FOOD DRUG COSMETIC LAW JOURNAL

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FOOD DRUG COSMETIC LAW JOURNAL

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TO THE READER

The JOURNAL's first article again deals with the Medical Device Amendments, specifically with "Well-Controlled Investigations Under the Medical Device Amendments of 1976." *Philip Sperber*, a member of the Legal Department of Cavitron Corp., uses a step-by-step approach to outline the requirements of a well-controlled investigation of the safety and effectiveness of a medical device. He first explains the product development protocol procedure and then describes the different phases of the complete investigation. Throughout the paper, he provides detailed listings of the requirements and recommendations of each phase. His article begins on page 485.

Philip L. White, Sc. D., expresses his concern over what he calls cancerophobia and the public's demands for absolute safety of foods. In an article beginning on page 497, the Director of Foods and Nutrition of the American Medical Association points out the scientific and philosophical problems associated with trying to meet those demands. "Alternatives to Peril" was presented at the Food and Drug Law Institute's Food Update XV, which was held in Scottsdale, Arizona on April 25—29, 1976.

Pharmaceutical Update VI. The following papers were presented at the Food and Drug Law Institute's Pharmaceutical Update VI, which was held in Cherry Hill, New Jersey on May 19 and 20, 1976.

Anthony L. Young, an associate of the law firm of Wald, Harkrader & Ross, discusses the effect of the Freedom of Information Act and the Federal Advisory Committee Act on the pharmaceutical industry. Concentrating on the Acts in terms of the industry's relationship with the Food and Drug Administration, he assesses the Agency's attitudes in complying with the Acts' provisions. Included in the article are summaries of the number of information requests, grants and denials, the number and actions of advisory committees, and analysis of relevant court decisions. "Recent Developments Under FOIA and FACA Directly Affecting the Pharmaceutical Industry" begins on page 507.

Analysis of the evolutionary period that followed the passage of the 1962 Drug Amendments begins *William R. Pendergast's* article, "Evolving Approaches to the Regulation of Prescription Drugs." Among the ideas discussed in the paper are the validity of animal testing, the evaluation of well-controlled clinical studies, the use of scientific data as proprietary information, old drug monographs and the Food and Drug Administration's surveillance of manufacturer's testing. Mr. Pendergast, whose article begins on page 521, is a member of the law firm of McMurray and Pendergast.

In "New Regulatory Concepts in Rx Labeling for Patients," beginning on page 531, *William F. Weigel* discusses the advisability of patient package inserts for prescription drugs. In addition to outlining the possible problems, advantages and disadvantages of such inserts, he also mentions previous experience with patient brochures in over-the-counter products, proposed federal legislation, and the legality of FDA regulation in this area. Mr. Weigel is a member of the law firm of Rogers, Hoge & Hills.

In Memoriam.—Harvey L. Hensel, a contributor to this JOURNAL, passed away on July 21, 1976 at age 58. Mr. Hensel was a distinguished food lawyer, Assistant General Counsel for Swift & Company, and Chairman of the Food Drug Cosmetic Law Committee of the Corporation, Banking and Business Law Section of the American Bar Association. For many years Mr. Hensel was also an officer of the Industry Committee on Packaging and Labeling, in which capacity he made valuable contributions to the cause of uniformity of the laws relating to food, and weights and measures.

Memorial contributions may be made to Mayo Clinic Leukemia Research, Rochester, Minnesota.

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Well-Controlled Investigations Under the Medical Device Amendments of 1976

By PHILIP SPERBER

Mr. Sperber Is a Member of the Legal Department of Cavitron Corp.

THE MANNER in which a health care firm conducts new-product investigations to determine safety and efficacy is the key to commercial success in future years in view of the newly enacted device amendments to the Federal Food, Drug and Cosmetic Act, Title 21, U. S. Code.

The only reference of the Medical Device Amendments of 1976 to well-controlled investigations required by the product development protocol, exemption for investigational use and premarket approval application procedures, is in Section 513(a)(3). It is stated that clinical investigations should be carried out where appropriate by experts qualified by training and experience to evaluate the effectiveness of the device—from which investigations it can fairly and responsibly be concluded, by qualified experts, that the device will have the effect it purports and is safe under the conditions of use prescribed. An exception is also stated in that such well-controlled investigations are not necessary if there already exists valid scientific evidence which is sufficient to determine effectiveness and safety. Where the exception is inapplicable, today's health care manufacturer should use as a guide the well-controlled drug investigation procedures for new drug application and investigational new drug situations, plus lots of common sense in the many instances where the drug controls are physically impossible or simply not feasible for use with devices.

I. The Product Development Protocol: Why, When and How?

Let's consider the medical device which had not been developed and introduced to the marketplace prior to enactment of the Medical Device Amendments of 1976, which is not substantially equivalent to a device which was introduced prior to enactment of the Amendments and which has not been classified in Class I (general controls) or Class II (performance standards). Under Section 513(f)(1), such a device automatically is classified in Class III (premarket approval).

In this situation, an application for approval of a product development protocol should be filed promptly with the Secretary pursuant to Section 515(f) of the Amendments. This enables you simultaneously to develop the medical device and to collect the data necessary to demonstrate safety and efficacy, in accordance with the requirements and objectives of the protocol. After the protocol is carried out and the objectives showing reasonable assurance of safety and efficacy are met, a notice of completion of the approved protocol is submitted to the Secretary. If the Secretary declares the protocol completed, such an order is equivalent to approval of an application for premarket approval for the device.

There are four distinct phases in the well-controlled investigation of safety and efficacy of a medical device. First is its design and construction. The next two preclinical phases are *in vitro* and animal testing. The last phase is clinical evaluation involving *in vivo* testing.

The application for a product development protocol normally will involve outlining a detailed plan for the successful completion of all four phases of the investigation. For instance, the application will have to describe preclinical trials of the device, the results required from such trials prior to commencement of clinical trials of the device, and permissible variations in preclinical trials. The clinical trials, results required from such trials, and permissible variations therein also must be described in the application.

II. Record Keeping

Throughout all four phases of the well-controlled investigation, detailed records must be kept by both the sponsor of the investigations and the investigators. This includes a chronological record of the detailed design of the device and all changes made during its development during the preclinical and clinical phases. The same record keeping obligations apply to labeling and changes made thereto. Each investigator also must keep detailed records of all conditions of tests he has conducted and all results obtained, favorable and adverse.

Specifically, a detailed description, drawings and a sample of each medical device prototype designed during the development process of the four phases of the investigation should be kept for Food and Drug Administration (FDA) inspection. Each redesign, improvement and component and material change during the device development process should be identified, should be dated and should have an explanation as to the reasoning behind the change.

Likewise, there also should be a description of methods of manufacture, quality control, manufacturing facilities, labeling, methods of packing, methods of shipment, methods of storage, methods of installation and, if appropriate, methods of maintenance. As with product design, a historical record should also be kept of all changes in the matters mentioned in the preceding sentence and the reasons therefor.

If not all the manufacturing, control, packaging and installation operations are handled by the company itself, an agreement should be entered into with the vendors, subcontractors, distributors and other outsiders performing outside functions. They should agree to maintain the records needed by the company for the outside aspects of the operations to be examined by the FDA. The problem with this requirement is if the manufacture of a component or subassembly of the medical device by the vendor comprises secret know-how. The vendor may not be willing to disclose records containing these trade secrets even though he or she is given assurances of confidentiality by the company and the FDA.

III. The Design Phase of the Product Development Protocol

In addition to the records already discussed, it is extremely important that the objectives of the device to be designed be documented. In addition to recording a description of how the device will be beneficial in diagnosis or therapy, there also should be a written consideration of conventional apparatus and techniques and the rationale why the benefit-to-risk factor of the device and manner of use envisioned will be an improvement over current practice and equipment. Desired features and functions as well as the design constraints affecting the safety and efficacy of the device to be developed should be considered and evaluated, and this also should be documented.

IV. The *In Vitro* Testing Phase of the Product Development Protocol

The detailed measurements, experimentation and testing to determine safety and efficacy should be documented with the same care

that laboratory notebooks are kept for patent purposes. Testing protocol is basically twofold.

First, the essential performance characteristics that were stated as objectives in the design phase are to be tested for in order to determine reliability, accuracy and tolerance.

Second, the device should be tested to determine the risk of injury to the patient due to mechanical, electrical or radiation emission failure, improper use by the surgeon, inadequate endurance or reliability, environmental conditions (temperature, humidity, altitude, vibration, electromagnetic interference, exposure to chemicals, etc.) and poor design. Typical tests which should be made are: measurements of heat and energy generated; failure mode analysis of shock and other hazards; what type of static and dynamic pressure conditions are produced; durability of the instruments being inserted into the tissue to prevent flaking, breakage, etc.; effectiveness of the sterilization procedure during operating conditions; and the extent radiation emission may vary after calibration and may lessen or increase after long periods of use.

The testing protocol for performance characteristics and safe operation and use should be conducted with reference to the safety and efficacy of conventional devices. The current literature on such conventional devices, their use and the diseases or conditions to be mitigated or diagnosed should be documented to add validity to the *in vitro* phase of the product development protocol.

V. The Animal Testing Phase of the Product Development Protocol

The FDA expects full reports of adequate preclinical tests by all methods reasonably applicable to a determination of the safety and efficacy of the device under the conditions of use suggested in the proposed labeling. The laboratory animal studies generally will be a prerequisite to approval of an application for an exemption for investigational use of a device. There will be exceptions, such as when it is not physically possible to run animal trials due to the nature of the medical device.

Since the FDA considers labeling to be one of the key elements of a well-controlled investigation, a proposed instruction manual and warning indicia on the device should be prepared prior to animal evaluation by the investigator. This labeling should contain: a description of the device and its operation; detailed user instructions for calibrating, operating and maintaining the device: a description of the surgical technique that the device is intended for, if appropriate; a

description of the purposes of the device in the diagnosis or treatment of conditions; suggested indications and contraindications for selecting the use of the device under certain circumstances; advantages and disadvantages of using the device with respect to performance (for instance, making the operation easier, shorter, etc.); risks and results (for instance, the operation generally is more successful than with conventional devices, hospitalization and rehabilitation time is reduced, etc.); and warnings with respect to equipment operation and its use.

If the medical device is to be shipped to an animal investigator outside the company, the device and instruction manual should have the following warning thereon: "CAUTION—This is a new medical device for investigational use only in laboratory research animals, or for tests *in vitro*. Not for use in humans."

Detailed Protocol

Prior to any animal investigation, there should be a detailed plan or protocol stating the objectives of the animal study, in order to determine what must be done to assure safety and efficacy prior to clinical investigation. For instance, animal trials should be conducted to study the fluid dynamics set up by the instrument in the tissue after insertion; to study the disposition of fluids introduced into the tissue or fragmented particles that must not remain; to study the biological compatibility of any material or fluid introduced and remaining in the tissue; to study any unwanted tissue damage due to heat, radiation, vibration and other forms of energy introduced by the device; and to study other pathological aspects of the investigation.

One animal investigator is normally sufficient. The type and number of animals to be used in preclinical trials will vary with the number of different medical applications the device has, the number of apparent hazards that the device may have, and the extent that the device needs to be redesigned and perfected to assure safety and efficacy prior to clinical investigations.

It should be the responsibility of the investigator to record all findings, observations, parameters studied, adverse reactions (even those that may be incidental), methodology, results and interpretation of the testing, energy level and duration of use, and a description of the animal (weight, sex, maturity, condition, etc.) for each animal tested with the device.

The name, address and qualifications of the laboratory animal investigator who performed the studies and evaluated the results; the facilities where the investigations were conducted and where the records are available for inspection; the date that the medical device for animal trial was shipped; and the model number or other identification of the shipped device should be documented.

Both the documentation of the sponsor and the records of the investigator should be kept for a period of at least two years after the medical device receives premarket clearance or product development protocol completion approval or commercial abandonment of the device, whichever occurs later.

If at some point in the animal trials, it is decided that the device must be redesigned in certain respects, there should be at least some *in vitro* testing after the redesign—before additional animal trials are run. The FDA pays close attention to the adequacy of preclinical investigations.

VI. The Exemption for Investigational Use

When the investigator and the sponsor have concluded that adequate information has been obtained from the animal trials to support the safety and efficacy of the device, an application should be filed with the FDA for an exemption for investigational use of the device for clinical investigation pursuant to Section 520(g).

As with the product development protocol application, an application for exemption from the premarket approval restriction for investigational use will have to outline various procedures and conditions relating to the duration of clinical testing to be conducted; the number of human subjects to be used, descriptions of the testing methods and procedures, signed agreements from investigators, approval by local institutional review committees, and other matters.

VII. The Clinical Investigation

It is desirable that initial trials on a limited number of humans be conducted by a single investigator. This preliminary investigation is for the purpose of verifying safety and efficacy conclusions reached during the preclinical stage prior to full-scale clinical investigation. It may be that the initial trials on humans will result in modification of the experimental design and the need for additional animal data before proceeding with the clinical investigation.

The clinical investigation protocol will be based on facts accumulated in the preclinical phases and will consist of trials con-

ducted by several investigators following the same protocol (with reasonable variations and alternatives). Although a drug company may use 50 physicians throughout the country during clinical investigation, three or four independent competent investigators conducting human trials with the device should provide ample assessment of safety and efficacy for approval of product development protocol completion in the normal situation.

