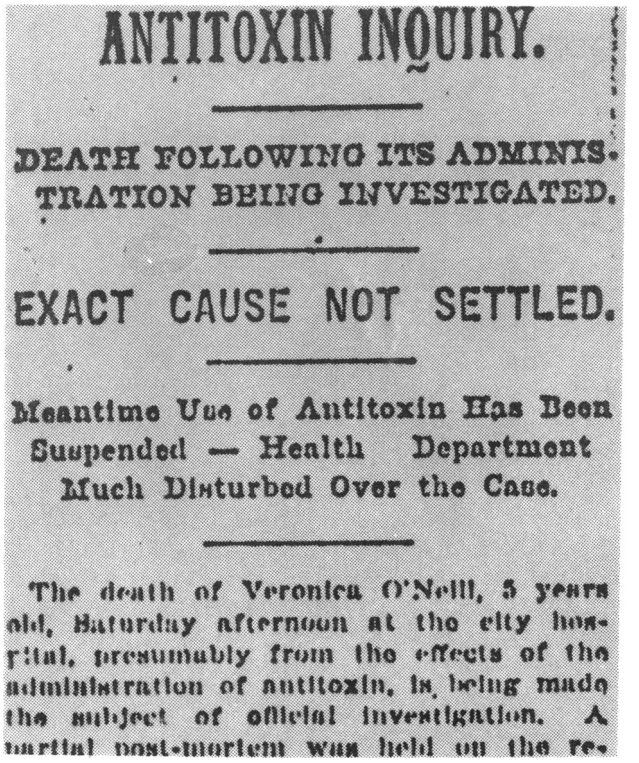
In tracing this trajectory and in assessing the kinds of problems that may make its extension more difficult and the knowledge that can make it easier, it is first necessary to distinguish the original FDA food and drug programs from the three comparatively recent accessions: the Bureau of Biologics, the Bureau of Radiological Health, and the National Center for Toxicological Research. These three activities—partly because the primary period of their conceptual evolution came before they became part of FDA and partly because of their natural orientation—exhibit in a far more definitive way this movement backward toward the source.

Bureau of Biologics

The most explicit example of the movement toward the source is the work of the Bureau of Biologics. The birth of the Bureau actually predates what is now known as the Food and Drug Administration, since biologics regulation began 4 years before the 1906 Food and Drug Act became law. The Bureau of Biologics differs also from the food, drug, medical device, and cosmetics regulatory activities of FDA in that, from the beginning, it was more directly engaged in "source" concerns because many biologics—notably vaccines, antitoxins, and therapeutic serums—concern prevention of specific illness. Bio-



ANTITOXIN INQUIRY.

DEATH FOLLOWING ITS ADMINISTRATION BEING INVESTIGATED.

EXACT CAUSE NOT SETTLED.

Meantime Use of Antitoxin Has Been Suspended — Health Department Much Disturbed Over the Case.

The death of Veronica O'Neill, 5 years old, Saturday afternoon at the city hospital, presumably from the effects of the administration of antitoxin, is being made the subject of official investigation. A partial post-mortem was held on the re-

On October 30, 1901, the St. Louis Globe-Democrat published its first report on an outbreak of tetanus from city-made diphtheria antitoxin. Twelve children died, ten recovered. Congress reacted to the tragedy by passing the Biologics Control Act of July 1, 1902.

logics regulation also differs in the sense that it quite early established patterns that are only now being followed or considered in the more traditional areas of food and drug regulations. For example, the 1902 Biologics Control Act and the regulations that stemmed from it contained provisions requiring plant inspections, including unannounced inspections, formal new product applications, product recalls, authority to issue and revoke licenses, and good manufacturing and laboratory practices including such requisites as competent and trained personnel, retention of production and control batch records, and dating requirements. Thus, biologics as a class of substances generally involved a disposition to concentrate on the source; and biologics as a class of regulation involved reaching back to the basic steps in the manufacturing and distribution process that would eliminate the source of faulty or violative products.

