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THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis, contributions and comments are invited.

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TO THE READER

Twentieth Annual Meeting of The Section on Food, Drug & Cosmetic Law of The New York State Bar Association.—Several of the papers presented at this meeting appeared in the April issue. Contained in this issue are two other articles from this meeting. In the first article, *Sherwood E. Silliman,* a member of the New York and Florida Bars, discusses some problems of multiple product liability litigation in the drug industry. He concludes that the drug company and its general counsel must give maximum aid to each local counsel retained to defend its cases.

Austin S. Phillips, an attorney with American Cyanamid Company, is concerned with the threatened erosion of patent systems and its effects on the food and drug industries. Without the possibility of the limited protection of patents, he fears that research and production will deteriorate.

Investigational Drugs: Experimentation or Medical Practice.—In this article beginning on page 256, *Walter W. Beachboard,* Secretary and General Counsel of Smith Kline & French Laboratories in Philadelphia, emphasizes the difference between investigational drugs and experimental drugs, suggesting that lack of clear definitions has led to confusion of the two terms. In fact, he asserts that there is no qualitative difference between a standard drug and an investigational drug, while the difference between standard drugs and experimental drugs is great.

Investigational New Drugs and the Army.—This is the topic of a paper by *Maurice Levin,* a retired colonel in the U. S. Army. He explains that Department of Defense *Instructions* and Army *Regulations* provide exceptional procedure in the clinical investigation of new drugs, but not with regard to new drug applications.

Food Law in the Europe of Tomorrow.—*Dr. Paul M. Karl,* a lawyer from Hamburg, Germany, reports on this international symposium in his article beginning on page 284. The symposium held in Brussels in November, 1964, emphasized the need for harmonization of European food laws, especially with the gradual integration of the all-European economy.

FDA Planning for Regulation of Prescription Drug Advertising.—*Dr. Joseph F. Sadusk, Jr., M.D.,* Medical Director of the FDA, presented a paper on this topic at the Pharmaceutical Advertising Club Meeting in February in New York City. His statements, beginning on page 299, explain that the primary mission of the FDA is to obtain truthful, exact, and balanced descriptions of the nature, quality and properties of the drugs advertised.

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Some Problems of Multiple Product Liability Litigation in the Drug Industry

By SHERWOOD E. SILLIMAN

Mr. Silliman Is a Member of the New York and Florida Bars. This Article and the Succeeding One by Mr. Phillips Were Presented at The Twentieth Annual Meeting of The Section on Food, Drug & Cosmetic Law of The New York State Bar Association. Other Papers Delivered at This Meeting Appeared in the April Issue.

LET US ASSUME THAT THE X DRUG COMPANY voluntarily withdrew from sale a drug that had been widely sold on prescription for over a year because of accumulating reports of side effects and other reasons. Following this, the company was sued in state and federal courts in numerous jurisdictions. Under these circumstances, what are some of the problems the defendant faces in such multiple litigation?

Early in the litigation it may happen that a group of the plaintiffs' attorneys, who are members of the National Association of Trial Lawyers (formerly National Association of Claimants Counsel of America), will band together to pool their knowledge, finance and exchange depositions, interrogatories, documents and settlement figures, all of which will be helpful in preparing the plaintiffs' cases for trial. Meetings of this plaintiffs' group will be held from time to time to exchange information and strategy. To meet this situation, it is suggested that the defendant select a single firm of lawyers to

deal with the plaintiffs' group on the subject of depositions of its officers, third party witnesses, production of documents and other related matters.

A series of meetings of groups of local counsels, with the defendants' general counsel and his staff to aid local counsel in the preparation of the defense and to familiarize them with the various facets of the drug business as they bear on the defense of the action, will be found most helpful. At these conferences ideas can be exchanged and strategy developed to aid in the preparation of the defense to the cases. Out of these meetings, local counsel and general counsel and his staff will become acquainted. Thereafter, there will be a freer flow of information between local attorneys selected by the insurance company and the defendant corporation.

As the cases approach trial, other problems will arise, such as an attempt by plaintiff's counsel where there are several cases pending in the same court to have them consolidated for trial under Rule 42 of the Federal Rules of Civil Procedure or related state statutes. Rule 42 reads:

> (a) Consolidation. When actions involving a common question of law or fact are pending before the court, it may order a joint hearing or trial of any or all of the matters in issue in the actions; it may order all the actions consolidated; and it may make such orders concerning proceedings therein as may tend to avoid unnecessary costs or delay.

This rule is rather favored by the federal judiciary who strive to keep up-to-date trial dockets. However, its application can be prejudicial to the defendant in multiple drug litigation. Say the court consolidates four actions for trial before the same judge and jury. True, each of the plaintiffs allegedly took the same drug but here the common question of fact ceases. Each of the plaintiffs' medical histories before each took the drug differs. One plaintiff may have been markedly aided by the drug and another not. The alleged ailments may be quite different and the intervals or periods during which each plaintiff took the drug will undoubtedly vary as well as the dose in some cases.

Because of the differing periods of time when the drug was taken, evidence may be relevant in one case but have little or nothing to do with any of the other plaintiffs in the consolidated cases. This situation cannot be corrected by proper instructions by the judge. *Witzke v. Doyle,* 3 Misc. 2nd 323, 146 N.Y.S. 2nd 515, 517 Supreme Court,

Appellate Term. This was a case where consolidation was refused under state law. In rendering the decision, the court said:

> Proper instructions by the trial court to the jury cannot be relied on as complete assurance of removal of such prejudice.

As a practicable matter, it is self-evident that consolidation will aid a weak case when combined with a strong case, whether it be on causation or liability. This alone should be sufficient grounds to refuse the consolidation. *U. S. v. Lustig,* 16 F.R.D. 378. This decision, refusing consolidation, was rendered by Knox, Chief Judge of the Southern District Court of New York. The judge, quoting *U. S. v. Knauer,* 149 Fed. 2d 519, 520 said:

> The court should not consolidate the trial, even where the court sits as a chancellor in cases where the issues affecting various defendants are certain to lead to confusion or prejudice to any one or all of the defendants.

Although there are no reported decisions to my knowledge in the federal courts dealing with consolidation of drug cases under Rule 42, a close analogy is *Michalek v. U. S. Gypsum Co.,* 1 F.R.D. 244 (W.D.N.Y. 1940). This was a case where the plaintiffs were employees of a mining company and were allegedly injured by harmful dust. Denying the consolidation, the court said:

> The motion papers show that although the work of all the plaintiffs was performed in the same mine that the location where each plaintiff was employed and the exposure to the source of the alleged harmful dust was different in each case. The extent of the injuries to each plaintiff is also different. Under the circumstances I think the plaintiffs' rights would be substantially prejudiced by a joint trial.

There is a precedent in the New York State courts. *Goldblatt v. Wm. S. Merrell Company, et al.* Supreme Court, New York County, reported *New York Law Journal,* January 8, 1964. Two actions were involved in this proceeding. The two complaints were almost identical in form. Plaintiffs in both actions moved on the pleadings to consolidate the two cases. The defendant Richardson-Merrell Inc., on the other hand, moved on the pleadings to sever the causes of action of each of the plaintiffs who were alleging injuries due to the ingestion of a drug manufactured and sold on prescription by the defendant. There were 17 plaintiffs, each asserting a cause of action as a user of the drug MER/29; the other four were husbands of the users. The court granted defendant's motion for severance saying:

> The defendant, by cross-motion seeks to sever "each separate claim asserted herein by individual plaintiffs, or plaintiffs suing as husband and wife, and requiring separate trials of each claim, upon the grounds that different questions of law and fact are presented in the various claims; the medical issues herein presented as to each injured individual are too complex and varied to be decided

before one jury; and that substantial justice can only be achieved by separate trials of such issues." The defendant concedes that the "actions all allege identical causes of action against defendant . . ." However, they seriously urge, amongst other things, that the factual issues pertaining to causation and ultimate liability in each cause of action will materially differ since the extent and manner of prescription will vary in each instance. Moreover, the medical history of each plaintiff, his family medical history, and other factors will also play an important part in this causation area, with varying results. Perforce, defendant points out, no one jury can possibly understand, absorb and weigh the divers medical pictures of liability and injuries that will be presented by these plaintiffs. I agree with this contention. . . . It appears that the only matter which is common to the plaintiffs is the fact that they allegedly consumed the drug in question. The uncommon and difficult question will be the causal relationship between the circumstances in the taking of the drug and the numerous and various injuries resulting therefrom. It is also to be noted that a consolidation or a joint trial would seriously prejudice the defendants if the same jury is called upon to resolve the issues, including damages (and punitive damages are sought). The conglomerate mass effect might easily excite the jury to the detriment of the defendant, let alone lessen a true appreciation and assimilation of each claim to be decided separately.