The number of subjects used, that the FDA will deem reasonably necessary to establish safety and efficacy data, will vary with the following factors:

(1) the number of animal trials conducted and their success;

(2) the number of patients per year needing treatment or diagnosis that can be performed by the device;

(3) the number of patients per year an investigator can treat with the device;

(4) the number of different treatment or diagnostic applications of the device;

(5) the scope of the patient population that can be treated or diagnosed by the device (for instance, will use be limited to a particular segment, thereby limiting trials to a particular sex or age group?); and

(6) the cost of producing prototypes of the device.

As a rough rule of thumb, a range of 25 to 75 patients treated or diagnosed by the device should be sufficient in the normal situation. However, a pharmaceutical firm might use 5000 subjects in its clinical investigation.

Maximum Research Information

As with the animal investigation phase, a detailed plan or protocol should be documented and given to each of the investigators together with all proposed labeling and preclinical data prior to human trials. The protocol must be designed so that it can produce maximum research information at minimum hazard to the patient, and it should be in the patient's best interest at all times. The protocol must provide for the consequences and courses of action in the event the device fails or fails to achieve its expected results. All of the hypotheses, methods, controls, patient selection, tests and observations to be made, and other definitive criteria for evaluation, must be documented in detail to assure standardization and uniformity among the independent investigations being conducted and to assure

well-controlled clinical data. In addition to the detailed description of the clinical trials, the protocol should specify the results from such trials to be obtained for proving safety and efficacy of the device, including permissible variations in the results.

Particular attention should be paid to the method of selection of the subjects to assure that they are suitable for the purposes of the study. Diagnostic criteria of the condition to be treated or diagnosed by the device should be documented for all investigators. If the device is not directed toward any specific segment of the population, there should be a sufficient number of trials conducted on groupings of differing age, sex and severity or duration of the condition. Special care must be taken to assure that the investigators use the same methods of observation and recording results, including the variables measured, quantitation and assessment. For instance, if the investigator does not record the specific parameters such as frequency, power, pressure, depth, etc., the FDA may find this to be an uncontrolled investigation because comparative data and results between the investigator's subjects and between his subjects and those of other investigators may not be possible.

Uncontrolled or partially controlled studies are not acceptable as the sole basis for claims of safety and efficacy, although such studies may provide collaborative support. The clinical investigation protocol must outline in detail the steps to be taken in order to minimize bias on the part of the subjects, observers and investigators. Furthermore, the protocol should contain detailed designs of *modus operandi* for using control agents and methods of blinding in clinical trials.

Control Procedure

The common control procedure used in the drug field is the placebo control. This involves comparing the results of using a new drug with an inactive preparation designed to resemble the test drug in matched groups of subjects. Although this is inapplicable to medical device testing, there are other methods of setting up controls.

First, in situations where the disease to be treated is terminal and at an advanced stage, the no-treatment control can be used. One group of subjects is treated with the medical device and the other comparable group remains untreated. The longevity and mortality rate of the subjects in each group is then compared.

Second, a more suitable procedure could be an active treatment control. Here, a conventional device or regimen of therapy is used

on the control group and the test device is used by a matched group of subjects.

Third, in circumstances where the disease or condition is predictable and may be compared quantitatively with prior experience historically derived from adequately documented history of the disease or condition, in comparable patients or populations with no treatment, a historical control may be used. In other words, the results of trials on a group of subjects with the test device is compared with the resultant condition that can be expected from such subjects with no treatment at all.

Finally, in appropriate situations, the crossover control also may be used during clinical trials of a medical device. This basically would entail the use of a conventional device on part of the tissue being treated or diagnosed and then the test device on another portion of the same tissue as was treated with the conventional device.

Nonbiased Investigations

In human trials of a drug, the sponsor will normally design one or more types of studies to assure nonbiased investigations, such as the following:

(1) single-blind (the patient does not know whether he is receiving the test drug or a placebo);

(2) double-blind (neither the patient nor the investigator knows whether the test drug or placebo is being given to the subject);

(3) crossover (first the placebo is given and then the drug);

(4) double crossover (after the drug is given in the crossover, the placebo is subsequently given to the subject); and

(5) randomized (unsystematic switching between the placebo, reference compound and test drug.

The above-listed designs of the clinical investigation generally are inapplicable to clinical trials with medical devices. Probably one of the only practical methods of ensuring no bias would be what could be called a "review-blind" procedure. This could be accomplished by having an independent, competent observer present during the clinical trials, who would evaluate the results obtained with the test device and the conventional device without knowing which is which. The problem with this is that the devices would have to be black-boxed in some manner since the observer might be familiar

with the particular conventional device used. A more preferable review-blind would be to have a review committee or investigator (such as a pathologist) examine the patient and tissue treated after the trials are done, without knowing whether the subject was treated with the test device or with a conventional method of therapy or diagnosis.

Information and Assurances

When the medical device to be investigated is shipped or delivered to the clinician, the labeling on the device and in the instruction manual should conspicuously state: "CAUTION: New drug—Limited by federal law to investigational use." Before shipment or before commencement of clinical trials, each investigator involved should sign a statement giving the following information and assurances:

(1) education (schools, degrees and dates);

(2) postgraduate training (institutions, dates and nature of training);

(3) teaching or research experience (institutions, dates and brief descriptions);

(4) medical and professional experience (institutional affiliations, nature of practice, dates);

(5) pertinent publications (journals, titles and identifying references);

(6) assurance that a local institutional review committee will initially and periodically review and approve the clinical study;

(7) description of the clinical laboratory facilities to be used;

(8) outline of the plan of investigation, including the approximate number of subjects to be treated, the number to be employed as controls, if any, clinical uses to be investigated, characteristics of subjects by age, sex and condition, the kinds of clinical tests and observations to be undertaken, the estimated duration of the investigation and a description of report forms to be used to maintain an adequate record of observations and test results;

(9) assurance that the investigator has received full information concerning the preclinical investigations that justify the clinical trials;

(10) assurance that periodic progress reports will be submitted to the sponsor;

(11) assurance that any adverse effects shall be reported to the sponsor promptly and, if alarming, shall be reported immediately so that other investigators can be notified by the sponsor;

(12) assurance that the device will be used only on subjects under the investigator's personal supervision or under the supervision of the investigators responsible to him (identifying those investigators) and that the device will not be supplied to any other investigator or clinic for administration to subjects;

(13) assurance that the investigator will inform each subject, including subjects used as controls, or their representatives, that the device is being used for investigational purposes and that the consent of each of said subjects or representatives thereof is obtained, except, where in the investigator's professional judgment, such consent is contrary to the best interests of the subject (such as in a life-threatening situation where it is not feasible to obtain informed consent in time); and

(14) assurance that the investigator will report to the local institutional review committee any emergent problems, serious adverse reactions or proposed procedural changes affecting the

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tion of both the sponsor and the investigators must be retained for at least two years after the device has either received approval or has been abandoned, whichever occurs later.

VIII. Application for Premarket Approval

Now let's consider the situation where the medical device was developed and introduced prior to enactment of the Medical Device Amendments of 1976, or it was introduced after enactment but the device is substantially equivalent to a device introduced after enactment and has not been classified in Classes I or II. The necessity for a product development protocol application and an exemption for investigational use application is absent here because, pursuant to Section 501(f)(2)(B), premarket approval for the device is not required until 90 days after the Secretary promulgates a premarket approval regulation for the device and, in no event, earlier than 30 calendar months after automatic classification into Class III upon enactment of the Amendments or subsequent classification into Class III. The necessity for an application for a product development protocol is also inapplicable because the product already has been developed and has been introduced to the marketplace.

What is required is the filing of an application for premarket approval pursuant to Section 515(c). This application must contain documentation concerning all investigations which have been made; methods, controls and all other relevant information to assure the Secretary of safety and efficacy.

If the type of well-controlled investigations that have been discussed herein were not made prior to development and introduction, they should be commenced promptly. Although you will have at least 30 months after enactment of the Amendments, plus an additional period of time if the premarket classification has not yet been promulgated for the particular device, there are risks in delay.

For instance, the Secretary has a half year to issue an order approving or rejecting the application for premarket approval. If it is rejected, the Secretary will require measures similar to a product development protocol in order to place the premarket approval application in approvable form, and this could take a substantial amount of time. If the time period for obtaining premarket approval runs out in the interim, all devices on the marketplace would be considered adulterated pursuant to Section 501. This means that the Secretary could take any one of several actions varying in degree of harshness against all such adulterated devices on the market.

[The End]

Alternatives to Peril

By PHILIP L. WHITE, Sc. D.

Dr. White Is Director of Foods and Nutrition of the American Medical Association.

MAN, IN HIS FLIGHT FROM HOPE, soars over the plains of salvation, but he neither recognizes nor appreciates what they offer to him. In his soaring, he seems to favor the cold drafts of threat more than the warm thermals of comfort. It is as though by contending with the cold drafts of threat he hopes to control his own destiny. This is disquieting; why does he not utilize the warm thermals of comfort that arise from the plains of salvation? Even those who do, however, from time to time also glance around anxiously to mark the locations of the cold drafts of threat.

We live in trying times, times to try man's soul. The incidence of carcinoma of the stomach is declining and no one can explain why it should be so. Man weeps. Epidemiologists are embarrassed by the decrease in the death rate from diseases of the heart. It must be something other than cholesterol!

Everyone was depressed by the headline in the *New York Times* for January 29, 1976: "Cancer Toll Rise in '75 a Mistake . . . Apparently Dramatic Trend in First 7 months Laid to the Vagaries of Data." Later, in the *New York Times* of March 5, 1976, the Director of the National Center for Health Statistics in a letter said: "Don't get your hopes up!"

CBS thrills the nation with a TV Special, "The American Way of Cancer."

Consumer advocates demand that bacon carry a label warning: "Eating Bacon is Dangerous to Your Health; Boil, don't Bake."

Red No. 2 is banned because an ill-fated animal study did not prove that it could not cause cancer.

Representative Delaney publishes a Congressional memorandum calling for an immediate suspension of all artificial fluoridation of

drinking water so there can be compliance with the existing Delaney Cancer Amendment; fluoride, he says, causes cancer. The Amendment requires the Food and Drug Administration (FDA) to ban any carcinogen in food and drink.[1] The National Health Federation offers form letters to be sent to your congressmen demanding legislation implementing Representative Delaney's memorandum for $1.00 per 100, plus postage.

Fund Cut

The National Cancer Institute faces a fund cut. Scientists are looking for carcinogens that the public has already found. The cut in funds is a threat, for more people make a living from cancer than there are people dying of it.

We have progressed from the philosophy, "Take hart healthe is possible," to the present preoccupation, "Take heed, you are surrounded by death." Death has become an environmental hazard. As Lewis Thomas said:

"It is extraordinary that we have just now become convinced of our bad health, our constant jeopardy of disease and death, at the very time when facts should be telling us the opposite. In a more rational world, you'd think we would be staging bicentennial ceremonies for the celebration of our general good shape. In the year 1974 out of a population of around 220 million, only 1.9 million died, or just under 1 per cent—not at all a discouraging record once you accept the fact of mortality itself. . . . Despite the persisting roster of still unsolved major diseases—cancer, heart disease, stroke, etc.—most of us have a clear, unimpeded run at a longer and healthier lifetime than could have been foreseen by any earlier generation."[2]

But as historian Kenneth Clark stated: "Our days are numbered in the best of times."

The preoccupation with disease and peril has evoked some very cogent editorials. Franz Ingelfinger, editor of the *New England Journal of Medicine*, wrote:

"American Cancerophobia, in brief, is a disease as serious to society as cancer is to the individual—and morally more devastating. In this state of affairs, many are to blame—not only high pressure advertisers foment and exploit our cancerophobia, but also the well-meaning and yet harmful practices of other groups: activist consumer organizations, politicians, and even the American Cancer Society, which point direly accusatory fingers at you if you do not give money to 'cure cancer.'"[3]

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[1] *Congressional Record*, pp. 57172—57176 (July 21, 1975).

[2] Thomas, Lewis, "Notes of a Biology-Watcher, The Health Care System," *New England Journal of Medicine* 293: 1245—1246 (Dec. 11, 1975).

[3] Ingelfinger, Franz J., "Cancer! Alarm! Cancer!" *New England Journal of Medicine* 293: 1319—1320, (Dec. 18, 1975).

Jonas Salk devised a remedy for people worried about cancer-causing substances: "The best thing to do," he said, "is quit reading the newspaper."[4]

Everywhere one reads bold predictions of the increase in longevity that could be achieved by the control of leading causes of death. In a January 25, 1976 United Press International Release, Science Editor Al Rossiter stated: "If coronary heart disease could be wiped out, the average lifespan of American men could be increased by 8 to 10 years, by some estimates. Elimination of cancer would extend the average life by almost 2.5 years."