Bureau of Radiological Health

The Bureau of Radiological Health, which was transferred to FDA in 1971 from another area of the Public Health Service, also differs in that, from its inception, it concentrated on reaching backward toward the source through its responsibility for reducing unnecessary exposure of patients to radiation from diagnostic or therapeutic procedures and for preventing human exposure to radiation from consumer and industrial electronic products, both ionizing and non-ionizing. Ionizing products include X-ray machines, fluoroscopes, computed tomographic (CT) scanners, and accelerators, as well as devices such as color TV sets that can emit unnecessary ionizing radiation from high voltage circuits. Non-ionizing products include microwave as well as light and sonic radiation.

The Bureau is especially interested in the major source of exposure to manmade ionizing radiation in the United States: large-scale use of diagnostic X-ray procedures in the healing arts. Of particular public health concern is that, based on FDA-conducted national surveys of X-ray use, approximately 241 million examinations would have been performed last year.

In addition, a further increase in the overall number of radiologic examinations, and possibly in the average radiation exposure per capita, may be witnessed as a result of the introduction of CT scanners in the United States in 1973. Already, approximately 700 CT scanners are being used each year on about 2 million patients.

And, of course, mammography has also contributed to increased exposure (from more X-rays per person as well as more persons being exposed) over a short period of time. This procedure, in which relatively large amounts of radiation are delivered to a particularly radiosensitive tissue, was scarcely used as recently as 15 years ago. It is now being performed on approximately 2 million women in the United States annually.

In view of the preceding facts, FDA not only reaches back toward the source by regulations designed to assure the safety of radiation-emitting products and in encouraging prudent radiation-use practices, it is reaching back even further through a biological research effort that aims at providing a scientific basis for the Agency's initiatives in regard to radiation. FDA is convinced that only by understanding the hazards and being able to quantify the risks from various kinds and doses can it set sensible program priorities.

The Bureau of Radiological Health contributes to this bio-effects research on the consequences of low-level radiation exposure with a program of experimental and epidemiologic studies conducted

through grants, contracts, and intramural research One example that may have direct public health implications concerns prenatal exposure to radiation.

Irradiation during prenatal development can evoke a variety of biological effects. Experimental research in rodents has established that gross visible defects are possible from radiation exposures in the range of 5 to 12 rads during early pregnancy. Many of these defects accompany faulty development of the central nervous system. Later in pregnancy, radiation exposure can affect behavior, learning, and coordination. Other experimental radiation effects include interference with expression of genetic information and retarded growth and development. Hence, FDA has for years been urging cautious use of X-rays in pregnancy and now also suggests caution in use of ultrasound for fetal monitoring.

National Center for Toxicological Research

From its inception, the National Center for Toxicological Research (NCTR), which is housed in buildings once used for the manufacture of antipersonnel biological weapons near Jefferson in central Arkansas, was envisaged as a fundamental national resource in the effort to reach backward toward the source of the biological effects of potentially toxic chemical compounds. To this end, NCTR supports research in four major areas:

—developing improved methodologies and test protocols for evaluating the human health and environmental risks of toxic chemicals;

—facilitating the extrapolation of toxicological data from laboratory animals to man;

—studying the metabolism of toxic chemicals in animals; and

—determining the adverse health effects resulting from long-term, low-level exposure to potentially toxic chemicals found in man's environment; currently, the carcinogenicity, teratogenicity, and mutagenicity of various chemicals are being assessed.

Other FDA Components

Unlike Biologics, Radiological Health, and NCTR, the other program components of the Food and Drug Administration—the Bureaus of Foods, Drugs, Medical Devices, and Veterinary Medicine—have been characterized by a slower, but accelerating movement toward the source in line with the growth of scientific knowledge, public understanding, and statutory authority.

Former U.S. Surgeon General Jesse L. Steinfeld, in an article discussing the history and prospects of the Public Health Service, coined a phrase—"technogenic diseases"—to describe illnesses that are rooted in our rapidly developing and spreading technology (*1*).