This case was appealed to the Appellate Division, First Department. The appeal was heard together with a separate motion for the assignment of one justice of the Supreme Court, New York County, to preside over, hear and determine all motions, applications, proceedings and other matters in connection with approximately 180 separate causes of action which are the subject of numerous actions in the Supreme Court, New York and Bronx Counties, to recover damages arising out of alleged personal injuries in the ingestion of the drug MER/29. The attorneys for defendant Richardson-Merrell, Inc., foresaw many advantages in handling the pretrial proceedings as well as the trial of these numerous cases by one judge selected by the Appellate Division.

The Appellate Division in a decision reported in the *New York Law Journal* December 23, 1964, 22 A.D. 2d 886, granted the defendant's motion and designated Hon. Saul S. Streit to hold Trial and Special Terms in which all motions and matters relating to discovery shall be heard and to which all trials of the New York and Bronx Counties cases shall be assigned. In connection therewith, the appeals court modified the lower court's order for severance and vacated the order without prejudice to renewing same before Judge Streit depending upon what may develop during the course of pretrial procedures. The court said:

. . . it may appear that many of the causes of action should be consolidated or jointly tried, or on the other hand, that certain of the causes of action set forth in the complaints in the subject actions should be severed and tried separately or with other similar cases.

There are other obvious problems that will arise in multiple litigation. What does the defendant do when judges in Missouri, Florida and Indiana set cases to be tried on the same day? How can witnesses be in all these locations at the same time? Well, first counsel for the company will plead for a continuance of one or more of the cases on the ground of priority of trial date setting in one of the cases in order that defendant's witnesses can be available at each of the trials. If this fails, counsel does the best he can to juggle witnesses in and out of court via jet airplanes. Just another example of the fast pace of modern life. Who was it that mentioned the "laws delay?" The multiple defendant litigant will be praying for the law's delays for such is the time that tries the soul of the defendant's witnesses and his counsel.

Counsel for the defendant in such multiple litigation wants to expedite the trial of a weak case and settle the more difficult ones. There is no formula for this. Some skill can be exercised but more often luck on the call of the calendar may help the defendant.

I have given only a few of the problems that will beset the defendant's harassed general counsel and his staff in multiple litigation. There are many more of varying degrees of importance, but I leave with you the most important point of all: Each local counsel retained to defend one *or one hundred* cases is the advocate who must stand before judge and jury to defend his client. The role of the drug company and its general counsel is to give that local counsel, in Eldorado, Arkansas, San Francisco or wherever he practices, the utmost aid and comfort, realizing that in the last analysis the defense of each case rests on local counsel. **[The End]**

SEMINAR TO BE HELD ON DRUG PRODUCTION CONTROLS

A seminar emphasizing "current good manufacturing practices" in drug production will be held at the Wisconsin Center in Madison, Wisconsin, the week of August 23, 1965. The University of Wisconsin School of Pharmacy and the Extension Services in Pharmacy, the Pharmaceutical Manufacturers Association, and the FDA are cooperating to arrange this Seminar on Control Procedures in Drug Production.

The faculty of Wisconsin's School of Pharmacy will conduct the seminar with the assistance of outside lecturers selected by the cooperating groups. Topics to be covered include: general principles of quality control; buildings, engineering, and maintenance; raw materials control; packaging and labeling control; quality control administration; drug control inspection; drug recalls; personnel management.

The Stake of the Food and Drug Industries in the Threatened Erosion of Patent Systems

By AUSTIN S. PHILLIPS

Mr. Phillips Is an Attorney with the American Cyanamid Co.

UNDER THE AUSPICES OF THE UNITED STATES PATENT OFFICE, we are this year celebrating the 175th year of the passage of our first patent statute on April 10, 1790. While this was, indeed, an event to be commemorated, modest we must remain when one recalls that the first true patent law was enacted in the Republic of Venice in 1474, while England began granting patents to inventors in 1560, although its patent law was first codified in 1623. We were, however, one year ahead of the French who established their law in 1791. In this year it has been stated that 118 countries grant some form of patent protection.

Basically, we think of a patent as a contract between the government and an inventor or his assignee by which, in return for the public disclosure of the particular new and useful advance in an art, the patent owner is granted the right to exclude others from using the invention for a limited period of time. Conversely put, a patent owner and his licensees are assured of the freedom of use of the invention within its scope, as against, for example, a later conceiver of the same advance.

Dr. Vannevar Bush well described the principal objectives of an effective patent system when he wrote:

> First, it aims to stimulate both inventions and the assiduous search for new applications of knowledge . . . by placing the inventor in a position to secure a

reward. Second, it seeks to create conditions whereby the venture of funds to finance the hazardous introduction into public use of new devices or processes will be warranted. This is done by protecting the industrial pioneer for a limited time against the uncontrolled competition of those who have not taken the initial financial risk. Third, it aims to prevent the creation of an industry permeated by . . . intense secrecy . . . by extending a temporary monopoly to those who . . . will make a full disclosure of their new ideas so that they may be utilized to the full by those skilled in the particular art.

Patent Laws in Various Countries

In the case of important inventions, patent applications are ordinarily filed not only in the country of the inventor or owner but in a number of other countries as well, the laws of which differ from jurisdiction to jurisdiction. Their basic aims of encouraging disclosure, fostering research, and protecting investment in research are similar. The duration of patents granted presently varies generally between 16 and 20 years, our own, of course, having been 17 years since 1861. The extent of protection differs also. In all countries the patent owner may exclude others than licensees from making patented products or from using patented processes in the country in which the patent is granted. With regard to imported infringing products, variance occurs. In the United States, only the holder of a product patent has a cause of action for infringement if an imported, unlicensed product covered by the patent is used or sold here. In a number of countries abroad, notably Europe, the holder of a patent covering a process has such a cause of action if a product, made elsewhere by the process of the patent in question, is used or sold without license in the country which has granted the patent.

International Administration of Patent Rights

A number of treaties or conventions exist, developed on the lines of the law merchant to facilitate international administration of patent rights, such as the International Convention of 1883, as amended, concepts of which, for example, are that signatories undertake to treat foreign applicants as they do their own nationals and to grant priority of invention based upon the date of the original filing in a signatory nation if certain rules are observed.

More recently we have seen in development concepts such as the proposed European Patent Law to be effective in the countries of the Common Market, a similar activity in the Scandinavian group, and in South America.

An element in these developments has been the explosion of technical information since World War II, and the emergence of immensely complex data which, at least in countries under the systems of which examination for novelty is involved, will delay patent issuances. This is occurring in the United States notwithstanding increased staffs and efficiency, data storage, and other efforts. It is receiving Congressional attention.

There is a movement discernible, however, which is not in the direction of increased competence and efficiency in the prosecution and issuance of patents. Quite the reverse; it is in the direction of erosion. The stake of the food and drug industries in the threatened erosion of patent systems may well be the stake of the cosmetic and all other industries.