Healthy Hypochondriacs

Soon only degenerative diseases will remain unsolved, and when they are controlled, people will die only of natural causes. Lewis Thomas set our goal—to make aging and dying a healthy process. He goes on to suggest that preoccupation with human fragility could lead to the time when we all become doctors, ". . . spending our days screening each other for disease. The new danger to our well-being, if we continue to listen to all the talk, is in becoming a nation of healthy hypochondriacs, living gingerly, worrying ourselves half to death."[5]

Was it not Pogo who said, "We have met the enemy and they is us"?

With so much attention being given in the media to correlations that shake out of epidemiological studies, it really is no wonder the public is preoccupied with cancerophobia. The skilled application of the epidemiologic process has succeeded in linking nearly every nutrient or major food component to one loathsome disease or another. The only recourse is to hold back change and progress so that the epidemiologist can prove cause and effect.

"Impasse"

"Cholesterol is poisonous
So never, never eat it.
Sugar, too, may murder you
There is no way to beat it.
And fatty food may do you in
Be certain to avoid it.
Some food was rich in vitamins
But processing destroyed it.
So let your life be ordered
By each documented fact
And die of malnutrition
But with arteries intact."[6]

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[4] *Chicago Sun-Times* (March 17, 1976).

[5] *Supra* note 2.

[6] Kritchevsky, D., "Impasse," *New England Journal of Medicine* 262:619 (1960).

Fun from Fiber

Medical pundits have been having their fill of fun from fiber. Howard M. Spiro mused as follows: ". . . the patient is on a high fiber diet to prevent diverticular disease and colon cancer and now that his child is a vegetarian, for more doctrinaire reasons, they can meet in one great gassy festival of love over cauliflower, broccoli and carrots; spinach which stood for the authority of the parents and divided the generations in the 1920's, now symbolizes their unity."[7] Should dietary prudence, which taught us to eschew butter and eggs, urge us now to chew bran? Samuel Vaisrub in the *Journal of the American Medical Association* wrote,

"The answer to this question would be easier if the fiber feeding was only a matter of mastication and ingestion. Unfortunately, it also entails nondigestion and elimination. Attendant borborygmi, flatulence, frequent defecation of soft bulky stools, and a constant awareness of bowel activity are hardly conducive to a serene state of mind. Fiber may stir the gut but it is unlikely to stir the imagination or quicken the pulse."[8]

A few scientists still make sense. Yerushalmy and Palmer state: "The estimates of (their) health effects are frequently based on a combination of conventional wisdom and superficial association. There is often little evidence to support a causal relationship. The error of equating association with causality has been referred to in epidemiology as the ecologic fallacy."[9]

Public preoccupation with chronic diseases and with environmental hazards is a garrote tightening slowly around the throats of the pathologist and the toxicologist. The demand is for protection from environmental hazards that threaten longevity. The scientist can help and perhaps can reduce some of the hazards associated with environmental chemicals, but many of the apparent environmental hazards in reality, are related directly to voluntary habits under one's personal control.

A great deal of attention is paid to uncertain or implied risks while other large and unequivocal risks to health are essentially ignored. These risks and other voluntary social habits are major or even overwhelming contributing factors influencing early death. Among the unequivocal risks are to be found excessive use of alcohol and tobacco,

[7] Spiro, Howard M., "The Rough and the Smooth," *New England Journal of Medicine* 293:83—85 (July 10, 1975).

[8] Vaisrub, Samuel, "Fiber Feeding —Fad or Finger of Fate?" *JAMA* 235: 182 (Jan. 12, 1976).

[9] Yerushalmy, J. and Palmer, C. E., "On the Methodology of the Investigation of Etiological Factors in Chronic Disease," *J. Chronic Diseases* 10:27—40 (1954).

drugs, lack of proper exercise, automobiles and (according to some authorities) choice of dietary composition.[10]

Unequivocal Risks

Proper attention paid to these unequivocal risks certainly would improve the quality of life for many. But are people ready to make decisions about their personal life-styles that would reduce such risks? Some have already made changes, but the majority of people simply are not interested.

The other aspect—that of uncertain hazards, those associated with environmental chemicals—is influenced by public pressures of a different nature. For here, the public demands protection, where in the other instance it seems to be unwilling to take the necessary steps for its own personal protection. In the past, unless experts could provide satisfactory and convincing evidence of the adverse effects of environmental chemicals, their opinions were neglected or even rejected. Contrary to that earlier situation, it is now frequently assumed that a hazard exists even when no satisfactory evidence for it can be provided. Today, as a result of strong social pressures, experts are asked to provide scientific evidence of absolute safety. All of these attitudes are extreme ones. A World Health Organization (WHO) Expert Committee pointed out that when the existence or the absence of adverse effects cannot be established definitely, it is for the responsible public health authorities to decide whether a preventive or a conservative attitude should be adopted.[11]

The implementation of that recommendation calls for the exercise of informed judgment and, as we shall soon see, informed judgment is sometimes ignored. A case in point is the non-part played by the National Toxicology Advisory Committee in the FDA decision to remove Red No. 2 from the marketplace. Canada, on the other hand, chose to accept informed judgment in its decision to keep Red No. 2.

Absolute Safety

Food safety is an ever present challenge. This is another situation in which scientists are searching for carcinogens the public already knows about. Scientists are being asked to reduce or eliminate

[10] Report of the Panel on Chemicals and Health of the President's Science Advisory Committee (Sept. 1973).

[11] Health Aspects of Environmental Pollution Control: Planning and Implementation of National Programmes, Technical Report Series 554, WHO, Geneva (1974).

unknown hazards and those known hazards that spring from causes still unknown. Furthermore, when certain sectors of the public become aware of a possible chemical hazard often based on incomplete evidence, they then demand its removal or, at best, demand evidence of absolute safety. By extension, the demand is for absolute proof of safety.

When required by the public to prove absolute safety from unknown hazards, we are asked to eliminate unknown hazards or those known hazards that emerge from causes unknown. One, therefore, is required to prove a negative, that is, to prove the absence of a hazard (to take a little scientific license).

Research Into the Negative

To prove the negative, one must be prepared to prove experimentally the presence of nothing. Not a real trial for most of us. However, to prove the presence of absolutely nothing (the antithesis of demonstrating the totality of everything or proving absolute safety), one must be careful never to have believed in its presence. This is a little like an approach our minister uses when chatting with an atheist. "Now, tell me about this God you don't believe in." He usually gets a three-minute monologue on the bad features of the God the person does not believe in! Having once believed in God, one cannot then deny His presence. Once having believed that a food additive is a carcinogen, one can never believe that it is not, so don't even think about it. By this logic, I believe one safely could look for a non-cocarcinogen when he has the other half of the co(prime)-carcinogen. I am not sure, but I would not look for one of those either. Is there such a thing as a non-potentiator of a non-cocarcinogen? I suspect one could prove the absence of one of those things.

There is no question that demonstrating the absence of nothing is intellectually stimulating, but considerable time would be required to establish one's career. There would be few examples of favorable termination of research into the negative because that would be tantamount to successfully not finding what you are looking for.

There are lessons to be learned from past experiences with food nonsafety. Is it possible that cyclamate protects against the carcinogenicity of saccharin and that the FDA may have removed the wrong half of the combination tested for safety? The FDA Red No. 2 study, on the other hand, may have provided the paradigm of how not to perform a toxicologic experiment. Too many technical things went wrong;

not all bases were covered. That study offers an important lesson also. The botched study "accepted" as a valid test for evaluating risk provides a standard of nonexcellence for those who must plan negative research. In an offhand way, this reminded me of a headine I saw a few years ago: "Agnew Papers Found Missing." In summary, a fruitful culmination of research to identify unknown hazards from causes still undetermined is successfully not finding what you are looking for. But then, not finding something does not prove its absence.

The requirement to identify the unknown cause of diseases or hazards not yet defined exemplifies the jargon of safety evaluation. We have a greater chance of dying from it than living with it.

The science of biology is influenced heavily by the statistical philosophy that lack of proof of no effect is a probability problem that can be resolved by feeding more animals excessively high doses. The dosage is to be increased until the limiting factor becomes the nutrient density of the test diet. Ultimately, a toxicological threshold is approached, heralded by the call for nutritionists to assemble human diets that resemble toxicologic experimental diets. The response will be: "There ain't no room for no food!" Then the option will be to nourish the animals by vein and administer the test-compound by mouth. Someone said twenty million Frenchmen couldn't be wrong. Where else but in America would they say that twenty million mice cannot be wrong?

Red No. 2

The statistical philosophy can be illustrated in another way that relates to biological data. Regarding the Red No. 2 study, Dr. Herbert Blumenthal, Director of the FDA's Division of Toxicology, is quoted as having said: "While the statistics used in this particular analysis may point to carcinogenesis, the biological analyses and interpretation do not." He went on to say that he would not have requested a statistical evaluation of the study.[12]

A new science is developing, a science known as politoscience. This is a social science in which informed scientific judgment is disallowed or ignored. Informed judgment or expert opinion is required when factual information is incomplete or absent. Incomplete knowledge is unacceptable for there must have been an experimental or statistical error. Informed judgment is no longer a privilege for the

[12] *Food Chemical News* 17, No. 47, 27 (Feb. 9, 1976).

scientist (he probably had an industry grant, anyhow). Disallowing informed judgment automatically makes everybody an expert and we have politoscience. Legislative staffs would collect, collate and interpret scientific information. Scientific issues could be resolved by the democratic process. Peer review would be a prerogative of the courts. The recommended daily allowance table would be reduced to just two columns, calories and cholesterol.

Let's take politoscience to its ultimate conclusion. Since it was reported that people who died of an infectious disease seldom developed cancer, the Congressional Select Committee on Cancer Control assumed that an immunity to cancer developed in response to the infectious disease. Medical scientists, however, failed to isolate any immune bodies or to induce the immunity by conventional means. The Congress then decided to remove all restraints on infectious disease. The cancer incidence dropped to next to nothing in just two generations. The Congressional Bureau of Health Statistics, to its dismay, then discovered that life expectancy had fallen to 40 years, just as in 1900. There was little cancer and almost no heart disease. People died of ague, apoplexy, conniptions, vapours, dyspepsia, plague, pox and ptomaine.

Cancerophobia

It was clearly turning into a strange world. Cancerophobia and atherosclerotaphobia reinforced by politoscience was having a pronounced effect on industry.

All colors and dyes were suspected of causing cancer or hyperkinesis or both. No natural or synthetic colors could be used in food, drink or drug, nor in anything that touched the body. Only those people who were color blind were surviving; the rest were dying of starvation since the aesthetic quality of food, drink and drug is a prime prerequisite to indulgence. The problem was solved by the development of colored lights and colored glasses specially designed to provide the necessary aesthetic colors for use when consuming breakfast, lunch or dinner. All snacking was done in the dark and man soon learned to drink with his eyes closed. Television casts returned to black and white since advertisers no longer could depend on product color to generate sales. To the unaided eye, breakfast cereals appeared the color of blah, except for King Vitamin which fluoresced an iridescent blue from the added riboflavin and the thiochrome from degraded thiamin. It was indeed turning into a strange world.

This is not too different from the world that we know today for we also do some strange things, such as consuming massive doses of vitamins to cure cancer, heart disease, schizophrenia—even the common cold.

Sanctum Sanctorum Vitaminum

Vitamins have become a substitute for prayer.
And food a substitute for vitamins.
And love a substitute for food.
And alcohol a substitute for love.
And alcohol produces liver cirrhosis.
Therefore, prayer causes liver damage.

Alternatives to Peril

Are there alternatives to peril? Is man destined to live in a sea of cancer-causing chemicals? Such was the suggestion of Dr. Frank J. Rauscher, Jr. at the American Cancer Society annual science writer's seminar. Dr. Rauscher is quoted as stating: "Every year for the last ten years more than 250,000 new compounds have been put on the market. Practically none of the new compounds have been tested for their cancer causing potential."[13] With $150,000 and three years for the testing of each one, the ten-year accumulation of 2,500,000 new compounds would require 7.5 million man-(and rat-)years of testing and 375 billion dollars in expense, assuming no more inflation and no screening of the compounds. During the 7.5 million years of testing, 2×10^{13} new compounds would be introduced and their testing - - - -, well, enough.

Does progress sustain peril, are they synonymous? Alvin Toffler, in his book *Future Shock*, asserted that progress was indeed perilous for those who were not prepared properly for it. Preparation for progress, appropriate information to those to be affected by it, certainly should help. But, at the same time, peril cannot be the cost of progress, for progress is in reality a reduction in peril. Is there not a progression of events that backs industry into corners of its own making?

[13] *Chicago Tribune* (March 30, 1976).

Alternatives to Peril

Advertising creates the need,
The consumer sustains it.

Industry expands demand,
The stockholder sustains it.

Demand exceeds the natural,
The artificial sustains it.

The artificial breeds concern,
The naturalist sustains it.

The concern yields peril,
And panic sustains it.

The alternative to peril?
Information disdains it.