Foods. In a very real sense, Federal food safety regulation derived from a clear recognition of technogenic diseases. By the turn of this century increasing urbanization had broken the direct connection for a growing number of Americans between the production and consumption of their food. The necessity to move, store, and market foods far from farm and feedlot changed both the methods and economics of food production. Chemical preservatives and other additives were employed, the impact of which on health was far from clearly understood. In some instances, the then comparatively primitive state of food processing technology, and the too often morally obtuse attitude of some processors, resulted in gross contamination of processed foods. One result was the passage of the 1906 Food and Drug Act; its primary emphasis was on food safety. This was the first Federal effort at reaching backward toward the source in regard to foods, and it was necessarily limited to the obvious kinds of adulteration. Each additional advance in food technology has produced the reality or potential of new forms of technogenic

J. F. McPhee's 1906 cartoon reflected the public's expectations concerning the "Wiley Act." The new law, it was hoped, would put a stop to food adulteration and quack remedies—the two major evils and targets of a 20-year crusade for Federal regulation of foods and drugs.

Dr. Harvey W. Wiley, founder of the FDA, in a Bureau of Chemistry laboratory, circa 1908. At this time the Bureau was beginning the testing and certification of production batches of coal tar colors—the first FDA program for consumer protection "at the source."

disease—and a further reaching backward toward the source by FDA.

Thus, continued progress in food technology made looking at food manufacturing operations merely for contamination by insects, filth, and the like entirely inadequate. The 1938 Food, Drug, and Cosmetic Act gave FDA additional powers to deal with the problems that might stem from this new technology in such areas as substances purposely added to food for some useful purpose (direct or intended additives); substances that have no planned function in food but become (or have a good chance of becoming) part of it during some phase of processing, packaging, or storing; and substances that are poisonous and deleterious but are so pervasive and unavoidable that to ban products containing them would mean eliminating a goodly portion of our food supply.

All of these changes in the law reflected or were in response to technological advance and the possibility of technogenic disease. This has challenged FDA to find ways of reaching further backward toward the source through more precise methods of toxicological analysis; through a re-examination of substances previously considered safe on the basis of possibly obsolete scientific data; and through research into such basic matters as the migration potential of certain molecules and the question of a threshold for carcinogens.

Just as the class of substances regulated by the Bureau of Foods has required an ever more insistent effort to reach back toward the source, so too has the regulatory means employed. Initially, under the 1906 Act, FDA could move only when a marketed substance violated the law. Thus, the Agency dealt with products. Now, the methods permitted under the 1938 Act and refined over the years entail reaching back to prevent dangerous products from ever reaching the marketplace by various forms of quality assurance regulations. For example, instead of confining itself to taking action should an improperly processed lot of canned mushrooms result in botulism, FDA seeks to prevent unsafe manufacturing practices.

The five major elements in this program to protect the consumer at the source are (*a*) "Current Good Manufacturing Practice Regulations;" (*b*) an "Emergency Permit Control System" to keep tabs on canners who are having trouble complying with good manufacturing practices for low-acid canned foods (specifically designed for the class of foods that permit contamination by viable *Clostridium botulinum*); (*c*) a comprehensive establishment inspection method, "Hazard Analysis of Critical Control Points," aimed at assuring continuing quality control in a food establishment throughout the year; (*d*) a "Cooperative Quality Assurance Program" in which manufacturers voluntarily agree to follow specific procedures established by FDA to assure safety and quality; and (*e*) as a check on the success of these and other efforts at the source, a continuing program of sampling food products on the retail market.

Just as technological advance required FDA to reach first beyond gross contamination to the subtle but often more hazardous threats posed by new molecular entities, the third advance in technology, involving a preponderance of processed foods, is generating a new effort to reach even further back toward the source: to gain more knowledge about proper nutrition and to assure that consumers have access to the nutrition and other information they need to make proper choices. To this end, FDA is following a double research strategy: on the one hand, learning more about nutrition and on the other, engaging in the most massive outreach effort ever undertaken by a Federal Agency to discover more about what kinds of food labeling information and information presentation consumers themselves want.