Its first indication occurred in 1939 during the Mussolini regime in Italy when in revision of patent laws adopted in 1859 the patentability of new and useful processes for the manufacture of pharmaceuticals was expressly eliminated. This was unique among modern industrial nations which, while the laws of some do not provide for the patentability of new food and drug products, as such, they do not discriminate against this art as compared with all other fields. This created a vacuum enabling Italian manufacturers so inclined to reproduce with impunity and at a saving of time and research risk and cost, inventions made by others and published in patents granted by other countries. As developed recently in civil and criminal proceedings, some of which are pending, a by-product has been produced in the form of conspiracy and theft of proprietary technical information and starting materials for use in a country in which the originator of new pharmaceuticals and processes for their manufacture has no forum for the adequate protection of industrial property, comparable to that in other countries. Even where there may be difference of view as to whether a process used in Italy is infringement, and regardless of nationality of the patent owner outside Italy whose original research is involved, the patent owner's ordinary recourse of settling the question in court directly with the alleged manufacturing infringer is not available. His recourse is to pursue his remedy against purchasers who might be his potential customers in other countries. Responsible members of the Italian pharmaceutical industry have advocated legislation establishing patent protection in this field for years but the vacuum continues to exist.

Recent Proposals in the Field of Food and Drug Patents

More recently, proposals have come forward in reports of commissions and in the form of proposed legislative acts in a similar vein in other countries. These range from advocacy of abolishment of all patents in the fields of foods and pharmaceuticals to substantial inroads on existing laws. The latter take the form of curtailment of the term of pharmaceutical patents to five or seven years, broadening the basis for cancellation, and establishing compulsory licenses to import as well as for local manufacture.

Several years ago, by parliamentary resolution, pharmaceutical patents in Turkey were, in effect, invalidated. Administratively in Iraq, there have been increasing delays in action on pharmaceutical patents. Brazil has enacted restrictive laws. Israel has broadened its compulsory license law.

Currently, the types of legislative action I have described are in various stages of consideration in India, Colombia, South Africa, the Philippines, Canada and New Zealand. In a report of one commission a statement which requires no comment was included:

> The abolition of patents as applied to drugs as a means of unilateral action by this country might be regarded as a means of securing for this country the fruits of research and invention in other countries without our making any contribution to the cost of new drugs.

It is to be hoped that balanced thinking by legislators motivated by appropriately sound long-term considerations will avoid any such final conclusions. Certainly, we can look for this in countries whose laws stem from British sources but it is that type of philosophy which justifies the expression of "piracy" which has been used by industry executives deeply concerned with the protection of substantial, private investments in research.

As an example of serious patent law erosion, it is reported but cannot be verified until a proposed act is made public in India that, although abandoning outright abolition of pharmaceutical patents, a revision of the 1911 patent law in its entirety will affect the reduction of the life of all patents to 14 years from the present 16 from their filing dates, except that patents covering processes for the manufacture of food, pharmaceuticals, pesticides, fungicides and insecticides will have a term of seven years from the filing date. It is believed that the present recognition of infringement by use or sale in India of products manufactured outside India by the process of an Indian patent will not be included; that neither product claims per se nor

claims to a product by the process are expected to be available in respect of new substances in the categories mentioned above, in respect of which also compulsory licenses will be available, immediately upon grant, with a maximum royalty of 2% of net sales value. The latter limitation is unique to my knowledge insofar as existing compulsory license laws in any country is concerned. It is understood that the proposed law may have ex post facto effect in that it would apply to existing patents as well as to future applications. It may remove the present right of appeal to the courts from decisions of the Patent Controller regarding applications for compulsory licenses which under the present law are available upon grant as to pharmaceutical and food inventions. Such reviews, it is reported, would be handled administratively under the proposed law.

In Colombia we are informed that a resolution has been before the Congress providing that, after its effective date, new inventions, improvements or advancements of chemical substances used in the pharmaceutical industry will not confer upon their creators exclusive rights and a patent granted will only carry the right to collect a royalty in Colombian funds not higher than 10% of the international prices of the raw materials prevailing at the time of grant and that local manufacturers may obtain the raw material from any manufacturer who offers it in the world markets.

In our own country, Congress has wisely resisted incursions of this sort, including discriminatingly foreshortening patent terms in any one field or otherwise discouraging research efforts and progress by establishing short term exclusive protection followed by compulsory licensing. Our vigilance is justified in continuing to safeguard a system which has been so productive for the economic and public welfare and for the progress of mankind.

A discussion of "patent erosion" with a professional group principally concerned with the drug industry cannot overlook another aspect which presently is not a legislative change. Indeed, at least in theory, it is not limited to that industry. This is the problem of the recent administrative use by the United States Government of the so-called "1910 Act, as amended" (28 U.S.C. 1498). You will recall that this statute provides in part that whenever an invention covered by a patent of the United States is used or manufactured by or for the United States without a license of the owner or lawful right to use or manufacture the same, the owner's remedy shall be by action against the United States in the Court of Claims for his reasonable and entire

compensation. Legislative sanction has existed for settling such claims by negotiation with the head of an agency or department prior to filing such suit. The process has apparently become limited to claims involving the Department of Defense which considers and negotiates adjustments of them.

It is in the public interest that supplies to the Government should never be interrupted by an injunction in a private controversy or if required items are in short supply or substandard in quality, nor should officers be held personally responsible for unwitting infringement when acting in their official capacities. However, since 1958, opinions of the Comptroller General of the United States have directed procurement agencies to buy at the lowest price consistent with required quality without regard for patent rights in view of compensation available to patent owners pursuant to 28 U.S.C. 1498. A permissive statute has become mandatory. The results? In an Air Force case, a contract was awarded to an unlicensed manufacturer over competitive bids of two licensed bidders at a price just below the royalty the lowest licensed bidder was under obligation to pay to its licensors. These happened to be individual inventors not themselves manufacturers who presumably were compensated by an equivalent royalty.

Insofar as the American drug industry is concerned, substantial contracts have been and are being awarded for unlicensed products manufactured abroad, principally in Italy, frequently on a basis exempting the contractor from indemnifying the Government against infringement while licensed bidders remain under obligation to pay royalties to licensors.

During World War II, legal and procurement officers were admonished to avoid claims under the "1910 Act." Patents which were not deemed invalid were respected to the extent possible. The policy since 1958 is an erosion of that position. The justification is the "saving" of public funds. In an opinion in 1960, the Comptroller General wrote that contentions that award to an Italian concern would weaken American industry, deprive the government of tax revenue, and adversely affect our monetary trade balance, are arguments of a political or economic nature which could not be considered by him except as they may be embodied in pertinent statutory enactments.

Congressman Roudebush has acted on that observation by reintroducing a bill identified as H. R. 150 in the 89th Congress. This is an amendment of 28 U.S.C. 1498 which would limit the use of this

permissive statute to situations where the Secretary of Defense or his delegate determines that the national security of the United States requires the use or manufacture of a patented invention which has not been licensed by the patentee. This bill deserves the thoughtful consideration of the Bar and its support of an enunciation of the clear intent of the Congress, taking into account considerations materially affecting American industry without hampering appropriate needs of the Government.

Other governments have comparable laws, and some, subsequent to 1958, have been similarly utilizing them. Holders of British patents and their manufacturing licensees have experienced comparable inroads, principally involving Italian-made pharmaceuticals unlicensed for use under British patents. A decision has been rendered which is presently under appeal that the procurement of pharmaceuticals for use in the National Health Scheme (essentially a civilian rather than a governmental end-use, as we would consider it) is "in the service of the Crown" notwithstanding the argument that such a use was unknown at the time section 46 and following of the Patents Act was enacted. Canada, while scrupulously concerned with its statutory obligation to compensate patent holders, uses its similar law for governmental purposes.

Reliance on Patent System

The pharmaceutical industry, in common with all modern industry, relies heavily on the patent system and the lawful protection it affords to develop profitable and growing enterprises. It is the possibility of the limited protection of patents which spurs this private industry to invest millions of dollars per year in research for new drugs. It is the full disclosure provisions of our current patent law which enables research to be advanced by all and competitors to refine and further supplant existing drugs and, through their own continuing research, provide a continuous flow of new and better drugs. While always subject to improvement, the system has produced in the public interest. That production will deteriorate if and to the extent that we accept its erosion.