The conclusion is: Tell the consumer why you do what you do, and if it cannot be justified, do not do it. Remember, that the informed consumer can make judgments; the uninformed consumer makes accusations.[14] **[The End]**

RADIOACTIVE DRUGS MAY BE MARKETED PENDING APPROVAL OF AN NDA

Commercial distribution of radioactive drugs, including radioactive biological products, whose exemption from the requirement of a new drug application (NDA) would have terminated on August 20, 1976, may continue pending final approval of an NDA by the Food and Drug Administration (FDA). The extension provided by an August 17 FDA Order, affects those drugs for which, on or before August 20, an approvable notice for an NDA had been issued. The approvable notice indicates that the FDA is prepared to approve the NDA after submission of additional information. Marketing of the drugs for which an approvable notice has been issued may continue until the issuance of a nonapprovable notice for the NDA or until November 20, 1976, whichever comes first.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,694

[14] White, P. L., Public Readiness for Nutrition Information, Supplement No. 13, Näringsforskning, Marabou, Sundbyberg, Sweden (Aug. 30, 1975).

Recent Developments Under FOIA and FACA Directly Affecting the Pharmaceutical Industry

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OPENNESS IN GOVERNMENT has, for the past several years, been a point of focus for Congress, regulatory agencies and the courts. Legislation such as the Freedom of Information Act (FOIA)[1] and the Federal Advisory Committee Act (FACA)[2] has been followed by extensive litigation and more recently by detailed agency regulations such as those promulgated by the Food and Drug Administration (FDA).[3] Although FOIA has been on the books for nine years and FACA for almost four, these laws are only now beginning to have a significant impact on the pharmaceutical industry.

Before exploring in detail these two acts, two preliminary points are in order. First, FOIA and FACA are procedural in nature, and while the FDA's preoccupation with them might lead a layman to conclude otherwise, they do not amend the Federal Food, Drug and Cosmetic Act.[4] Yet, like other basically procedural statutes,[5] they impose requirements that must be observed if the purposes of the underlying Acts are to be achieved.

Second, my remarks are not directed toward a discussion of these statutes in general, but are limited to recent developments affecting the pharmaceutical industry. At the outset, however, I should observe

[1] 5 U. S. C. Sec. 552.
[2] 5 U. S.C . App. I.
[3] 21 CFR Part 4.
[4] 21 U. S. C. Sec. 321 *et seq.*
[5] For example, the Administrative Procedure Act, 5 U. S. C. Sec. 551 *et seq.*, and the National Environmental Policy Act, 42 U. S. C. Sec. 4321 *et seq.*

that it is often the rule that the occasional judicial gloss that is added to a statute is subsumed in its day-to-day administration at a regulatory agency. The FDA is no exception. With these preliminary thoughts in mind, I now turn to a detailed look at the statutes in question.

I. The Federal Advisory Committee Act

The FDA now has established 24 advisory committees with jurisdiction over prescription drugs and biologics. These committees evaluate data concerning the safety and efficacy of those products. Another 15 are actively reviewing all nonprescription drug products. From this plethora of committees one would hardly suspect that a principal purpose of FACA was to limit the use of such committees to "those that are essential."[6] Despite this legislative purpose, the FDA's extensive use of advisory committees is not difficult to explain. Commissioner Schmidt recently stated[7] that he has "encouraged more use of advisory committees by the Agency" because such committees, "composed of individuals from the private sector, can monitor the performance of the Agency" and "bring needed expertise and experience[,] ... lend credibility to [its] actions, serve a valuable educational function, and provide a forum for public discussion of important issues."[8]

The Commissioner's statements followed a House Committee report[9] criticizing the Agency's alleged improper use of advisory committees and were made on the eve of new medical device legislation mandating such use.[10] In its most relevant parts, the House Report concludes that the FDA has improperly closed committee meetings, has improperly influenced advisory committees by injecting legal issues into their scientific deliberations and has implemented committee recommendations based on less than complete evidence.[11] More general conclusions were that the FDA's use of committees has

[6] 5 U. S. C. App. I, Sec. 2; Office of Management and Budget, Advisory Committee Management, Guidance Para. 3b., 39 *F. R.* 12389 (Apr. 5, 1974).

[7] *Medical Device Regulation (Without Interference)*, Hans L. Hecht Memorial Lecture, University of Utah, April 22, 1976, p. 17.

[8] The use of outside consultants to assist the FDA in carrying out its statutory functions is nothing new. As long ago as 1951, Deputy Commissioner Larrick was telling the Senate Subcommittee on Health that certain new drug applications were not approved until "after consultation with national authorities." Hearings on S. 1186 and H. R. 3298 Before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, 82nd Congress, 1st Session 16 (1951).

[9] Use of Advisory Committees by the Food and Drug Administration, Eleventh Report of the Committee on Government Operations, H. R. Rep. No. 94-787, 94th Congress, 2nd Session (1976).

[10] See Conference Report on S. 510, H. R. Rep. No. 94-1090, 94th Congress, 2nd Session (1976).

[11] H. R. Rep. No. 94-787, *supra*, Findings and Conclusions 6, 8 and 15, pp. 6—11.

contributed to a lowering of drug approval standards and that the Agency uses committees to gain the support of the scientific community for regulatory decisions.[12] While the Report may be partly responsible for the FDA's recent shift in policy toward more openness in the activities of the Agency's advisory committees, it does little more than summarize the results of several years of hearings[13] that effectuated some change at the time they were held. Therefore, in my view, the report will have little impact on the FDA and, therefore, on the pharmaceutical industry.

Advisory Committees

The FDA's use of advisory committees has created legal issues which fall into two broad categories. The first is whether a given group or amalgamation of individuals is an advisory committee, and the second is the extent to which the deliberations of committees subject to the Act must be open to the public.

The first question was recently answered in the case of *Consumers Union v. Department of Health, Education and Welfare* (HEW).[14] The controversy arose when an attorney for Consumers Union asked and was refused permission by the FDA to attend meetings of the Cosmetic, Toiletry and Fragrance Association (CTFA) and the Agency to discuss a voluntary cosmetic ingredient review program. The direct question before the Court was whether such meetings rose to the level of advisory committee meetings so as to be covered by the Act. The Court held that the meetings were not covered because they "were not called to consider proposals dealing with pending *agency* action"[15] and because CTFA was not "advising the FDA"[16] about a government program. Rather, the Court concluded, these were "consultations concerning the group's [CTFA's] own proposal" at which the CTFA was seeking "FDA's comments and advice."[17]

The Court found the case distinguishable from the situation in *Food Chemical News v. Davis*.[18] There, the Bureau of Alcohol, Tobacco

[12] H. R. Rep. No. 94-787, *supra*, Finding and Conclusions 4 and 5, pp. 5—6.

[13] Hearings on Use of Advisory Committees by the Food and Drug Administration, Parts 1—3, Before a Subcommittee of the House Committee on Government Operations, 93rd Congress, 2nd Session, 94th Congress, 1st Session (1974—1975).

[14] No. 75-1250 (DC DofC March 12, 1976).

[15] *Consumers Union*, *supra*, slip opinion at 6. (Emphasis in original.)

[16] *Id.*, slip opinion at 7.

[17] *Ibid.*

[18] 378 F. Supp. 1048 (DC DofC 1974).

and Firearms of the Treasury Department sought the advice of industry and consumer groups on possible amendments to regulations dealing with labeling of distilled spirits. Such meetings were held to be covered by FACA because the Bureau controlled the regulatory situation. By contrast, in CTFA's case, the FDA lacked specific authority[19] to mandate cosmetic ingredient testing.[20] This last point was important to the Court because of FACA's directive that agencies, not their advisors, determine "action to be taken and policy to be expressed."[21]

The FDA's Advice

The teaching of the *Consumers Union* case is that private industry may solicit the FDA's advice on matters outside the Agency's direct jurisdiction without fear that the procedural requirements of FACA must be satisfied. The opposite would prevail, however, according to the implications of this decision, where an outside group and the Agency met to discuss matters which clearly (or arguably) fall within the FDA's direct jurisdiction. Regularized meetings, such as the monthly FDA/*ad hoc* consumer representative meeting, are already open to the public, as are the more occasional FDA/industry conferences, such as the upcoming series on medical device legislation. In these situations, openness—the principal bone of contention under FACA—obviously is not at issue. *Ad hoc* industry/FDA meetings, such as those occasionally held before or after the FDA lowers its regulatory boom, might well be required to be open under the *Consumers Union* rationale.

Such a result would have a significant negative impact on the pharmaceutical industry, I submit, because it would inhibit the free flow of communications.

The FDA also appears to take this view. In the proposed regulations on Administrative Practices and Procedures, the FDA flatly takes the position that the Act does not apply to "routine meetings, discussions, and other dealings, including exchanges of views, between the Agency and any committee representing or advocating the particular interests of consumers, industry, professional organizations, or others."[22] One district court opinion has agreed with the FDA

[19] *Consumers Union v. Department of HEW*, *supra*, slip opinion at 6, n. 4.

[20] "CTFA in its own discretion was ultimately to decide whether or not to initiate a testing program." *Consumers Union v. Department of HEW*, *supra*, slip opinion at 8. "Indeed, there are serious questions as to whether FDA had the authority to sponsor an ingredient testing program." *Ibid.*

[21] 5 U. S. C. App. I, Sec. 9(b).

[22] Administrative Practices and Procedures, Notice of Proposed Rule-making, 40 *F. R.* 40682, 40707 (Sept. 3, 1975).

position.[23] Of course, it remains to be seen whether appellate courts will concur with this position.

The FDA's other judicial experience with FACA came in *Wolfe v. Weinberger.*[24] That case involved the efforts of the Health Research Group's Dr. Sidney Wolfe to obtain copies of verbatim transcripts of the closed sessions of the FDA's Panel on Review of Over-the-Counter (OTC) Antacid Drug Products. The FDA refused to disclose the transcripts because they reflected "the deliberations of those engaged in the policy-making process, and [are] thus exempt from disclosure" under the Freedom of Information Act[25] as inter-agency or intra-agency memoranda.[26] The District Court disagreed and ordered the transcripts released. The basis for the holding was that the transcripts were not exempt from disclosure under that Act because the panel was not an "agency" as defined for purposes of FOIA in that it lacked independent authority to make decisions.[27] Thus its transcripts were not entitled to protection as an "inter-agency or intra-agency memorandum."[28]

Agency Memoranda

The Court was right, of course: The panel is not an agency. This issue is important to FACA because advisory committee meetings may be closed only upon the reasoned invocation[29] of one of the nine exemptions from disclosure under FOIA.[30] When a committee is discussing trade secret information, it is relatively simple to close a meeting by invoking FOIA's exemption four, which protects trade secrets. Where the committee is merely discussing non-trade secret issues, however, such as general recognition of the efficacy of aspirin, the only possible exemption is the one relating to "inter-agency or intra-agency memoranda." Thus, the FDA was compelled to argue in *Wolfe,* ultimately without success, that its advisory committee was an agency.

The Court in *Wolfe* went on *in dicta* to suggest that the inter-agency/intra-agency memoranda exemption applies to closed meet-

[23] *Nader v. Baroody,* 396 F. Supp. 1231, 1233 (DC DofC 1975), appeal docketed, No. 75-1969 (CA DofC) ("... the Act was not intended to apply to all amorphous, ad hoc group meetings ...."); *cf. Lombardo v. Handler,* 397 F. Supp. 792 (DC DofC 1975), appeal docketed, No. 75-1959 (CA DofC) (holding the National Academy of Sciences not covered by FACA).

[24] 403 F. Supp. 238 (DC DofC 1975).

[25] *Id.,* at 239.

[26] 5 U. S. C. Sec. 552(b)(5).

[27] *Id.,* at 241.

[28] *Ibid.*

[29] *Gates v. Schlesinger,* 366 F. Supp. 797, 800 (DC DofC 1973).

[30] 5 U. S. C. App. I, Sec. 10(d).

ings of advisory committees only where the committee is considering or discussing "an actual agency memorandum otherwise protected by the exemption."[31] No such memoranda were being considered by the Antacid Advisory Committee. Moreover, the Committee's transcripts were not part of the Agency's deliberative process since the FDA eschewed reliance upon them.[32]

Because most of the meetings of the Antacid Review Panel were held prior to the enactment of FACA, the Court noted that its application of the statute to the case was "problematical."[33] This, and the pendency of a case presenting similar issues in the United States Court of Appeals for the District of Columbia, caused the FDA to note its disagreement with the Court's view in a *Federal Register* notice.[34] The antacid transcripts, however, were released.

Aviation Consumer Action Project Case

On April 6, 1976, the Court of Appeals decided the pending case entitled *Aviation Consumer Action Project v. Washburn*.[35] The Court held that meetings of an advisory committee may properly be closed where the "head of an agency determines [they are] concerned with inter-agency or intra-agency memorand[a]."[36] The Court noted that FACA on its face permitted this result by incorporation of FOIA's exemptions. The consumer group's second argument, that disclosure of such memoranda to advisory committee members amounts to disclosure to the public, thereby vitiating the exemption, was also rejected. Thus, the *dicta* in *Wolfe*, that discussions of inter- or intra-agency memoranda may be closed, appears to be good law.

The Court of Appeals went further, however, and adopted the rationale often advanced by the FDA for closing advisory committee meetings, that is, that the inter-agency/intra-agency memoranda exemption and the policy behind it is

[31] *Wolfe v. Weinberger*, *supra* at 242; *cf. Nader v. Dunlop*, 370 F. Supp. 177 (DC DofC 1973); *Gates v. Schlesinger*, *supra* at 799 ("If the matters coming before an advisory committee are neither inter-agency or intra-agency affairs, exemption 5 of the [FOIA] is by its terms unavailable. . . .").