Veterinary medicine. Reaching backward toward the source has also increasingly involved the Bureau of Veterinary Medicine. This Bureau has broadened its focus from concentrating on inspecting feed mills to ensure that animal feed contaminants do not enter the food supply and reviewing drug applications for their safety and effectiveness for animals, to far more fundamental factors often at the outer limits of scientific knowledge, such as assurance that no cancer-producing drug residues enter the human food supply and that antibacterial drugs used in animal feeds are safe for human beings as well as being safe and effective for animals. In regard to this latter research effort, FDA questions whether antibacterials used for treatment of disease in man should be used at subtherapeutic levels in animal feeds unless evidence is submitted proving their safety for man, because recent research has indicated that bacteria drug resistance in animals can be transferred to bacteria in human beings.

To assure safe use of animal drugs, FDA reviews data submitted by sponsors and removes from the market those drugs that are unsafe and ineffective and those products for which no supportive data are generated. The Agency also sponsors workshops for medicated-feed manufacturers to educate industry on the use and restrictions of antibacterial drugs in animal feeds.

Medical devices. Until 1976, FDA's ability to regulate medical devices and diagnostic products was seriously limited. However, in that year Congress provided new statutory authority through the Medical Device Amendments to the basic Food, Drug, and Cosmetic Act. The new law defines a medical device as a health care product that does not achieve any of its principal intended purposes by chemical action within or on the body by being metabolized. Products that achieve their principal purpose by chemical action will continue to be classified as drugs.

The new law also enables FDA to reach back toward the source in dealing with the complex universe of medical devices. This is accomplished by authority to categorize all medical devices intended for human use into three regulatory classes based upon the extent of control necessary to insure the safety and efficacy of each such device. The three classes are:

Class I, General Controls: A device for which controls other than standard setting and premarket approval are sufficient to assure safety and effectiveness. Devices classified into this category will be subject only to the general controls applicable to all devices. These include existing controls prohibiting adulterated or misbranded devices and new controls, which include registration of device manufacturers; authority to ban certain devices; requirements respecting notification of risks and repair, replacement, or refund; requirements to keep records and make reports; requirements restricting the sale, distribution, or use of certain devices; and requirements with respect to good manufacturing practices.

Class II, Performance Standards: A device for which general controls are insufficient to assure safety and efficacy and for which there is sufficient information to establish a performance standard to provide such assurance. Devices classified into this category must meet applicable standards as they are prescribed by FDA.

Class III, Premarket Approval: A device for which insufficient information exists to assure that general controls and performance standard would provide reasonable assurance of safety and effectiveness and which is intended for a life-supporting or life-sustaining use or which presents a potential unreasonable risk of illness or injury. Devices classified into this category will require FDA approval before they can be marketed.

As additional evidence of this enhanced ability to reach back toward the source of potential problems, although the premarket approval procedure for devices is quite similar to new drug procedures, there is greater involvement of outside experts because the classification panels will review applications. Also, the law authorizes a procedure—termed a "product development protocol"—whereby the development of a product and the development of data necessary to demonstrate safety and effectiveness evolve simultaneously.

Cosmetics. It is only in regard to cosmetics—regulated through the Bureau of Foods—that FDA has been frustrated in the necessary movement backward toward the source. While the Agency is charged with assuring that cosmetics are not harmful under conditions of use and are truthfully packaged and labeled, an anomaly in the Food, Drug, and Cosmetic Act places the burden on FDA to prove harm rather than on industry to prove safety, as is true with drugs and food additives.

In addition, through another historical curiosity,

coal tar hair dyes are given special status that limits FDA's ability to regulate them.