Enlightenment, advocacy, and setting examples are what private persons can do with respect to laws of nations other than our own. Constructive, sound, and long-view thinking above ill or incompletely informed popular prejudices and political considerations is the universal challenge. **[The End]**

Investigational Drugs: Experimentation or Medical Practice

By WALTER W. BEACHBOARD

Mr. Beachboard Is Secretary and General Counsel of Smith Kline & French Laboratories in Philadelphia. He Is a Member of the Pennsylvania, New York, and New Jersey Bars.

SOCIETY HAS GREATLY BENEFITTED from the development of the so-called miracle drugs. In contrast with the situation that existed only a generation ago, we now have drugs for the prevention, mitigation or cure of: poliomyelitis, rheumatic fever, mental illness, tuberculosis, rickets, pneumonia, mastoiditis, influenza, diptheria, syphilis, whooping cough, measles and a host of other diseases.

It would seem axiomatic that no unreasonable restraint on the development of further drugs for the aid of mankind should be imposed. Unfortunately, the contrary is the case. The false concept that the use of new drugs in human beings is experimentation, the fact that patients must give a so-called informed consent and the suspicion that the use of new drugs is malpractice all stand as major obstacles in the way of therapeutic progress.

Any meaningful study of these obstacles must start with the Federal Food, Drug and Cosmetic Act (FDC Act).[1] This Act imposes controls over the entire process of developing new drugs, beginning with their first use in man.

The Federal Food, Drug and Cosmetic Act before and after the Drug Amendments of 1962

In basic outline the Act provides that no new drug can be introduced in interstate commerce unless a formal new drug application

[1] 21 U.S.C. 321, 331-337, 351-357, 371-392. A short history of the Act is contained in Sadusk, "The Physician and the Food and Drug Administration," 190 *Journal of the American Medical Association* A-907 (Dec. 1964).

(NDA) has been filed with the Federal Food and Drug Administration (FDA) and approved by that agency. However, exemptions from this requirement are authorized where the drug is "intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs."[2] This provision enables the drug manufacturer to ship drugs to physician-investigators designated to make the drug trials in human beings. This is the investigational stage and it is at this point that difficulty begins.

Beginning with the FDC Act amendments of 1938, new drugs were required to be cleared for safety with the FDA. In order to obtain such clearance the manufacturer had to submit to the FDA a formal NDA supported by voluminous data consisting principally of reports of case histories and other information on its use derived from the clinical experience of investigators. The FDA scientists studied the data and, if they found the drug safe as made by the applicant, the FDA allowed the NDA to become effective. Thereupon, the drug manufacturer could begin marketing the drug.

In general, the system worked well. However, there were gaps in the FDA's control over the use of the drug in the investigational stage.[3] In 1962 the thalidomide disaster focused attention on these gaps. The Drug Amendments of 1962, popularly known as the Kefauver-Harris Amendments, not only imposed a framework for tighter FDA controls over the use of investigational drugs but imposed the requirement that the FDA must affirmatively approve both the safety and the *effectiveness* of the drug.[4] Although the FDA had previously taken effectiveness into account, in balancing the risks against the benefits in passing on safety, the emphasis on the word effectiveness was bound to result in the imposition on the manufacturer of a greater burden of proof.[5]

The drug industry did not object to the new statutory requirements. However, serious fears were expressed that, as a result of the Congressional pressures and emotional atmosphere of 1962, the clear-

[2] Food, Drug and Cosmetic Act, 21 U.S.C. 355(i), FOOD DRUG COSMETIC LAW REPORTER ¶ 264.

[3] Before the Drug Amendments of 1962 the sponsor of a drug needed only an appropriate certificate from the investigator in order to ship an investigational drug in interstate commerce.

[4] Food, Drug and Cosmetic Act, 21 U.S.C. 355(b)(1), FOOD DRUG COSMETIC LAW REPORTER ¶ 257.

[5] Food, Drug and Cosmetic Act, 21 U.S.C. 355(d), FOOD DRUG COSMETIC LAW REPORTER ¶ 259.

ance of drugs would be delayed and that a number of valuable drugs would be blocked from the market. These fears have since been realized.[6] This has come about more because of the way in which the FDC Act, as amended in 1962, has been interpreted than through defects in the law itself. However, though the statutory deficiencies are few, they are serious.

The Lack of a Definition of Investigational Drugs in the Federal Act Is a Serious Defect

The FDC Act, as amended in 1962, fails to make any distinction between experimental and investigational drugs. The term "experiment" connotes drug trials intended to satisfy scientific inquiry or curiosity. It has been equated, in malpractice cases, with ignorant or unskilled departures from approved methods.[7] It also has the emotive quality of evoking memories of the medical experiments inflicted by Nazi doctors on concentration camp prisoners.[8]

The term "investigational," however, is not objectionable and should be applied consistently to drugs being investigated in accordance with the Act. The term is much clearer than the confusing word "new," now used in the FDC Act to describe these drugs. The adjective "new" is imprecise because it also describes drugs which are the subject of an approved NDA. Thus, a drug continues to be a new drug under the Act even though it has become one of the standard or fundamental drugs of medical practice.[9]

In section 505(i) the FDC Act comes close to providing a descriptive term by referring to drugs intended for *investigational* use. However, "investigational" modifies "use," not "drug," and the repeated references elsewhere to "new" drugs prevent the word "investigational" from becoming firmly established.

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[6] Even after it became clear that the FDA's policies under the Drug Amendments of 1962 would reduce the number and slow up the clearance of new drugs, there was still no objection to the "intent" of the statute. See Augustus Gibson, "The Effect of the Investigational Drug Regulations on Drug Research and Development," 19 Food Drug Cosmetic Law Journal 153 (1964).

[7] Ladimer, "Ethical and Legal Aspects of Medical Research on Human Beings," 3 *Journal of Public Law* 467, 511 (1954).

[8] The medical experiments fell into 15 categories: high-altitude, freezing, malaria, lost (mustard) gas, sulfanilamide, regeneration and transplantation, sea-water, epidemic, jaundice, typhus and other vaccines, poison, incendiary bomb, phlegmon, polygal, gas edema (phenol) and mass sterilization. Vol. I: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law*, No. 10 (1946-1949).

[9] Food, Drug and Cosmetic Act, 21 U.S.C. 355(e), Food Drug Cosmetic Law Reporter ¶ 260.

For want of an adjective a large segment of the public considers these drugs as experimental in the invidious sense. At least one member of Congress has gone so far as to describe the investigational drug process as involving the use of human beings as guinea pigs.[10] Thus, the dark cloud of impropriety has been cast over the entire process.

Essential to an understanding of the law on investigational drugs is an appreciation of the sharp difference between experimental drugs which are used primarily in volunteers for the advancement of scientific knowledge, and investigational drugs (of which our knowledge is perhaps not complete) which are used for the primary purpose of benefiting the patient.[11]

The Basic Difference between Investigational Drugs and Experimental Drugs

The selection of an investigational drug usually begins with screening procedures intended to select from many substances one that might be promising.[12] Usually the screening is conducted in the laboratory of the drug manufacturer. Testing in animals is the most common form of screening. However, a crude compound may be studied in a test tube for its ability to prevent the growth of organisms or in a tissue culture to determine its effect on living cells.

The process of testing in animals is complicated and time consuming. Sometimes an abnormal state is created in the animal, for instance, by removal of an endocrine gland. In testing substances for behavior, very elaborate equipment is devised and employed for continuously recording the animal's activity.

If evidence of a therapeutic use appears, the scope of the investigation is broadened. Of primary importance is a determination of the degree of toxicity. A large margin of safety is obviously a most desirable property in a new drug. Therefore, if the difference between the effective dose and the lethal dose is small, the compound is usually abandoned.

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[10] 108 *Congressional Record* 15334 (1961).