[32] *Wolfe v. Weinberger*, *supra* at 243. Compare, *Washington Research Project, Inc. v. Department of HEW*, 504 F. 2d 238, 250 (CA DofC 1974) (advisory committee report "part of the deliberative process" of the Agency and exempt from disclosure).

[33] *Wolfe v. Weinberger*, *supra* at 243.

[34] OTC Review Panel on Antacid Drug Products, Availability of Certain Transcripts of Closed Sessions, 40 *F. R.* 58165 (Dec. 15, 1975).

[35] No. 75-1086 (CA DofC April 6, 1976), petition for reconsideration *en banc* filed April 20, 1976.

[36] *Id.*, slip opinion at 10.

"particularly applicable to advisory committees, whose sole function is to advise the agency. The exemption is designed to encourage a free and candid exchange of ideas during the process of decision-making and to prevent predecisional disclosure of incipient policy or decisions that could disrupt agency procedures."[37]

This language parallels the FDA's most oft-cited grounds for closing meetings to protect the "free exchange of internal views, to avoid undue interference with committee operations"[38] and to permit "formulation of recommendations."[39]

The importance of the decision cannot be overstated: It permits an agency to close meetings at the drop of a memorandum. In the *Aviation Consumer Action Project* case, the memorandum merely set forth the issues to be discussed by the committee and was created for the express purpose of closing the meeting.[40] Because of the potential for mischief created by the decision, the plaintiffs have asked that it be reheard by the Circuit Court.

While the FDA's and the Circuit Court's interpretation of FACA would permit the closing of all committee discussions and deliberations,[41] it does not appear that this power will be used. It is now a widely held view at the FDA that more advisory committee discussions will be opened to the public. This is exemplified by the recent discussion of the safety and alleged carcinogenicity potential of FD&C Red No. 2 by the Toxicology Advisory Committee.

Wide Discretion

On the other hand, the *Aviation Consumer Action Project* case allows the FDA wide discretion in closing meetings. For example, several weeks ago, in affirming the Agency's refusal to release transcripts of closed advisory committee discussions regarding two approved diuretic drug products, the Assistant Secretary for Health cited the case.[42]

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[37] *Id.*, slip opinion at 13. (Citations omitted.)

[38] Notice of Meeting, Panel on Review of Dentifrices and Dental Care Agents, 41 *F. R.* 16595, 16597 (Apr. 20, 1976).

[39] Notice of Meeting, Panel on Review of Topical Analgesics, 41 *F. R.* 16595, 16600 (Apr. 20, 1976).

[40] *Aviation Consumer Action Project, supra*, Brief for Appellant at 4 n. 2; Brief for Appellee at 4.

[41] "A portion of a meeting may also be closed if the Commissioner determines: (1) that it involves interagency or intra-agency memoranda or discussion and deliberation of matters that, if in writing would constitute such memoranda, and which would therefore be exempt from disclosure; and (2) that is essential to close such portion of a meeting to protect the free exchange of internal views and to avoid undue interference with agency or committee operations." Notice of Meetings, 41 *F. R.* 16595, 16602 (Apr. 20, 1976).

[42] Letter from Assistant Secretary for Health Cooper to Anita Johnson, April 27, 1976.

This leads to the question, "Where lies the public interest?" Advisory committees, as was pointed out here a year ago, "form a basis for FDA decisions, as the 1973 Supreme Court decisions recognized."[43] This raises several issues. First, advisory committee review of a new drug product and the release of a conclusion that safety or efficacy is in doubt not only has legal significance but may also irreparably damage the drug's reputation among physicians and their patients. Yet, as Commissioner Schmidt has stated, "[i]t is remarkably difficult, if not impossible, to hold external, independent, part-time consultants responsible for their errors."[44] Second, if the recent open Toxicology Advisory Committee meetings are an example, it appears that FDA attorneys are prepared to push these committees as far as possible to get confirmation of the Agency's view.[45] One can only assume the same course is sometimes followed by Agency personnel who deal in private with the Bureau of Drugs' committees.

A balance must therefore be struck: deliberations open enough to prevent *ex parte* influence and to nip medical or scientific error in its incipiency and yet sufficiently closed so that errors may be corrected prior to their publication.

An open FDA advisory committee process will require that the Bureau present its positions and their justifications in open session. Panel discussions will be open to the public. Only the drafting of final reports and presentations or discussions of trade secrets or confidential data will be the subject of closed sessions. This is a substantial change from past practice. It provides the pharmaceutical industry with an opportunity to monitor the committees and their decisional processes and to respond prior to the cementing of committee conclusions. Most important to the FDA, however, openness will make it more difficult for the Agency's detractors to use secrecy as the predicate for their criticisms.

II. The Freedom of Information Act

As I stated earlier, FOIA is in its ninth year. The Act was passed in 1967, not, as some might believe, in late January 1975 when the FDA's Public Information regulations became effective.[46]

[43] McGrew, Jane Lang, "How to Let in the Sunshine Without Getting Burned: Protecting Your Rights Before Advisory Committees." 30 FOOD DRUG COSMETIC LAW JOURNAL 536, 537 (Sept. 1975).

[44] *The FDA in 1985*, Tulane Medical Symposium, New Orleans, La., Nov. 5, 1975.

[45] See Boffey, "Scientists and Bureaucrats: A Clash of Cultures on FDA Advisory Panel," Science (March 26, 1976) p. 1244.

[46] Public Information, 39 *F. R.* 44601 (Dec. 24, 1974).

Those regulations have generated thousands of detailed requests for information at the Agency. Additionally, the FDA's insistence that requests be logged for almost anything but press releases and publications has fattened the numbers. Finally, the wide availability of the log itself generates still more requests as it signals the availability of information and whets curiosity.

And how has the pharmaceutical industry fared under the onslaught? I am sure that everyone has his own horror story. Overall, however, it appears from the record that the FDA is living up to the promise of its regulations. For the most part, what it has said it will release is being released. What it said would be withheld is being withheld.

At the outset, however, the *Pharmaceutical Manufacturers Association* (PMA)[47] litigation, now at an end, must be noted. The first decision established that there is no general right of notice to the owner of allegedly trade secret information prior to its release by the FDA. But the Court assumed, "absent a contrary showing, that FDA's [notice provision would] be generously and liberally interpreted."[48]

In the second decision, the Court found also that "due process is guaranteed under the existing regulations and administrative scheme"[49] of providing notice prior to release in any "uncertain" cases. The Court also upheld the FDA's waiver provisions regarding release of trade secret information by its owner to a third party[50] as well as the retroactive application of the regulations to cover all data in the Agency's files.[51]

No Bureaucratic Impediments

It is my understanding that these decisions are being followed by the Bureau of Drugs. The guiding principle at the Bureau is that anyone handling an FOIA request may phone the owner of the requested information if there are any doubts as to its trade secret or confidential status. No permission need be obtained, no second opinion need be sought. There are no bureaucratic impediments; all that need to be done is to dial the phone.

Certainly there are problems with the *PMA* decisions which transcend the fact that the industry's view did not prevail. The

[47] *Pharmaceutical Manufacturers Association v. Weinberger*, 401 F. Supp. 444 (DC DofC 1975) (PMA I); *Pharmaceutical Manufacturers Association v. Weinberger*. No. 75-0725 (DC DofC Apr. 14, 1976) (PMA II).

[48] *PMA I, supra* at 449.

[49] *PMA II, supra*, slip opinion at 4.

[50] *PMA II, supra*, slip opinion at 8; 21 CFR Sec. 4.81.

[51] *PMA II, supra*, slip opinion at 8; 21 CFR Sec. 4. 25.

courts' acceptance of FDA expertise in trade secrets and confidential information is potentially pernicious.[52] This is because the Agency's prior blanket treatment of new drug application (NDA) material as trade secret leads me to believe that FDA personnel have little experience in this field. The danger of this suddenly acquired "expertise" is that courts will now defer to the Agency's judgment, thereby reducing the potential that FDA errors will be discovered and corrected.

There is evidence that such a trend has already begun. In *Morton-Norwich Products, Inc. v. Mathews*,[53] Judge Gessell said the following of the FDA: "[it] processes thousands of Freedom of Information Act requests a year. It has a specialized staff which proceeds with legal advice." In so saying, he denied the company's request that he review *in camera* data withheld by the Agency. His basic premise was that FOIA "must proceed in an atmosphere of confidence in government. If the agency cannot be trusted, the Act will never work."[54]

With the Court's words in mind, let us now turn to the administration of the Act by the FDA and the Assistant Secretary for Health as reflected in their decisions denying and reviewing denials of requests for information.

A. *The Assistant Secretary for Health*

Since January 1, 1975, the Assistant Secretary for Health has decided 30 appeals from FDA denials of requests for information. In 22 cases, he has affirmed the FDA. He has reversed in three and there have been five split decisions in which the FDA was partially reversed.

First, the reversals. In one case, the Agency had refused to release the methodology it used to analyze a sample of an allegedly defective drug product.[55] In another, the FDA was reversed on its refusal to release the investigational new drug (IND) submission dates on 91 approved new drugs.[56] Its computer had not been programmed with the information.[57]

The last reversal came at the beginning of this year. It involved the investigational use of LSD in five institutions. The FDA denied

[52] *PMA I, supra* at 446: *PMA II, supra*, slip opinion at 5.

[53] CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 38,056, (DC DofC 1976).

[54] *Ibid.*

[55] Letter from Assistant Secretary for Health Cooper to Kenneth G. Lemke, March 10, 1975.

[56] Letter from Assistant Secretary for Health Cooper to Bruce C. Ladd, July 9, 1975.

[57] See Letter from Bruce C. Ladd to Assistant Secretary for Health Cooper, June 17, 1975.

a news correspondent's request for the information. However, annual reports, adverse reactions and other information regarding the studies were later released.[58] While the release of IND materials is unusual, the reason here was that the FDA had listed all of the approved research projects in an article in *FDA Consumer*.[59]

Partial Grants and Denials

Partial grants and denials included the release of factual portions and denial of opinion portions of draft position papers submitted by members of the Panel on Review of Blood and Blood Derivatives.[60] Another decision released some of the FDA's quality assurance programs for its own laboratories, but denied internal audits and intra-agency memoranda.[61]

One of the more interesting decisions involved the release to a competitor of one company's safety tests on the competitor's product.[62] The case is unusual, if not startling, in that the material had been submitted voluntarily to the FDA by the testing company. The Agency apparently contemplated giving that company the opportunity to withdraw the material.[63] The FDA did not do so, however, and the tests were released after the competitor made out a strong case that much of the material was not trade secret.

In affirming FDA denials of requests for information, the Assistant Secretary for Health has invoked the trade secret exemption ten times with regard to such material as "raw" animal test data in NDA files,[64] product formulae,[65] customer lists,[66] as well as protocols and other materials from pending NDAs.[67] Data from IND files,[68] transcripts of closed advisory committee meetings dealing with new

[58] Letter from Assistant Secretary for Health Cooper to John J. Curley, Feb. 13, 1976.

[59] Letter from John J. Curley to Assistant Secretary for Health Cooper, Jan. 9, 1976.

[60] Letter from Assistant Secretary for Health Cooper to Mal Schecter, Feb. 12, 1976.

[61] Letter from Assistant Secretary for Health Cooper to Alan H. Kaplan, Feb. 13, 1976. See *Morton-Norwich Products, Inc. v. Mathews, supra.*

[62] Letter from Assistant Secretary for Health Cooper to Ashley L. Ford, June 24, 1975.

[63] Letter from Ashley L. Ford to FDA Assistant Commissioner John T. Walden, Apr. 24, 1975.

[64] For example, letter from Assistant Secretary for Health Cooper to Anita Johnson and Sidney Wolfe, M.D., Feb. 28, 1975.

[65] Letter from Assistant Secretary for Health Cooper to Ashley L. Ford. *supra.*

[66] Letter from Assistant Secretary for Health Cooper to Richard M. Cooper, July 11, 1975.

[67] For example, letter from Assistant Secretary for Health Cooper to Michael Weisman, Aug. 11, 1975.

[68] For example, letter from Assistant Secretary for Health Cooper to Deborah Rheubau, Apr. 18, 1976.

drugs,[69] and allegedly trade secret material submitted to an OTC Drug Product Review Panel[70] have also been withheld by the Assistant Secretary.

Similarly, invocation by the FDA of the intra-agency memoranda exemption has been upheld eight times to protect from disclosure such items as draft regulations,[71] a task force report,[72] and portions of an FDA investigation reflecting inspectors' opinions.[73] Finally, denials of establishment inspection reports in cases of ongoing investigations are routinely affirmed.[74]

On the whole, the Assistant Secretary has upheld FDA denials where there was a rational and legal basis for doing so. Where a denial was without legal justification, however, the FDA has been put to task, no matter how burdensome the task of compliance.

B. *The Food and Drug Administration.*

In 1975, the FDA processed 13,061 requests which were classified as FOIA requests and logged as such. Of these, only 184 were "denied" by the Agency. The exemption for trade secret or confidential material was relied on 82 times while the exemption for ongoing law enforcement investigations was relied on 59 times.[75] The pace has quickened this year. Already, 114 denials have been issued. Many of these, however, were from last year's requests. And it must be remembered that the FDA will have received almost 9,000 requests by June 1.