A study conducted by the General Accounting Office (GAO) pointed out that there is increasing evidence that some cosmetic products and ingredients carry a significant risk of injury to consumers and that, despite such evidence, efforts to regulate cosmetics have been hampered by a lack of adequate legislative authority. The GAO recommended that Congress act to eliminate this deficiency, with particular attention to empowering FDA to require:

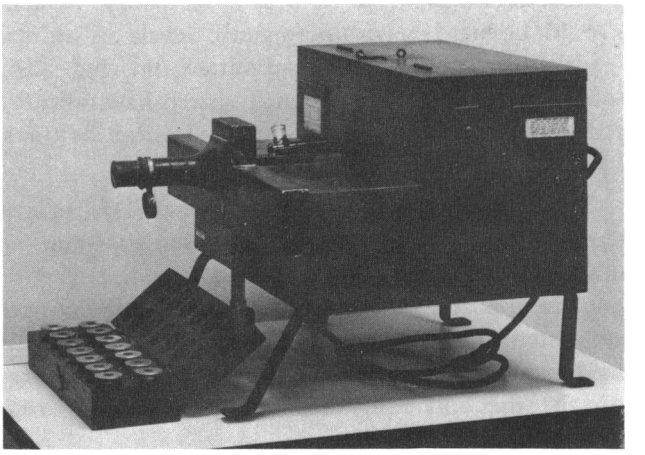
—mandatory registration of all cosmetic manufacturers, cosmetic products, and filing of ingredients statements;
—manufacturers to submit data to support the safety of products and ingredients;
—pre-market approval of certain classes of cosmetic products or ingredients when FDA deems approval necessary to protect the public health; and
—manufacturers to submit consumer complaints about adverse reactions to cosmetics.

FDA's limited ability to reach back toward the source inhibits the Agency's ability to carry out risk assessment of cosmetic ingredients.

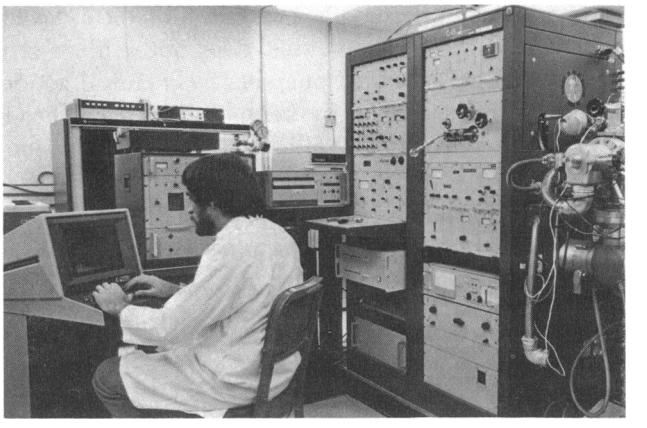
Risk to the consumer from cosmetics appears in two forms, acute injuries and long-term chronic effects. It is only recently that long-term effects have become of concern to the general public. In the past 5 to 7 years, a revolution has occurred in the kind of toxicological questions that are raised about cosmetics. This change parallels the growth in concern for chronic drug effects and the broad question of environmental carcinogens. Questions about cosmetic ingredients or contaminants with serious chronic effects or potential effects are increasingly asked by consumer advocates and others, including the GAO. Chemicals used in other common products are under suspicion as well.

Although FDA and the scientific community may have good answers concerning—or at least good methodologies to respond to—these questions for chemicals in foods and drugs that are ingested, there is no consensus for chemicals used on the skin. Many chemicals topically applied have never been tested; indeed, there is no consensus among toxicologists as to the relevance of existing tests. The Agency's toxicologists have little confidence in existing testing methodologies. Obviously, data derived from inadequate tests make a poor basis for risk assessment.