[11] The importance of this distinction is illustrated by an order of the New York City Department of Hospitals to the effect that "unless it is specifically designed to benefit the patient involved, no research using a patient as subject is permitted in any hospital or institution of the Department." General Order 462, Concerning Research Proposals, October 27, 1949.

[12] The investigational drug process is set forth in detail in Vol. 2: *Hearings before a Subcommittee of the House Committee on Government Operations (Drug Safety)*, 88th Congress 2nd Session (1964).

If the substance survives the lethal toxicity tests, then other tests are conducted in various species of animals to determine whether long-range damage may be done to the living organism. The animals are tested for such things as adverse effects on growth and their renal, hepatic and bone marrow function. Even though some animals may have exhibited no apparent bad effect, they are sacrificed and their tissues are subjected to careful microscopic examination by trained pathologists.

The decision to use the drug with patients is made only after the necessary opinions have been received from chemists, pharmacologists, biologists and physicians. Sometimes the drug is first given to healthy volunteers, whose consent must always be obtained in advance. Such use is for the purpose of exploring adverse effects or learning more of the drug's mechanism.

Scientists cannot predict with certainty that a drug will have the same effects in human beings as in animals. However, the salient point is that, before use in patients, enough is known about the drug's mechanism so that scientists have a reasonable expectation of desirable consequences. When the drug is first given to a patient, as opposed to a volunteer, it is to benefit him not just to see what effect it will produce.

Government Control over Investigational Drugs

Before an investigational drug can be used for human beings, the drug manufacturer must file with the FDA Form FD 1571 entitled "Notice of Claimed Investigational Exemption for a New Drug."[13] This form requires disclosure of the work that has been done with the drug, the plan for its use in man and a list of investigators who will be using the drug. The FDA may revoke the new drug exemption at any time if the manufacturer's reports to the FDA show that the plan is not properly designed or is not properly carried out.

Each physician who is to take part in the clinical trial is required to file with the drug manufacturer either Form FD 1572 or Form 1573 entitled "Statement of Investigator (Clinical Pharmacology)" and "Statement of Investigator," respectively.[14] These forms provide detailed information about the investigator's education and experience, his medical or other scientific publications, the identification of any hospital or other facilities which will be employed, the plan of in-

[13] 21 CFR Sec. 130.3(a)(2) (1963), FOOD DRUG COSMETIC LAW REPORTER ¶ 71,303.

[14] 21 CFR Secs. 130.3(a)(12) and (a)(13) (1963), FOOD DRUG COSMETIC LAW REPORTER ¶ 71,303.

vestigation which he will follow and a certification that he will obtain the necessary consents.

The drug manufacturer keeps in close touch with investigators and obtains frequent case histories and reports from them. The manufacturer is required to give the FDA current and complete information of the drug's evolution in the clinical trial program. Where discussions with the FDA are necessary, the drug manufacturer also receives the benefit of the comments of FDA scientists concerning the adequacy of the plan and the work being done by the investigators.

The entire investigational drug process is aimed at obtaining the FDA's approval of the NDA at a future date. The constant need for anticipating the FDA requirements for approving the NDA exerts an indirect but constant influence on the investigational drug process. Few activities are subject to greater government control than new drug investigation.

Extraordinary Skill and Care Involved in Use of Investigational Drugs

In contrast with its direct role in the use of the drug in animals, the drug manufacturer serves primarily in the role of sponsor, planner and advisor in the study of the drug's effects on human beings. In its capacity as sponsor of the program, the manufacturer appoints one of the physicians on its medical staff to act as monitor of the new drug program. The physician-monitor sends supplies of the drug to one or more outside medical specialists who carefully begin administration in volunteers or patients. This is the first phase of the clinical investigation.

When safety and a desirable therapeutic effect have been demonstrated in a small number of human beings, the drug is given to a few more qualified and experienced clinicians. This is the second phase. As in the first phase, the setting is usually university hospitals where continuous observation of the patient is possible and excellent laboratory facilities exist. These facilities are used extensively (and expensively) for the protection of the patient. The investigators frequently consult with advisory committees usually consisting of expert hospital clinicians who are specialists in their field.

The FDC Act requires substantial evidence of effectiveness.[15] Accordingly, in this second phase both the sponsor and investigators

[15] Food, Drug and Cosmetic Act, 21 U.S.C. 355(d)(5), FOOD DRUG COSMETIC LAW REPORTER ¶ 259.

focus their attention on a limited number of well-controlled studies, with special emphasis on the mechanism of the drug's action and therapeutic effectiveness.

As the coordinator of the investigation, the physician-monitor must keep in touch with investigators and relay to them additional information about the new drug as it becomes available. If any physician reports an adverse effect, the monitor has the responsibility not only of reporting the observation to the FDA but also of alerting other investigators.

When there is sufficient evidence that the drug can be safely administered not only to hospitalized patients but to out-patients in clinics or to persons visiting a physician in his office, the compound is ready for the third phase of the investigation.

In this third phase the drug must be tested under conditions of everyday use, that is, apart from complex laboratory tests and close hospital supervision. Accordingly, the sponsor sends supplies of the drug, together with a summary of the pertinent information concerning its use, to a relatively large number of physicians. In this stage hundreds of patients are treated with the drug and the FDA's demands for information on the entire process are increased accordingly.

After perhaps years of study, when the clinical and laboratory reports are all in, the sponsor must decide whether the new drug is valuable enough for general use by the medical profession. Not every drug is a "breakthrough;" some merely provide alternatives to existing therapy. However, to the patient who fails to respond or is sensitive to existing drugs the new one may be vitally important.

If the decision is favorable, the new drug application is prepared and filed with the FDA together with the voluminous data that has been compiled, sometimes as many as 8,000 pages. Upon the date of filing, the drug is ready for marketing in the opinion of the sponsor's medical staff. However, it must now undertake to prove to the FDA's scientists that this opinion is justified. This requires many months or years of tedious negotiation, the present complexity of which has been criticized sharply by drug manufacturers.[16]

If the FDA approves the NDA, the drug is ready for marketing. Even then the sponsor must continue collecting adverse reports, promptly investigating them and reporting them to the FDA and the

[16] Karl H. Beyer, Jr., "New and Investigational Drugs," 20 FOOD DRUG COSMETIC LAW JOURNAL 75 (February 1965). An FDA rebuttal is set forth in Winton B. Rankin, "Progress on Investigational Drugs," 19 FOOD DRUG COSMETIC LAW JOURNAL 237 (April, 1964).

medical profession. The instructions for use and other product literature must be revised as new information comes in. Information on new side effects, new uses and new dosage forms and schedules are part of a never-ending program.

Investigational Drugs Are Used in the Physician-Patient Relationship

At all stages in the history of a new drug, the drug manufacturer's medical staff stands ready to advise investigators and other physicians on the management of individual patients who are on the drug. Although the manufacturer's medical staff does not assume direct responsibility for the patient, it does exercise a primary duty to correlate and disseminate information on the drug provided by the investigators.

The investigator is the patient's physician and responsible for his welfare. The patient selected to receive the investigational drug is typically one who has not been doing well on standard therapy and who, his physician thinks, may do better with the investigational drug. The investigator takes the utmost care to prevent injury to the patient.[17] Furthermore, there is, by hypothesis, a reasonable scientific theory for using the drug. These factors lift investigational drugs out of pure experimentation and also away from quackery, such as is found in fake cancer cures. Under the above circumstances, the drug can clearly be given within the safeguards of the physician-patient relationship.[18]

Similarity Between Investigational and Standard Drugs

There is no qualitative difference between an investigational drug and a standard drug. A tremendous amount of scientific information is available on both classes of drugs and they both have their potential dangers. In fact, it is difficult to see a distinction even in degree where the drug is in the third stage of investigation, that is, actually in use by general practitioners and other physicians as an integral part of their practice.