Material Denied

It would appear from these statistics that the FDA is giving up a substantial amount of information. Not necessarily so. The FDA's policy is to construe requests under the FOIA so as to obviate denials. If this cannot be done, the requesters are often called and the

[69] Letter from Assistant Secretary for Health Cooper to Anita Johnson, Sept. 9, 1975.

[70] Letter from Assistant Secretary for Health Cooper to Alan H. Kaplan, Apr. 29, 1976; Letter from Assistant Secretary for Health Cooper to Anthony L. Young, June 2, 1975.

[71] Letter from Assistant Secretary for Health Cooper to Robert Pear, Apr. 1, 1976.

[72] Letter from Assistant Secretary for Health Cooper to David A. Eisenberg, Apr. 14, 1976.

[73] Letter from Assistant Secretary for Health Cooper to Wayne Center, Mar. 5, 1976.

[74] For example, letter from Assistant Secretary for Health Cooper to Colby S. Morgan, Jan. 23, 1976.

[75] Memorandum re: Annual Report to Congress on FOIA Activities from Edward J. Costello, Supervisor, Public Records and Document Center, FDA, to Freedom of Information Officers, Department of HEW, Jan. 28, 1976.

request is discussed in an effort to preclude a denial. It appears from the low number of denials that most people are satisfied with this approach. Moreover, most requests are from people sophisticated enough not to ask for exempt material.

Before closing, I will describe briefly some of the materials denied. Information on pending NDAs,[76] INDs,[77] NADAs,[78] and data submitted to the OTC Drug Product Review[79] are denied routinely. Manufacturing information,[80] quality control specifications,[81] and product formulae[82] are also denied without fanfare.

Some of the more interesting recent denials have included FDA/FTC correspondence on nutritional labeling[83] and an intra-agency "Report of FDA *Federal Register* Activity."[84] The names of the actual manufacturers of private label human and animal drug products are being withheld[85] as are progress reports on government contracts.[86] And the FDA will not release its target list of chronic violators of the food and drug laws.[87]

Of particular interest to the pharmaceutical industry may be the fact that the FDA has not released voluntarily submitted material that is trade secret.[88] This is the case even where the company has not requested and received a pre-submission promise of confidentiality.[89] The files I have reviewed in fact show the granting of only one such request.[90]

The FDA appears from the visible record to be releasing a great deal of information. If one looks at requests that have been granted, however, it is likely that the Agency has given away only part of its vast store. The record is now too voluminous to examine. Each owner of trade secret material must make his own judgment and, if necessary, complaint.

III. Conclusion

The FACA will have a substantial impact on the pharmaceutical industry because it will open up a process upon which the FDA has

[76] For example, F76-5101.
[77] For example, F76-6276.
[78] For example, F76-4808.
[79] For example, F76-3165.
[80] For example, F76-556.
[81] For example, F76-1809.
[82] For example, F76-4017.
[83] For example, F76-7002.
[84] For example, F75-11562.
[85] For example, F76-5943.
[86] For example, F76-2209.
[87] For example, F76-2545.
[88] For example, F76-2738.
[89] See 21 CFR Sec. 4.44.
[90] Letter from Assistant Commissioner John T. Walden to Manuel S. Klausner, Jan. 9, 1976.

come to rely in resolving difficult scientific and medical issues. The FOIA, which is slowly bringing to light substantial amounts of heretofore nonpublic information, will also have an impact. At a minimum, the release of such information will provide something of value to the company that is devoid of know-how, and thus perhaps affect the competitive structure of the industry. Criticism of the industry will also be facilitated, in a new demonstration of the axiom that knowledge is power. The task for industry will be to anticipate these developments and to make the accommodations necessary for survival. [The End]

"NEW GENERATION" OF COUGH-COLD REMEDIES SEEN

Ten drug ingredients sold previously only on a physician's prescription can now be sold directly to consumers for treatment of the common cold and other respiratory symptoms pending a final regulatory decision on over-the-counter (OTC) cough and cold remedies, the Food and Drug Administration (FDA) has stated. Sherwin Gardner, Acting Commissioner of Food and Drugs, declared that the FDA's review panel on OTC cough-cold products has provided the Agency with the assurances necessary to permit "a new generation" of cough and cold remedies which will provide more effective relief without compromising safety.

Issuance of the panel's report concludes its three-year review of the ingredients used in 35,000 to 50,000 products sold without prescription for the treatment of the common cold and allergies. According to the report, the major issue confronted during the review concerned the use of several ingredients in a single product. About 90 percent of the products studied contain such a combination of ingredients. The panel's report recommended that any ingredient contained in an OTC combination product also be available as a single ingredient so that consumers may easily select a single ingredient for a specific symptom. It also recommended that no combination product contain more than three ingredients. Of the 120 claimed active ingredients reviewed by the panel, 44 were classified as safe and effective and 15 were classified as unsafe and/or ineffective. More study to determine safety and effectiveness was recommended for the remaining 60 ingredients.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,703

Evolving Approaches to the Regulation of Prescription Drugs

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THE DICTIONARY defines "evolution" as a process of change, generally in a certain direction. In my opinion, the regulation of prescription drugs today is in a state of sharp and rapid evolution —evolving from the trial-and-error period of the last 15 years, I believe, to a more scientifically sound basis for regulation. This basis, on the one hand, will insure the more rapid development of new drugs based upon realistic and competent scientific criteria, and, on the other hand, will assure the public that all prescription drugs are in fact safe and effective and accurately promoted and, that when problems occur, as inevitably they will, the government and the regulated industry can and will respond quickly to achieve a satisfactory solution. But this positive evolution will have its price and, for the industry, that price may be high. To understand this evolution, it is necessary to describe, at least briefly, the process of change that has already taken place.

About 15 years have slipped by since the passage of the 1962 Drug Amendments. Prior to that time, the development, labeling and advertising of prescription drugs were largely in the hands of the pharmaceutical industry with the Food and Drug Administration (FDA) playing a relatively passive role as a regulatory agency. Before 1962, the FDA had virtually no control over the advertising of prescription drugs, no premarket clearance authority over the efficacy of such drugs, no authority to prescribe, in detail, the methods of manufacturing prescription drugs (or any other products).

The Agency did not even have the authority to determine what drugs were made by whom or where.

The testing of prescription drugs for efficacy was left to the sole and, generally, unfettered discretion of the companies marketing them and, at the same time, the science of clinical studies was not nearly so advanced as it is today. Double-blind studies, and certainly triple-blind studies with crossovers of patient populations, were something done infrequently. Their large-scale use was unheard of, both within the industry and at the FDA. Prior to 1962, testing for new drug applications (NDAs) was confined largely to determining safety. The data submitted to the FDA for NDAs were often brief but, generally without too much difficulty, the FDA gave approval in a routine fashion.

The 1962 Amendments changed all of this—literally overnight—when, on October 10, 1962, President Kennedy signed the law. At this moment, the FDA immediately took on the responsibility to regulate the advertising of prescription drugs, to demand the submission of substantial evidence of efficacy before new prescription drugs could be brought to the market and, in fact, as we later learned, to demand that same quantity and quality of evidence for prescription drugs then on the market. At the same time, the Agency was given new and extensive authority to determine the good manufacturing practices for prescription drugs, and to impose those requirements, by law, upon the pharmaceutical industry. It would understate the case to observe that this sudden influx of authority to the FDA resulted in a good deal of confusion, acrimony and uncertainty.

Clinical and Pre-Clinical Testing

Over the next decade, both sides—the FDA and the industry—groped to determine how to implement all these new laws; to determine, for instance, what kind of clinical and pre-clinical testing would be necessary under the substantial evidence law to justify the marketing of prescription drugs—both those going onto the market and those already there. Mistakes were made—concededly by both sides. The FDA especially had its problems for, during this period, it was understaffed, both quantitatively and qualitatively and, from what we read lately, morale was so low that many employees at the Agency simply were not functioning. Inevitably there was much bitterness and misunderstanding between the Agency and those who had dealings with it. Anyone who attended meetings with FDA representatives during those years can recall very well the frustrations that occurred.

Such meetings were often a total waste of time since either or both sides were totally unprepared for what was to be discussed, or each was prepared to discuss a subject other than that which actually was discussed. In an understandable abundance of caution, FDA employees, especially since they had so little guidance, asked for more and more clinical and pre-clinical testing of more and more complexity. In addition, they required the submission of literally mountains of animal data of questionable value to any realistic determination of the safety and efficacy of drugs and then asked for further data to answer academic questions raised by the first set of data submitted.

Naturally, this atmosphere of confusion and contentiousness lent itself to extensive litigation. By rough count, there are between 55 and 60 written opinions in lawsuits brought by the pharmaceutical industry against the FDA since 1962. This does not even include actions brought, in traditional fashion, by the FDA. That figure—50—60 opinions—is all the more astonishing when one appreciates that in the twenty-odd years prior to the passage of the 1962 Act, the pharmaceutical industry had never sued the FDA. The few such suits on file by any companies had been brought by food manufacturers.

Prior Evolutionary Process

In very brief summary, that's the evolutionary period through which we have just passed. It is an interesting story and deserves more extensive treatment. It would be very easy to conclude from this brief description that nothing good can come of this evolutionary process, that the FDA and the pharmaceutical industry cannot function together and do the job demanded of them by the 1962 law and that, therefore, perhaps out of despair rather than any other reason, the Congress and public should consider drastically revising the drug law. I don't feel that way.

As you will see when I discuss what I suspect will be the process of evolution in the next few years, the prior evolutionary process has not been totally negative. In fact, it has taught us a great deal. In spite of all the acrimony and litigation (or perhaps because of it), we learned a great deal. Just as a preliminary matter we learned that the FDA has to be funded adequately for if it is not it cannot function properly—and we know that is not in our interests. But also we learned other things and on that basis the evolution will proceed. What we learned is that any evolutionary change in the regulation of the

pharmaceutical industry will carry with it new legal questions that right now are totally unanticipated.

To begin with, I think all of us, both within the FDA and within the industry, are beginning to agree that, while premarket studies, both clinical and pre-clinical, tell us a great deal about the safety and efficacy of drugs, we never truly know how safe or how effective a drug is until it is in wide use in the population. Statistical analyses of premarket investigations are important but never are the whole answer. Because of this, I believe that we soon shall see a very rapid development of Phase IV investigations or surveillance procedures to evaluate—post-clearance—how safe and effective our drugs really are. Legislation to this effect already has been drafted in both houses of Congress. However, I do not think that the FDA will wait for legislation. On the contrary, I think we soon shall see, probably on a narrow-product basis at the beginning, the development of post-market surveillance systems, including, in some cases, the concept of a monitored release of drugs for marketing, perhaps along the line of the British system. That system permits the United Kingdom Committee on the Safety of Medicine to restrict the use of some post-clearance drugs, designed for particularly severe diseases, to physicians with the facilities to treat and to monitor patients with those diseases.

British System

Under the British system, a drug once cleared for marketing nevertheless can be restricted to a monitored release system by which a clinician is permitted to use the drug only if he or she has the facilities to use it safely and effectively and only if he or she agrees to and does report to the relevant government agency his or her experience with the drug for a limited time period—usually one year. This system is designed to permit the United Kingdom Committee to make a more informed decision about the safety (and presumably efficacy) of a drug than was possible at the time it was initially approved for marketing. While I have reservations about the wholesale adoption of such a system, I have no doubt that something like it will become the rule rather than the exception here. Such a change obviously will have a direct impact on the pharmaceutical industry, for it will surely slow down the initial introduction of new drugs and also add to the cost of those drugs. Furthermore, monitoring such Phase IV investigations will be complex and burdensome, especially to the smaller manufacturers. It also will carry with it complex legal problems of informed patient consent and product liability responsibility.

If, for example, a drug initially is limited to use only in certain types of medical facilities, what is the legal duty of a company to insure that no one uses the drug otherwise? Will all advertising and labeling have to state that the drug is still under investigation? If so, do we become guarantors of the drug to each patient who uses it? Furthermore, will this Phase IV system legally require us to follow up on patients long after they have stopped taking the drug? These are just a few of the questions. In the long run, however, a Phase IV system should be beneficial both to the industry and to the public.

Animal Testing

Secondly, in looking at this evolution, I think we shall see an improvement in types of studies, particularly pre-clinical studies, that will be required by the FDA in the development of new prescription drugs and in the justification for the continued marketing of the existing drugs. Recently, at a conference on the question of drug development and marketing, Dr. J. Richard Crout, Director of the Bureau of Drugs, posed three questions, the first one of which was: "How much attention should we pay to animal toxicity, especially that which is untestable in man except by the test of the marketplace?"[1] He pointed out, as an example, that the scientific community does not have a universal solution to the problem of a drug that is carcinogenic in animals and yet may be of such health benefit to man. The question being asked more and more is: "What is the true value of routine animal testing which, on the one hand, delays any final resolution of the question of the drug's safety and efficacy while, on the other hand, provides little or no scientific data useful to the decision maker?" I think better judgments are being made every day on the value of animal studies which, until recently, routinely had been demanded by the FDA.