The current law forces FDA to make safety decisions based on the risk associated with the substance under conditions of use. Demonstrated human toxicity such as that for DES or thalidomide is seldom available. There is no Delaney Clause (banning carcinogenic food or color additives) for cosmetics; in fact, carcinogens have no special status in the law governing cosmetics regulation. In addition, toxicologists have serious doubts about the relevance of animal feeding studies to topically applied chemicals in the absence of skin penetration data. Yet, FDA is increasingly being forced to make decisions based upon ingestion data. Hence, it is feared that the toxicological and risk assessment decisions currently being made for cosmetics will not gain widespread support in the scientific community and that this



Clifford-Brice spectrophotometer, developed by FDA scientists in the 1930s, a major advance from traditional bench chemistry, was the forerunner of equipment which now detects and measures impurities in parts per billion. The new generation of laboratory instruments increased FDA's analytical capability approximately a million fold—the difference between about 10 parts per million in the 1940s and less than 1 part per billion today.



The continuing revolution in analytical techniques is typified by this high-resolution double-focusing mass spectrometer in the FDA Washington headquarters laboratories. This advanced unit is used to identify food toxicants in a range to 1 part per billion, depending on the sample. The 6,500 lb. assembly is supported by an air cushion to prevent vibration

will damage the Agency's credibility both with the public sector and the courts. There was a time in toxicology when the skin was considered an impenetrable barrier. Now that view has changed, and it is known that many substances will penetrate the skin, especially when combined with certain vehicles. Unfortunately, there is no supportable model that predicts or explains what occurs.

To reach back toward these kinds of problems, FDA badly needs answers to such questions as, is a cosmetic ingredient:

—toxic or carcinogenic or mutagenic to animals upon ingestion? How many species?

—capable of penetrating the skin? Metabolized into something else after penetration?

Regulations

Without doubt, the history of regulation of therapeutic drugs in the United States most clearly illustrates the painful and halting nature of the effort to reach back toward the source of problems or potential problems.

The 1906 Act provided meager authority to regulate drugs. Indeed, the philosophy of regulation was far more moralistic than scientific. Thus, the focus of the law in regard to drugs was on substances that today would not be considered drugs—the quack medicines that could offer no real therapeutic benefit and were in fact never intended to offer such benefit; substances that were the fraudulent issue of the marriage of greed and bizarre theories about illness. In dealing with this class of substances, the law offered primarily moral remedies: the label should not lie. If it were claimed that a medicine had certain ingredients, it must possess those ingredients. The manufacturer, in short, was prevented from misinforming. The law, therefore, made no pretense of reaching back toward the source in the sense of requiring proof that a drug would have a beneficial physiological effect. In fact, there was no requirement that a drug prove itself to be safe before marketing.

Lack of this elemental backward movement was made tragically evident in 1937 when the chief chemist of the Massengill Company of Bristol, Tenn., devised a palatable solvent for medicine's first "miracle drug," sulfanilamide. The solvent chosen was a diethylene glycol and water mixture flavored with raspberry extract. This compound was tested for taste and flavor, and soon the first shipment of 240 gallons of what was called "Elixir Sulfanilamide" began reaching the marketplace.

Unfortunately, diethylene glycol—used commercially to produce antifreeze and brake fluid—is a deadly poison, and before FDA managed to track down the last bottle, 107 people had perished. When the public discovered that the product had not been tested for safety on animals before distribution, that the law did not require such tests, and that only a technicality (the fact that "elixirs" by definition must contain alcohol and Elixir Sulfanilamide did not) permitted FDA to take action, there was an irresistible demand that Congress provide greater protection. Within a few months, Congress responded by passing the Food, Drug, and Cosmetic Act of 1938. The new law established, among other basic principles, that FDA had the authority to require pre-clearing new drugs before they could enter the marketplace. Thus, the 1938 law established for drugs what had been established for meats since passage of the Meat Inspection Act 32 years earlier: the necessity of preventing injury. And this, of course, represented a profound backward motion toward the source.