[17] The standard of the "greatest care possible" was enunciated in *Bails v. Boulinger*, 4 D.L.R. 1083 (Can. 1904). See also to the same effect Modell, "Let Each New Patient Be a New Experience," 174 *Journal of the American Medical Association* 1717, 1719 (1960).

[18] "But performing experiments and operations exclusively from the patient's own advantage does not prevent their turning out profitably to science." Claude Bernard as cited in Bean, "Testament of Duty: Some Strictures on Moral Responsibilities in Clinical Research," 39 *J. Lab. & Clin. Med.* 3, 9 (1952).

The distinction is even harder to see where the investigational drug is not a brand new composition of matter, with unknown and potentially dangerous characteristics. An investigational drug is frequently a minor variant of a drug whose properties are well known. An investigational drug may also be a standard drug used for new purposes.

For example, an antibiotic ointment for the cure of a skin allergy would be an investigational drug because antibiotics are not officially approved for use in allergies.

Suppose the physician diagnoses the skin allergy as a bacterial infection. Not until after the antibiotic has failed, does he have evidence that he is dealing with an allergy. Was the physician guilty of malpractice for prescribing the ointment which, in retrospect, was an investigational drug? The answer is "no" because experimentation in this sense is inherent in the practice of medicine.

Government Recognition That Investigational Drugs Are Used in the Physician-Patient Relationship

The obvious conclusion that persons receiving an investigational drug are not the subject of experimentation receives support in the FDC Act itself. Section 505(i)(1) of the Act provides that the investigator must agree that:

> . . . patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him.

The use of the word "patient" instead of "human being" (used in the consent exception discussed below) constitutes a recognition by Congress that investigational drugs are used in the physician-patient relationship. The FDA also recognizes investigational drugs as valuable therapeutic agents by permitting noninvestigator physicians to use them in exceptional cases.[19] The National Institutes of Health, of course, have engaged in extensive drug investigations of the same sort as that sponsored by drug manufacturers and other nongovernmental agencies.[20]

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[19] Paragraph (f) of the investigator's certificate requires him not to transship investigational drugs. However, the FDA allows exceptions where a noninvestigator physician has a patient in critical condition. Augustus Gibson, "The Effect of the Investigational Drug Regulations on Drug Research and Development," 19 FOOD DRUG COSMETIC LAW JOURNAL 153, 158 (April, 1964).

[20] Sessoms, "Guiding Principles in Medical Research Involving Humans, National Institute of Health," 32 *J.A.H.A.* 44 (1958).

Investigational Drugs May Be Used Experimentally

An investigational drug may be used in normal healthy persons or in patients primarily to test its safety, determine dosage ranges or pursue some other scientific objective. Unless the drug is a preventive, like a polio or rabies vaccine, the drug cannot possibly be of benefit to them. Accordingly, they are not true patients but the subjects of a carefully supervised experiment whose consent must always be obtained.[21]

Failure to distinguish the above situation from the one where the drug is being used for the patient's benefit has been one of the principal causes of confusion in the law and in the development of medical codes of ethics. The Kefauver-Harris Amendments contribute to this confusion by failing to distinguish between volunteers and patients. In fact, both categories of persons are not only treated alike but lumped together as "human beings".[22]

Another situation which has caused confusion is the one involving group therapy. Here the investigator wants to cure his patients in the group by using an investigational drug which he hopes is better than existing therapy for the members of the group. Various techniques such as "double blind" and "Roman square" studies are employed.

These techniques sometimes require withholding of the investigational drug, or even the standard drug, from the patient without his knowledge or the prior knowledge of his physician. This is accomplished by the use of code numbers, placebos and other devices in order to insure objectivity in evaluating results.

Where the members of the group are patients who are not doing well on existing therapy, each member is benefited by participating in the study. The investigator thoroughly explores the patient's physicial condition and, without undue risk to the patient, may discover a mode of therapy superior to that which has been theretofore available. Extreme care, however, must be taken to make sure that no member of the group deteriorates in health because of drug withdrawal. If such care is not taken, the question of pure experimentation and malpractice may arise.

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[21] As shown earlier in this article an informed consent represents a goal rather than a practicality.

[22] Food, Drug and Cosmetic Act, 21 U.S.C. 355(i), FOOD DRUG COSMETIC LAW REPORTER ¶ 264.

The Investigational Use of Drugs as a Branch of Medicine

Teaching hospitals and many large hospitals have areas set apart for the use of investigational drugs, sometimes under a name like "Research Center." Furthermore, the American College of Clinical Pharmacology and Chemotherapy has been founded to establish boards of competence for clinical investigators. Regardless of the desirability of such boards, this action by the College stamps the investigational use of drugs as an integral part of the practice of medicine. It is a medical specialty like psychiatry, surgery, opthamology and obstetrics.

The investigational use of drugs must be treated as a branch of medicine for a most practical reason. If investigational drugs are not recognized as respectable therapeutic agents, medical progress will go into a steady decline, at least in this country.[23] In order to provide a safeguard against this result, Congress should amend the FDC Act by defining investigational drugs and by clarifying all phraseology inconsistent with their use in the physician-patient relationship.

The Consent Provision in the Kefauver-Harris Amendments

In the deliberations leading to the Kefauver-Harris Amendments, Congress became concerned with an important aspect of the physician-patient relationship. Some members of Congress felt that physicians should be required by law to agree not to give patients investigational drugs without the patient's consent. On the other hand, many members of Congress did not want to interfere with the practice of medicine.[24]

Congress resolved its dilemma by an oblique legislative approach. Instead of providing for control by the FDA, the Kefauver-Harris Amendments impose the general requirement that the physician certify to the *sponsor* that the patient's consent will be obtained. Such a certificate is made a prerequisite to the exemption needed to ship investigational drugs in interstate commerce. No penalties are imposed on the physician for failure to abide by the terms of his certificate. However, the physician risks the loss of his standing with the FDA as a qualified investigator if he fails to obtain the patient's

[23] "Dr. Robert A. Haines, Mental Hygiene and Correction Director disclosed today he has ordered his department to cease using drugs which do not have final U.S. Food and Drug Administration approval. He acted after an American Medical Association publication indicated physicians are personally liable for legal action in using non-approved drugs." *Columbus Dispatch,* September 15, 1961. According to the *Drug Trade News,* March 15, 1965, the Cleveland Clinic has gone back to "testing."

[24] 109 *Congressional Record* 17398 (1962).

consent pursuant to the certificate to be given to the sponsor as required by FDA regulations.

The precise statutory requirement,[25] together with the all important exception, is set forth below:

> . . . such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that *they will inform any human beings* to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, *that such drugs are being used for investigational purposes and will obtain the consent of such human beings* or their representatives, *except where they deem it not feasible or,* in their professional judgment, *contrary to the best interests of such human beings.* Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. [Author's italics.]

The statutory language, if left alone, would give the investigator all the latitude he needs. Unfortunately, there are numerous indications that the words used in the statute will be interpreted in such a way as to impair their utility.

Express or Implied Consent

The first difficulty occurs with the word "consent." At common law, the consent may be express, implied in fact or implied in law.[26] However, for the benefit of investigators, the American Medical Association (AMA) has prepared a formal consent and release form[27] to be executed by patients being treated with drugs under clinical investigation. If investigators are induced to use such forms, the result is sure to be a chilling of the physician-patient relationship and a reduction in the use of investigational drugs.

Informed Consent Is Impossible

Even greater difficulty arises out of the AMA's position that a consent, to be valid, must be an informed consent.[28] The statute itself merely provides that the patient or subject must be informed

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[25] Food, Drug and Cosmetic Act, 21 U.S.C. 355(i), FOOD DRUG COSMETIC LAW REPORTER ¶ 264.

[26] *Lester v. Aetna Casualty & Surety Co.*, 240 F. 2d 676 (1957), cert. den. 354 U.S. 923 77 S. Ct. 1383 (1957); *State v. Housekeeper,* 70 Md. 162, 16 Atl. 382 (1889) (involving surgery). Consent is not necessary or is implied in emergencies. *Restatement, Torts,* Sec. 62.