I do not mean to suggest that animal testing is going to be a thing of the past—far from it. A lot of work will continue to be done and some of it will be extraordinarily complex. But I do believe that there has been significant recognition that a lot of the animal work done over the past 15 years, while it has developed literally mountains of paper, probably answered few of the questions posed. As this thinking becomes settled, the time lag in developing new drugs may shorten.

Thirdly, I think there has been a great deal of improvement, in the evolutionary process over the last 15 years, as to our understanding of what constitutes a well-controlled clinical study. For many years,

[1] Helms, *Drug Development and Marketing*, 197 (1975).

this was an area of often heated debate between industry and Agency representatives. Lawsuits were even filed about such scientific questions. The industry, for several years, has worked with the FDA to develop test protocols for classes of drugs that will provide a degree of certainty to planning new products. Whether we like the answers we got, we at least now have them and can plan our product development accordingly. I do not think we lost all the battles. Clinical studies, while they are still difficult and time-consuming, are not nearly the disaster to which we appeared to be heading in the mid-1960's. Both sides learned a great deal over the years—certainly we learned that obstinacy is never an alternative to negotiation. The Supreme Court told us that.

Proprietary Information

These evolutionary changes that I have noted would seem to indicate that the sun has risen on a cloudless day and that all our problems are solved. Far from it. The evolution contains some serious problems for us as well. Perhaps the most serious to which we seem to be evolving is the question of the proprietary value of investigational new drugs (INDs) and NDAs and the scientific material contained in them. Since 1938, the pharmaceutical industry has regarded as valuable proprietary information the scientific data submitted to the FDA in support of NDAs. This became even more so with the passage of the 1962 Act when data to support efficacy claims were also required. Lately, however, over and over again in speeches and comments, FDA officials and consumer groups charge that this is improper and that to regard such data as proprietary information stifles innovation and competition and unfairly denies, to the consumer and to the medical profession, the right to evaluate the scientific basis by which the Agency approves new drugs. At that same drug development and marketing conference that I mentioned earlier, Dr. Crout posed another question, one which he described as very important. He asked: "To what extent are the data derived from a clinical trial to be considered the proprietary property of a drug firm rather than a societal asset?"[2] He went on to argue that the drug industry cannot simultaneously say that data submitted to the FDA are proprietary information which cannot be viewed in public and also complain about Agency decisions made in private. He further argued that keeping proprietary data out of the public view keeps the regulatory approval process at the FDA out of the open environment in which scientific decisions usually are made. Obviously, there is a present and strong

[2] *Ibid.*

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concern that the ground rules, developed over the last 40 years, which have granted valuable proprietary rights to the holders of NDAs should be changed—changed in the direction of taking away those rights. This concern is a direct outgrowth of the evolutionary process of the last 15 years for, as a result of that process, NDAs are both more expensive and valuable and the public is more aware of what governmental regulation of drugs means to them.

I think that, in the continuing process of regulating evolution, this is a very serious question that we are going to face. If we believe that INDs and NDAs are a valuable proprietary right of the company that files them, then we must make our position understood by those in Congress who can change the rules, as well as those at the FDA who may well attempt to change the rules without legislative authority. If we are not successful in this effort, then, in the next few years, we may see more piggyback NDAs riding on the primary work of a company which has expended major sums of money in the development of a new product. These piggyback NDAs, filed and approved at a fraction of the cost of the original submission, will have a clear impact on the profitability inherent in the introduction of new drugs. This evolutionary approach to the regulation of prescription drugs—the opening of NDAs and INDs to public (and competitor) access—could have the greatest impact of all the changes which I see on the horizon for prescription drugs.

New Legal Problems

There are other changes bearing new legal problems, however, which can be easily predicted if you read the Congressional testimony of FDA officials and if you read the daily paper and trade press in discussing the problems of other pharmaceutical companies. For instance, while there may be some decrease in the pre-clinical studies required for the development and justification of prescription drugs, I think that we shall see a much closer surveillance of the manner in which these tests are conducted. We shall see more and more FDA investigations of the quality and the reliability of these studies, either with or without the help of new legislative authority from Congress. Such increased surveillance of pre-clinical studies obviously will have a direct impact on the rapidity with which new drugs are brought to the market and, in fact, could well jeopardize the continued marketability of new products now holding approved NDAs.

Since probably virtually every drug company uses outside laboratories for some of its testing, it is important to recognize some of

the legal issues raised by the FDA's increased surveillance of such laboratories. The jurisdiction of the FDA is limited to the shipment in interstate commerce of drugs. The law prohibits certain acts when they are done either prior to, during or after a shipment in interstate commerce. The most important prohibition, for our purposes, is the one that prohibits the introduction, or delivery for introduction, into interstate commerce of any drug in violation of the new drug statute. A laboratory which is testing a drug, either in animals or in humans, generally receives the drug labeled "for investigational use" as required by the regulation, and ships it in that fashion. Thus, such shipments literally comply with the statute. If the record keeping for those studies is inadequate or if the FDA is of the opinion that the studies somehow were done improperly or incorrectly, what section of the Federal Food, Drug and Cosmetic Act is violated and, in any event, by what statutory authority can the FDA investigate the matter? These questions are now unanswered. Concerning inspection authority, the statute says, in regard to prescription drugs, that the FDA can inspect any factory, warehouse or "consulting laboratory" in which those products are held to inspect the records to determine whether the drugs are adulterated or misbranded or otherwise prohibited from shipment in interstate commerce. What is a "consulting laboratory" and what act of misbranding or adulteration occurs when a laboratory maintains inadequate records? It is difficult to find a section of the law that fits the problem.

Contract Laboratories

A clinical or pre-clinical laboratory plainly does not stand on the same legal footing as a company that files an IND incorporating data from that laboratory. As representatives of manufacturing companies, you should be aware of this, especially since many of your contract laboratories, as FDA surveillance of their work increases, will be seeking guidance from you on the questions of the scope of the Agency's rights to inspect and of their legal responsibility to you and to the FDA.

Another area of increased surveillance (and work which already is under way) is the problem of bioequivalency and quality assurance of generics versus trade name drugs. This has had a direct impact on the government's attempts to lower the price of drugs in the Medicare and Medicaid programs. It will also have a direct impact on the development of piggyback NDAs.

Finally, according to the testimony of Dr. Crout, there also will be increased attention to the practices of the pharmaceutical industry in financing educational projects for the medical profession. Dr. Crout has voiced his suspicion that such financial assistance by the pharmaceutical industry carries with it a built-in bias in favor of drugs and that, accordingly, such practices should be evaluated carefully to make sure that, under no circumstances, do they slide over into the area of drug advertising. If they do, such practices will have to meet the requirements of the prescription drug advertising regulations. New regulations to cover this problem have been promised. This type of increased surveillance should not have too great an impact upon the industry but, if it is carried on with too heavy a bureaucratic hand, it could well cause a further deterioration in the necessary relationship between the pharmaceutical industry and the medical profession, a deterioration which manifestly would not be to the benefit of anyone, either the public or the industry.

Old Drug Monographs

I should like to close with one often-mentioned item of the evolutionary process which is especially critical. This is the development of old drug monographs for prescription drugs. For several years, FDA officials have announced that the Agency is working on the development of a monograph system for prescription drugs along the lines of the over-the-counter (OTC) drug monograph regulations. These monographs would dictate what prescription drugs could be sold and brought to the market without NDAs, what products would require NDAs, and under what circumstances. The monographs also would set forth, in a standard format, the claims and advertising that could be done for prescription drugs and, in general, would standardize the development, manufacture and marketing of prescription drugs.

This would clearly be a very long-range project and it has not yet been proposed officially. Given the complexities of the issues and our experience with the methodology in the OTC area as well as the unique legal problems associated with NDAs, the process for going through all the products now on the market and writing monographs for each class of products surely would be as long or longer than that which has already taken place, and will be needed, for the OTCs. Thus, I do not see this idea having a final impact upon the pharmaceutical industry for several years. I might observe also that FDA officials speak less today than they have in the past about this proposal. I do not know whether this means it has been shelved

temporarily by the press of other business or that a tacit decision has been reached to drop the matter. At any rate, the prescription drug monograph proposal is not something on the immediate scene for the pharmaceutical industry. But when it does come to pass, its impact will be far greater than all of the other changes put together.

Depending on how the proposal is implemented (if it is), the value of NDAs obtained to date could be impaired. I suspect it could stifle the introduction of new products. In any event, even if those contingencies were avoided, the monograph proposal would still be a massive effort requiring many man-hours, both within the industry and within the FDA, man-hours which perhaps could more profitably be devoted to the introduction, and approval for introduction, of genuinely new products. It is the sort of bureaucratic exercise that has the superficial appearance of tidying things up, of putting in regulatory order, all the various classes of prescription drugs. But it may be a form of tidiness which we cannot afford. In any event, I hope that before we launch too far into such an enterprise we, and the FDA, will carefully assess the benefit-to-risk ratio for this proposal.

[The End]

HEALTH RISK OF CONTINUED SACCHARIN USE CITED IN GAO REPORT

The use of the artificial sweetener saccharin while studies of its cancer-causing potential are being resolved may pose an unnecessary risk to the public, according to a report prepared by the General Accounting Office (GAO). The Food and Drug Administration (FDA) now permits use of the additive pending the completion of a six-year safety study in mid-1978. Noting that this appears contrary to the FDA's intent of permitting the use of food additives which are undergoing such tests for a "limited period of time," the GAO suggested that the Secretary of Health, Education, and Welfare direct the FDA to re-evaluate its justification of saccharin use while testing continues. The report further suggested that the FDA should consider the need to provide a higher margin of safety and to reduce the permissible levels of the impurity *O*-tolunesulfanamide (OTS) in saccharin to the lowest level achievable under present manufacturing technology.

In response to the report, the FDA noted that it is awaiting the completion of Canadian government studies early next year before changing the status of saccharin. The Agency also indicated that it will soon amend its food additive regulations to ensure that OTS will not appear in saccharin in other than trace amounts.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,706

New Regulatory Concepts in Rx Labeling for Patients

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DRUGS—IN THEORY, AT LEAST—traditionally have been marketed by two different and distinct methods. Over-the-counter (OTC) drugs are offered directly to the consumer for use in self-medication. The safety and effectiveness of such OTC drugs depend entirely upon their labeling. The user is given full directions and information as to the conditions for which the drug is offered, when and how to use it, how much to take and warnings against overuse and misuse. The choice to use or not to use the drug thus rests entirely with the consumer. On the other hand, there exists for the consumer a great deal of mystique about prescription drugs. The patient has no choice but to take what his physician prescribes for him, often not knowing for what condition he is taking the drug or even what the drug is. The pharmacist hands him a bottle with a label that tells him little, other than how many doses a day he should take. As a rule, he is generally uninformed about his prescription drugs.

The labeling of prescription drugs—and the exemption for directions for use on the patient label—are based upon the assumption that "Doctor knows best." That assumption, however, has been the subject of serious question in recent years. It makes sense that patients should have the right to more information about the prescription drugs they take, provided that such information will lead to improved therapy. The problem then centers principally about how much information should be given and how can it best be disseminated.

The idea of patient package inserts is not a novel one. For years, many practitioners have voluntarily and routinely used written instruction sheets to supplement their oral instructions in order to in-

form their patients more fully about the nature of their illnesses and the use of their medications, possible side effects, drug interaction, diet restrictions, etc. Of course, the best-known use of patient brochures has been in connection with various types of contraceptives. Patient brochures have been officially required to accompany oral contraceptives since 1970. In 1973, patient information was required for injectible contraceptives and for diethylstilbestrol (DES), when used as a post-coital "morning after" emergency contraceptive. Intrauterine devices, estrogens and hearing aids also have been identified as likely candidates for required patient information. Indeed, a Food and Drug Administration (FDA) proposal for a hearing aid brochure was published for comment in the *Federal Register* of April 21, 1976. It also should be noted that the FDA some time ago established a Patient Prescription Drug Labeling Project which has been investigating the desirability of patient package inserts. The FDA also has conducted a survey of users of oral contraceptives to determine the effect and usefulness of the patient brochures for those drugs, and it is now sponsoring a study in several West Coast clinics which is testing experimental package inserts with patients of different educational levels. In appraising these results, we should bear in mind that oral contraceptives are taken by well people on an entirely voluntary basis and thus provide little help in evaluating the present proposal.

Proposed Federal Legislation

So, while not new, patient package inserts have attracted much recent attention as a result of a petition filed in March of 1975 with the FDA requesting it to expand its written patient information requirements beyond contraceptive drugs and as a result of proposed federal legislation introduced in both the House and the Senate. The bills (H. R. 11617, the Rogers Drug Safety Bill, and S. 2697, sponsored by Senator Kennedy) would require that patient package inserts accompany virtually every prescription drug that is dispensed or sold. The FDA petition was filed by the Center for Law and Social Policy on behalf of a number of consumer groups (The Consumers Union of the United States, Inc., Consumer Action for Improved Food and Drugs, National Organization for Women, Women's Equity Action League, and Women's Legal Defense Fund). The petitioners requested the Agency to require that written warning information be included both on the labels and in patient package inserts to accompany certain prescription drugs thought by the petitioners most likely to cause adverse side effects or interactions with other drugs or for

which verbal instructions might not be adequate. Such drugs, according to the petitioners, include those that pose dangers to pregnant or breast-feeding women, drugs such as hypnotics and tranquilizers that are used widely and can pose serious dangers, and drugs such as amphetamines and chloramphenicol that the petitioners claim have been overprescribed in the past and can have serious side effects.