In 1962, as a result of yet another tragic episode, the European thalidomide disaster, Congress enacted a number of additional amendments to the drug section of the law. Among these were requirements that human subjects participating in drug research give informed consent, that all clinical testing of investigational drugs be conducted under applications approved by the FDA, that new drugs be proved effective as well as safe for their intended use before marketing, and that the standard for scientific evidence acceptable for demonstrating effectiveness be "adequate and well controlled investigations, including clinical investigations, conducted by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The importance of this rigorous requirement for clinical trials of impeccable scientific quality can hardly be exaggerated, and it certainly represents a backward motion toward the source that was of fundamental importance to drug development and evaluation in the United States.

In the 17 years since adoption of these amendments new problems have arisen, more subtle than the disasters that gained overwhelming support for drug law revision in 1938 and 1962, but nonetheless requiring attention. These subtle problems involve serious, though uncommon, adverse events that confound otherwise valuable therapeutic agents. Among many examples are the phenomenon of blood dyscrasias following ingestion of the antibiotic chloramphenicol, the relationship between endometrial carcinoma and estrogens, and thromboembolism from

oral contraceptives. Again, another backward motion is required toward the source, this time in finding ways to resolve such major issues as the extent of risk acceptable for chemicals in the environment, the impact of regulation on the innovative process, and the proper role of the Government in making more explicit benefit and risk decisions about drugs as well as food additives.

These and other problems are now being considered by the Congress, which is reviewing legislative proposals offered by Senators Edward Kennedy, Jacob Javits, Gaylord Nelson, and Harrison Williams and Congressman Paul Rogers. This Administration has also drafted proposals that reflect the concerns of the Review Panel on New Drug Development, various Congressional staffs, other executive agencies, public interest groups, and industry and professional associations.

Next Steps Backward

Among the steps considered necessary for the next basic movement backward toward the source of emerging drug problems are the following features of the new drug laws proposals:

—eliminating the variation in standards for marketing of drugs based on date of introduction and type of drug (for example, "old" drug, "new" drug, antibiotic, insulin, biologic) and establishing a new system of manufacturer and product licenses, together with a public standard (drug monograph) for each drug entity. This step would eliminate the present "grandfathering" of old drugs, give the Secretary (and, by delegation, FDA) the flexibility to establish requirements appropriate to different classes of drugs and simplify the process of approving subsequent manufacturers' versions of a new drug.

—authorizing approval of drugs on condition that distribution be restricted when needed to assure safe and effective use of the drug. Also, the statute would authorize the Secretary to require sponsors to conduct postmarketing studies for the purpose of answering questions about a drug's safety or effectiveness that do not justify delaying approval or that arise after initial marketing but do not justify withdrawal. The new proposals would also authorize the Secretary to require licensees to maintain a system for compiling and reporting data on drug use and experience for specific drugs and for a limited period of time.

—redefining and augmenting the safety and effectiveness criteria by which drugs are now evaluated by adding a standard that explicitly directs FDA to weigh risks and overall benefits. Without further definition, the terms "safe" and "effective" are misleading; no drug is absolutely without risk and few drugs are always effective. Moreover, these terms fail to reflect risks associated with the use of drugs. A standard that explicitly authorizes the balancing of comprehensive risks against benefits would more accurately describe the considerations that are properly used to evaluate new drugs. Such a standard would also contribute to improved public understanding of the regulatory process.

—allowing FDA to make available to the public the laboratory, animal, and clinical research data submitted to support the approval of a new drug. Such information is of great potential value to the scientific community and the public. It is largely withheld from disclosure under present law. Bona fide trade secrets, such as manufacturing processes, would continue to be exempt from public disclosure. The law should also provide an opportunity for the public to evaluate and comment on the submitted data, both in writing and at an open hearing.

—providing statutory recognition to the differing regulatory needs of drugs in the earliest ("innovational") stage of clinical investigations and those in the more advanced ("developmental") stage. In both stages, the law would be concerned with the protection of human subjects; but only in the latter stage would substantial regulatory efforts be directed at assuring the quality, validity, and reliability of the investigations. These provisions could reduce the time for and costs of exploratory drug testing without loss of protection to human subjects.