[27] *Medicolegal Forms with Legal Analysis,* Form 29 (1961).

[28] Winton B. Rankin, "Progress on Investigational Drugs," 19 FOOD DRUG COSMETIC LAW JOURNAL 237, 238 (April, 1964). *Medicolegal Forms with Legal Analysis,* Sections 7 and 8 (1961). See also Hirsh, "Informed Consent to Treatment," 176 *Journal of the American Medical Association* 436 (1961).

that drugs are being used for investigational purposes.[29] The consent called for in the statute is based on this information, not on full information concerning the risks involved. Therefore, a fully informed consent in the technical sense described does not appear to be required by the statute.

If Congress intended to impose the criterion of informed consent, then it has placed a needless and nearly impossible burden on the physician. The thalidomide incident itself vividly illustrates this point.

In the early part of 1962, at the time of the shocking pictures of deformed babies, thalidomide had been marketed in other countries as a sedative for approximately five years. It had been used by millions of people in England, Canada and elsewhere in the British Commonwealth. In Germany it was sold in two strengths, neither of which even required a physician's prescription. The drug had been cleared with numerous foreign health departments, many of which required data similar to that required by our own FDA in approving new drug applications. However, it had never been cleared for use in the United States and was, therefore, an investigational drug.

There was no known method whereby its capacity for producing deformities in unborn children could be determined. Even today, with the benefit of hindsight, it is questionable whether there is any method that would enable investigators to predict its dreadful effects on unborn children. If the news of the harmful effects in Europe had not reached the FDA while thalidomide was in the investigational stage, the FDA, in all likelihood, would have approved the NDA. Such an approval would not have been the result of any lack of skill or efficiency on the part of an agency of the United States Government. The approval and ensuing tragedy would have been caused only by the inadequacies of scientific knowledge at the time in question. Where the specific dangers are unknown, a general warning that a drug's potential for harm has not been thoroughly investigated is of little worth in helping the patient to evaluate the risks.

Any requirement that the physician must obtain an informed consent would be based on the false premise that the patient is capable of making a scientific decision.[30] Suppose, for example, a phase I

[29] For critique of phrase "for investigational purposes" see Boyer, "Medical Liability in Drug Trials," 270 *New England Journal of Medicine*, 777, 778 (1964).

[30] *Hales v. Ranis*, 162 Mo. A. 46, 141 S.W. 917 (1911). In this case, involving x-ray treatment of eczema, the court said the plaintiff was unlearned as to the science of medicine and in no position to judge the risk involved. The medical view is in accord with this: Beecher, "Experimentation in Man," 169 *Journal of the American Medical Association* 109, 112 (Jan. 31, 1959).

investigator decides to explain in detail the risks of using a drug resulting from work in a brand new field of chemistry. He would review the animal work on the particular drug and then proceed with a discussion of the side effects in humans of drugs most closely related from a chemical and pharmacological standpoint. Even if he were a medical student, the patient would become confused.

As a rule, the physician is not under a duty to warn the patient of the dangers of standard drugs despite the fact that all potent drugs have serious adverse effects in some people. The reason for this is that the patient is without the necessary training or experience to balance the risks against the benefits. The situation is much the same in the case of investigational drugs. The *known* risks are of the same order as those encountered in the case of standard medication.

As in the case of standard drugs, insistence upon an informed consent to an investigational drug is tantamount to asking the patient to become a consultant to his own doctor. This is inconsistent with the normal physician-patient relationship in which the patient trusts his physician and depends on him to tell him what treatment to follow.

The Exception to the Statutory Consent Requirement

Under the exception provided in the FDC Act the physician-investigator need not inform the patient or obtain his consent where the physician deems it not feasible or contrary to the patient's interests.[31] Such an exception has been sanctioned in at least one court case.[32] Obvious examples of where an exception should be made are the cancer patient and the patient who is unconscious at the time he needs treatment.

Despite the unique thalidomide tragedy, the fact remains that in the hands of qualified experts investigational drugs are remarkably safe.[33] In phases I and II, the typical investigator is a specialist in the therapeutic field under investigation, an expert in the handling of

[31] Accord: *Fischer v. Wilmington General Hospital,* 51 Del. 554, 149 A. 2d 749 (1959). *DiFillippo v. Preston,* 53 Del. 539, 173 A. 2d 333 (1961).

[32] *Hunt v. Bradshaw,* 242 N.C. 517, 88 S.E. 2d 762 (1955). Failure to explain the risks of a delicate surgical operation was condoned and the need for reassuring the patient was recognized herein. In the volunteer situation an attempt at giving a full explanation and obtaining an informed consent is justified.

[33] Modell, "Let Each New Patient Be a New Experience," 174 *Journal of the American Medical Association* 1717, 1719 (1960).

investigational drugs and a professor of medicine. Almost always he is at the top of his profession.

The Unfairness of Informing the Patient

It is questionable whether it is even fair to the patient to give him an opportunity to veto an investigational drug. In the early days of sulfa drugs, for example, such a veto could have cost the patient his life.

Furthermore, the mere fact that the patient knows he is taking an investigational drug may be a detriment. If an apprehensive patient learns that he is taking a drug which has not been officially determined to be safe, the drug's chances of helping him are diminished. Conversely, an optimistic patient will disregard the risks and think only of the newness of the drug which he hopes will provide a miracle for his ailment. In this situation, the beneficial effects of the drug may be over-estimated because of psychological factors.

Because of the disadvantages of informing the patient that he is taking an investigational drug, the exception provided by the Act should be maintained intact. Unfortunately, there are indications in the regulations issued under the statute that this will not be done.

The Narrowing by Regulation of the Statutory Exception

The first danger to the valuable statutory exception occurs in the FDA's investigational use regulations which specify the form of certificate to be signed by the investigator.[34] Under Form FD 1572 (phases I and II) the investigator certifies that he will inform patients that "drugs are being used for investigational purposes . . . *except where this is not feasible.*" [Author's italics.] This is in contrast with the statute which provides that the exception shall apply where the investigator *deems* it not feasible.

By substituting an objective standard for the subjective standard inherent in the investigator's personal judgment, the FDA has imposed a stricture on physicians not provided and perhaps not even contemplated by the Act. Under this provision doctors would not be in a position to make their own decision. They must try to decide whether a medical board of inquiry or a jury would decide differently on the feasibility of administering the drug in a particular case.

[34] 21 CFR Sec. 130.3(a)(12) (1963), FOOD DRUG COSMETIC LAW REPORTER ¶ 71,303.

The FDA has created another difficulty in the same regulation. Section 4g. of Form FD 1573, to be signed by investigators in the third phase, uses the word "subjects" rather than patients.[35] This tends to negate the physician-patient relationship. Thus, the physician is misled into the belief that his activities are experimental, rather than within the physician-patient relationship.

The Kefauver-Harris Amendments have been interpreted by hospitals and clinicians as establishing a general rule that the patient's consent must be obtained before administration of an investigational drug. Before the adoption of the statute, the matter was left to the discretion of the physician.

Notification in lieu of Informed Consent

In the case of surgery, cobalt irradiation, insulin shock treatment and the like, the medical profession has been advised[36] that:

(1) The patient should be fully informed of any unusual risks that may be involved;

(2) The patient should give the physician his consent in writing; and

(3) In his written consent the patient should acknowledge the physician's explanation.

In surgery and other radical procedures the dangers can usually be foreseen with considerable accuracy. However, in the case of investigational drugs, the greatest dangers are those which are latent. There is no way of satisfactorily explaining such dangers and, therefore, the doctrine of informed consent should not apply.

The obvious purpose of the consent provision of the Kefauver-Harris Amendments is to give patients, under ordinary circumstances, an opportunity to refuse to be treated with investigational drugs. This purpose can be achieved by simply notifying the patient in advance that the drug has not been cleared through the FDA. The patient can then either refuse or acquiesce in the treatment.