Patient Warning System

In requesting that written information be provided to the users of prescription drugs, the petitioners state: "Our patient warning system for prescription medication has simply not kept pace with new patterns of drug use. . . ." They further assert that the traditional oral communication between the physician and the patient is no longer sufficient by itself to protect the patient from the potential dangers of prescribed drugs. They contend that this has resulted, to a large extent, from the modern-day fragmented, impersonal medical care, the critical doctor shortage, patient apprehension and an increase in long-term, multiple drug therapy situations. According to the petition:

> "If the doctor fails to outline the precautions to be observed with the use of the prescribed drug, the written warnings would inform the patient of important side effects and interactions with other drugs. A patient who did not understand oral instructions might understand written instructions after he has returned to his more comfortable home surroundings. Written directions would provide a reminder to the patient who might forget oral instructions."

The first thing we must ask ourselves is whether present law authorizes the FDA to require patient package inserts on all or on some prescription drugs. No one has questioned this seriously, although it was considered a rather radical concept in 1970 when Commissioner Edwards proposed such inserts for oral contraceptives. The FDA based its authority on the vague concept of the "public interest." Obviously, the Agency may require that the information be made available to the physician as part of the labeling. The Agency then concludes that the physician can only use the drug safely and effectively by passing such written information along to the patient.

Section 502(f) of the Act requires that the labeling of drugs include adequate directions for use and adequate directions against misuse. Prescription drugs, however, are specifically exempted from this requirement by Section 503(b)(2). Thus, there would appear to be serious question about the FDA's authority to mandate patient

package inserts for such drugs. The Agency, however, has not acknowledged this possible legal deterrent.

Legal Authority

The FDA, assuming it had the legal authority to require patient package inserts, solicited comments on this consumer petition and held meetings with various professional, trade and consumer groups interested in or affected by such a patient information program. The House and Senate, for their parts, have been holding hearings on their respective drug bills for some time now. With all this activity in both the FDA and Congress, and in light of the far-reaching implications of a broad-scale patient information program, it is not surprising that there has been considerable discussion and disagreement among the several interested groups. Despite the variety of opinions, however, there appears to be a consensus that the implementation of a patient brochure program presents a number of problems. Among these, are the following problems.

Number of Problems

(1) Should the patient package inserts be mandated for *every prescription drug* or for only a few? If only for some drugs, what should the selection criteria be?

(2) *What kind* of information should the brochure contain? Should it include an extensive description of all of the possible side effects, adverse reactions, drug interactions, indications, contraindications, dosage information, etc., such as that now supplied in the usual physician package insert?

(3) *How* should information on sometimes highly technical subjects be communicated to a patient population characterized by varying levels of education and increasing illiteracy and which includes an increasing number of non-English speaking individuals?

(4) *Who* should be responsible for the distribution of this material: the manufacturer; the physician; the pharmacist; or some combination of them? And should the distribution be mandatory or discretionary?

(5) Will the requirement that patient information be given expose physicians to greater malpractice liability or pharmacists to greater legal liability, if they fail to give the brochure, or give the wrong or an out-of-date brochure? Would a patient brochure program increase the already expanded product liability exposure of the drug manufacturer?

(6) How would patient brochures be efficiently updated to accommodate new information about the drug? Would something like the "Dear Doctor" letters be feasible?

(7) How will patient package inserts affect the patient's drug-taking behavior? Will the brochure information cause the patient to adhere more strictly to the prescribed treatment program, or will the information intimidate the patient and lead to even greater "drug defaulting"?

These are all practical problems, but they must be answered before the industry can espouse or reject this new requirement. The FDA, for the most part, in its testimony on the Rogers Bill, seems to minimize these factors in its enthusiastic support of the basic concept.

The advocates of patient package inserts justify the proposal, pointing out many supposed potential advantages, which include the following listing.

Potential Advantages

(1) *Increased patient knowledge of, and ability to cope with, side effects and to detect and report adverse reactions.*—This, of course, is the most often-cited function and potential advantage of patient package inserts. By providing written information concerning the drug's possible side effects and adverse reactions, it is hoped that the patient will: (a) be better able to tolerate the customary and uncomfortable but harmless side effects; and (b) be better able to detect possible dangerous adverse reactions and be aware of the need to contact the physician, if symptoms of those reactions develop. However, if full information is given, as appears in the present package inserts, many patients may be too apprehensive to take the drug.

(2) *Improved patient compliance with the full course of therapy.*—Written patient information in addition to the physician's oral instructions also could increase the patient's awareness of the benefits of taking the drug according to the prescribed regimen, even if some unpleasant side effects occur and even if the disease symptoms are alleviated. Increased compliance with the *full* course of the drug therapy, of course, would increase the cure rate and decrease the rate of disease re-occurrence. On the other hand, full information may tend to decrease compliance in many patients.

(3) *Increased patient knowledge of the correct administration of the drug.*—The patient would be more likely to take the drug properly if he were provided with written information explaining exactly how

and when to take the drug, for example, "with meals," "before retiring," or "every four hours, but no more than three a day." Present, but often vague, label information to "take as directed" sometimes often is of little or no help to the confused or forgetful patient. The concept seems to have merit in this respect.

(4) *Improved patient knowledge and awareness of drug, food or alcohol interactions.*—Another purported advantage of patient brochures is their usefulness in alerting the patient to dangerous drug interactions in the case of multiple drug therapy. If the patient is taking several drugs simultaneously, of which some the prescribing physician might not be aware, the patient package insert could inform the patient of the need to avoid certain dangerous drug-to-drug interactions, including interaction with OTC drugs. The brochures could help accomplish this by identifying the drug by its generic and brand name, and by physically identifying it by its color or the shape of the tablet. Such identification could also help minimize the chances of patient mix-up of prescription drugs, in addition to facilitating the avoidance of drug interactions. Patient package inserts also could call attention to the fact that the ingestion of certain foods might inhibit or magnify the drug's effects. In addition, they could more fully inform the patient about the dangers of alcohol ingestion while on certain medication. If presented simply and understandably, this could be a real advantage.

(5) *Improved patient knowledge of warnings.*—Additionally, written patient information could increase the patient's recognition of drug warnings, for example, that it is dangerous to take certain drugs while operating machinery, driving a car, etc. Also, it could advise patients of those side effects that should be of no concern and those that should occasion a cessation of the drug therapy or should be called immediately to the physician's attention.

Possible Disadvantages

Although these advantages sound impressive, a number of groups have pointed out various possible disadvantages of patient package inserts. These *disadvantages* might include the following.

(1) *Patient alarm, confusion and misunderstanding.*—Perhaps the principal potential disadvantage of patient brochures is that the listing of the particular drug's various side effects, adverse reactions and warnings, if not placed in the proper perspective, could unduly frighten the patient, perhaps to the point of causing him to reject

the needed drug therapy or to develop the mentioned side effects on a psychosomatic basis. As Dr. James H. Sammons, Executive Vice President of the Americal Medical Association stated: "I think the real danger is that fright engendered by the insert may possibly outweigh the potential good." With a population of varying degrees of education and literacy, it could be difficult—perhaps impossible—to present in understandable lay language a discussion of the drug's benefits and risks, without giving a distorted view and without causing confusion. A little knowledge, in other words, may be a dangerous thing.

(2) *Patient self-medication.*—The converse of that situation would be the possibility that the information garnered from patient brochures might encourage some patients to "prescribe" unused drugs for themselves or others and so bypass a physician's treatment. Many patients now transfer their unused prescription drugs to third persons who do not receive any qualified information regarding such drugs. If instead of mitigating the deleterious effects of such self-medication, patient package inserts were to result in even more such activity, their purpose would be defeated.

(3) *Interference with existing professional relationships.*—Another potential disadvantage of patient brochures is that they could adversely impose upon the physician-patient relationship. This would be particularly true if such brochures are designed to be standardized or mandatory or if distribution is to be by someone other than the physician. Such a system would bypass the physician's right to decide what is best for the patient. And, the patient might suffer if discretionary distributive authority is not lodged in the physician, especially in those instances where it is inappropriate to dispense the patient brochure either because of the peculiarities of the patient or his condition.

(4) *Increased drug cost and delay in new drug approvals* (NDAs). —Two other potential disadvantages of patient brochures are: (a) increased drug cost; and (b) a prolonged NDA process. The cost of development and distribution of patient brochures—ultimately reflected in an increase in the price of prescription drugs—and the probability that patient brochures, accompanying a drug, would prolong the NDA process, are potentially significant disadvantages.

As indicated, the consumer petition and the Congressional hearings have given a number of organizations with diverse interests an opportunity to make known their thinking on patient package inserts.

To the best of my knowledge, no one has flatly opposed the concept, although all of them have substantial reservations and, to a large extent, believe that the idea is somewhat premature. Concerns revolve about possible product liability, interference with the physician-patient relationship, identity of the distributor, drugs to be covered, etc. Among the important suggested inclusions would be the following concerns.

Suggested Inclusions

(1) *Scope and detail.*—It would seem to be impractical and inappropriate to require that each insert include information on all possible side effects, adverse reactions, indications, dosage instructions, etc., as now appears in the usual physician package inserts. It has been suggested that the information be limited to:

(a) the generic and brand name of the drug;

(b) a physical identification of the drug to avoid mix-up;

(c) a statement of the benefits to be achieved from the drug and the reason why it has been prescribed;

(d) possible side effects and adverse reactions, designating which are trivial and which should occasion the patient's contacting his physician;

(e) possible interactions from drugs, foods or alcohol;

(f) instructions as to when and how to take the drug;

(g) storage directions; and

(h) precautionary information (for example, operation of automobiles and machinery).

(2) *Format and style.*—There is a real question whether meaningful information can be given in a manner that would be understandable to the average American citizen, particularly those of limited education and language fluency. It has been suggested that the brochures could appear in more than one language but would have to be directed to a relatively low educational level. The brochures that are being tested by the FDA on the West Coast have achieved simplicity, but, in doing so, have been unable to relate much worthwhile information.

(3) *Distribution.*—This has created a substantial difference of opinion among the interested groups. There are those who believe that the pharmacist should be responsible and others who feel strongly that only the physician should take on this responsibility. The latter would seem to be preferable, since most groups are of the

opinion that the physician should have the right to make or withhold distribution, depending upon his appraisal of the individual patient. Although the manufacturer will probably have to prepare the brochures, it is hardly in a position to control the distribution.

(4) *The drugs to be covered.*—Unless patient product inserts are required for all drugs, as has been proposed in the pending legislation, a real problem exists concerning the selection of the drugs to be covered. A number of criteria have been proposed and the consensus seems to be that priority should be given to:

(a) those drugs with serious side effects;

(b) those drugs subject to patient control and participation in the benefit-to-risk decision;

(c) those drugs for chronic use; and

(d) those drugs which are prescribed most frequently.

In light of the numerous and complex problems involved in this proposal, it would seem best to proceed slowly. This is not to say that there is no need to improve the methods of communicating to the patient important information about the drugs he takes. We must first determine, however, how much and what kind of information the patient needs and whether patient brochures are the best method of getting it to him. I believe the American Society of Internal Medicine has put it well. It recommends that patient insert information be included in a class of drugs only when it has proven in *clinical trials* that it "increases patient compliance, decreases the incidence of side effects, decreases the incidence of drug interactions or else results in improved patient health."

In conclusion, although patient brochures are not a new idea nor an idea which should be summarily dismissed, they would appear to me to be an idea whose time is yet to come. **[The End]**

ACTION CONTEMPLATED ON 84 COLOR ADDITIVES

A review of all color additives that have been provisionally listed for use since 1960 has been completed by the Food and Drug Administration's (FDA's) Bureau of Foods and, as a result, the FDA is considering terminating the provisional listing of 12 color additives, placing 20 others on the permanently approved list, and specifying additional industry tests and information required for decisions on the remaining 52 additives. Of these 52 colors, only 3 are listed for use in foods. The news was reported in an August 27 *FDA Talk Paper.*

Among the color additives which may be terminated are FD&C Red No. 4 and carbon black. Red No. 4 has been implicated in urinary bladder polyps and atrophy of the adrenals in dogs. The FDA is considering terminating the additive for use in maraschino cherries and ingested drugs, but, because of the apparent safety of external use, the Agency is considering permanently listing it for use in externally-applied drugs and cosmetics. Carbon black lacks adequate chemical specifications and an adequate method for detecting low levels of extractable polynuclear aromatics, some of which are known carcinogens. The additive is used in candies, such as jelly beans and licorice, and drugs and cosmetics. The remaining ten colors being considered for termination are provisionally listed for cosmetic use only; petitions for these these colors have been withdrawn by industry.

The FDA was expected to publish by September 30 its policy on the provisional list, termination of the provisional listing of the 12 colors, and the data required for the remaining additives. The permanent listing of 20 additives will be published by the end of the year.

CCH Food Drug Cosmetic Law Journal, ¶ 41,702

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