—according authority to require that package inserts, aimed at patients and expressed in lay language, be included with prescription drugs. Such labeling would give consumers the information they need to use drugs in accordance with prescribers' instructions and, in some cases, enable them to participate in an informed way in decisions about their own therapy. And,

—providing authority for the Commissioner, with adequate procedural safeguards, to remove a drug from the market before a formal evidentiary hearing when the public's health is endangered by continued marketing pending the outcome of a hearing. This procedure may now be used only when an "imminent hazard" is identified, and only by the Secretary.

These, then, are some of the ways that FDA has moved, or is seeking to move, further backward toward the source of those public health problems

within its domain. The movement is uneven, but its continuance and acceleration are vital if we are to build the kind of preventive strategy we need in an era marked by the introduction of new organic compounds never before encountered by organisms of any kind throughout the eons of biological evolution.

While I do not have a crystal ball (and would perhaps be afraid to use it if I did), I think it realistic to state that FDA will continue to learn more about how and what to regulate in the years to come and, without undue optimism, I think the Agency will also be gaining from an intensified research effort the kinds of basic knowledge—knowledge ever closer to the source—that will make regulation far more effective by making a great deal of it unnecessary.

Such a research effort, affecting every area of FDA activity, must respond to five basic principles:

First, an essential core of basic, undirected research focusing on fundamental processes. By "basic" I do not mean "reductionist." The population-based life sciences—biostatistics, epidemiology, various behavioral sciences—are not less basic than biochemistry and molecular genetics merely because they deal with larger aggregates.

Second, clear reognition that basic research is surrounded by, and must relate closely to, an area of applications research. There must always be adequate mission outlets to bring basic research results to fruition and always enough basic support to ensure that missions do not outrun their research base.

Third, a third class of research—now inadequately developed—that is intermediate in character between basic and applied needs much greater attention. Often, a $50,000 expenditure for a good idea on mission-oriented research can produce some fundamental knowledge more valuable in the long run than a test result. The development of such tuning mechanisms for the research zone between basic and applied ought to be a major objective for any long-term health plan.

Fourth, and particularly appropriate to FDA's effort to reach ever more effectively back toward the source, applied-research or mission-oriented health agencies must be given responsibilities for research and research planning. It follows that if the fine tuning discussed under the third principle is to be carried out, people who know the science must also know the mission. I believe the record indicates that basic scientists do not (and quite possibly should not) develop the knowledge of mission needed to perform that function. On the other hand, managers in the applied-research agencies often do not understand basic research well enough. This leads, inevitably, I think, to the conclusion that the applied-research agencies must have some excellent scientific capability somewhere, and that those parts of each mission-oriented agency should have a say in the research planning process.

Fifth, every research enterprise needs a cathedral. It seems to me that such a cathedral can be constructed in the area of reaching back toward the source in prevention or in a population health area. One attractive possibility is that of launching a major effort in prospective epidemiology. Public excitement and concern about the application phase of a research problem generate resources to support it and to attract the attention of able people to the disciplines involved. Scientists, no less than their public patrons, need the sense that a symbol of high social value is associated with their particular enterprise. Biomedical research in the 1950s and early 1960s had a number of such symbols going for it. First, there was the successful conquest of several major infectious diseases, notably poliomyelitis. There was also the dramatic capture of public attention by the success of basic research in solving the chemistry of heredity: in its way, the double helix became a cathedral.

More recent symbols have been conspicuously less successful. The "War on Cancer" was an attempt at symbol-making; but it has been spectacularly disappointing.

Public attention would be focused on a symbol-making experiment by virtue of its size and by virtue of the continuing "reporting back" feature; new findings would develop in a recurring fashion, and interest in various important scientific issues could be developed in advance.

Prevention and population health need a major shot in the arm. We have not yet succeeded in focusing public attention away from the treatment mode and toward the prevention mode—away from the individual boulders and back toward the source.

Reference

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