Guidelines for Notifying the Patient

Some patients may assume that they are being treated with standard drugs. Unless they are informed to the contrary, they may claim, after untoward consequences have developed, that important

[35] It is ironical that this third phase certificate refers only to subjects whereas the corresponding section 5g. of the certificate for phases I and II refers to both patients and subjects.

[36] Hirsch, "Informed Consent to Treatment," 176 *Journal of the American Medical Association* 436 (1961).

information was withheld from them and that they consented to treatment under a misapprehension of the facts. Since any unauthorized medical procedure may be a battery[37] the plaintiff's lawyer may raise still another specter to haunt the physician.

Clearly then a requirement that the patient shall usually be notified is reasonable. However, since any flat requirement constitutes an interference with the practice of medicine, it should not be rigid but geared to needs of the patient. The following guidelines are suggested:

1. In deciding whether to inform a patient that he is to be given an investigational drug the physician may take into consideration both the patient's need and the likelihood that the patient will be upset by the information.

2. (a) The requirement of notification will be satisfied by the physician's statement to the effect that he is administering an investigational drug which has not been approved by the U.S. Government for general use (or for the novel use) by the medical profession. In addition, the physician must provide such explanation as may be requested by the patient.

(b) The requirement of notification will also be satisfied where the patient realizes that he is being treated in a research environment such as a hospital research center or by a specialist noted for administering investigational drugs.

3. No consent will be required other than that implicit in the patient's acquiescence in the treatment after notification that he is to be put on an investigational drug.

The FDC Act and the investigational drug regulations should be amended so as to give greater latitude to the physician in the matter of consents and so as to eliminate the difficulties referred to above.

The Investigator's Tort Liability—A Review of the Case Law

When the physician-investigator administers an investigational drug to a patient, he is engaging in the practice of a medical specialty. In the absence of negligence or other wrongdoing, the question of malpractice should not even arise in such a setting. Yet the state of the law is so unsatisfactory that serious attention must be given to this question.

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[37] *Restatement, Torts,* Sections 13, 18, 59 (1934): Also see footnote 7 at 486.

As already shown, the investigator may run the risk of a suit based on a battery when he administers an investigational drug without the patient's informed consent. Furthermore, he is menaced by the legal doctrine, derived from negligence and quackery cases, which equates experimentation with malpractice.

Slater v. Baker,[38] decided in 1769, is probably the only case involving a physician of good repute who attempted a new procedure for the benefit of the patient. In this case a surgeon used a new bone-breaking device to refracture the plaintiff's improperly healed leg, with unfortunate results. The court decided against the defendant because, as far as the record was concerned, "this was the first experiment made with this new instrument." The absence of experimental work on animals, of course, distinguishes this case from situations involving investigational drugs.

Carpenter v. Blake,[39] decided in 1872, is the leading American case on the subject. There the physician failed to instruct the patient on how to take care of her elbow after the resetting of a dislocation. The court laid down the rule that the physician should not depart from "a system of treatment . . . followed for a long time." In *Owens v. McCleary,*[40] decided in 1926, the court stated that the physician's failure to treat hemorrhoids by the methods approved by his school of practice "evidences either ignorance or experimentation" and that the "law tolerates neither." However, no legitimate scientific background was involved in the physician's treatment.

Despite the above judicial statements, it is doubtful whether, even in the early days, there actually was a rule that the physician must abide by the treatments approved by his school of practice. For instance in *Jackson v. Burnham,*[41] decided in 1895, the court would have permitted the physician to "justify his experiment by some reasonable theory." In a more recent case, *Board of Medical Registration and Examination v. Kaadt,*[42] the physician treated patients suffer-

[38] 2 Wils. K. B. 359, 95 Eng. Rep. 860 (1767).

[39] 60 Barb. 488, 514 (N. Y. 1871); rev'd on other grounds, 50 N. Y. 696 (1872).

[40] 313 Mo. 213, 281 S.W. 682 (1926). To similar effect see *Sawdey v. Spokane Falls Ry. Co.,* 30 Wash. 349, 70 Pac. 972 (1902).

[41] 20 Col. 532, 39 Pac. 577 (1895). To similar effect see *Hodgson v. Bigelow,* 335 Pa. 497, 7 A. 2d 338 (1939) where the court would have allowed departures from established practice if justified by the circumstances.

[42] 225 Ind. 625, 76 N.E. (2d) 669 (1948) cf. *Fortner v. Koch,* 272 Mich. 273, 261 N.W. 762 (1935) where the court felt that the experiments "must not vary too radically from the accepted method of procedure."

ing from diabetes by a sugar rich diet. However, the court exhibited an enlightened attitude by saying that a physician is not limited to the most generally used treatments but that he must not try *untested* experiments on patients.

The quackery and negligence cases are not in point but the unfortunate language contained in the decisions continues to influence legal and medical writers.[43]

A Proposed Test for Liability

The test for liability in using investigational drugs should be the same as that for standard drugs, namely, whether the anticipated benefits outweigh the known risks.[44] A phase III investigator has at his command not only the standard drugs but also the drug under investigation. If this drug has been proved to be superior to standard therapy by use in hundreds of patients he not only has the right but also the duty to use it for a patient who badly needs it.

The only difference between a drug in phase III and the same drug in phase I or II is the amount of scientific knowledge relating to it. The difference then is one of degree and not of kind. Perhaps the physician should not use a drug in phase I or II unless the patient's need is greater than those in phase III. However, the mere fact that the drug is in phase I or II is not a reason for refusing to use it.

No Sharp Line Can Be Drawn Between Investigational and Approved Drugs

The absurdity of making a distinction between investigational drugs and standard drugs is shown by a drug which is in the NDA stage and awaiting FDA approval. The FDA is satisfied in all particulars with respect to the animal and human data and with respect to the preliminary draft of the proposed labeling. However, before formal approval it requires the manufacturer to produce labeling in final printed form.

After fulfillment of this requirement, the only obstacle in the way of formal approval of the drug is the FDA's clerical job of checking the final labeling against the approved draft. If, during this checking period, a drug is to be considered an experimental drug in the

[43] Note: "Responsibility of Physician for Use of Research Drugs," 185 *Journal of the American Medical Association* 141 (1955).

[44] See footnote 12 at p. 524.

invidious sense, investigators who administer it would be guilty of malpractice. However, the day after FDA approval these same investigators would be engaged in the normal practice of medicine.

The AMA Code of Ethics Does Not Apply to Investigational Drugs

In the absence of court decisions or specific statutes on the skilled use of new drugs in patients, the courts must look to codes of professional ethics as the basis for a decision on the propriety of the conduct subject to their judicial review.[45] Unfortunately, existing codes are of little help in determining the liability of the physician for the use of investigational drugs.

The Nuremberg Military Tribunal enunciated ten rules, commonly referred to as the *Nuremberg Code,* which would protect human beings from compulsion, futility, lack of skill and needless suffering in scientific experiments.[46] However, today in the United States the chief impact of this Code is on the use of healthy volunteers, not on the use of drugs in the physician-patient relationship.

Dr. A. C. Ivy was sent to Europe as a representative of the United States Government to study the war crimes of a medical nature which came before the Nuremberg Military Tribunal. The results of this study were reflected in a report of the Judicial Council adopted by the House of Delegates of the American Medical Association in December 1946. According to this report,[47] in order to conform to the principles of medical ethics of the AMA, the following requirements for experiments on human beings must be satisfied:

1. The *voluntary consent* of the person on whom the experiment is to be performed must be obtained. [Author's italics.]

2. The danger of each experiment must have been investigated previously by means of animal experimentation; and

3. The experiment must be performed under proper medical protection and management.

Since the term "voluntary consent" is taken directly, and blindly, from Rule 1 of the *Nuremberg Code,* it must mean informed consent as it does in the *Code.*[48] Also as in the *Code,* the above principles do

[45] Markel, "Legal Considerations in Experimental Design in Testing New Drugs on Humans," 18 FOOD DRUG COSMETIC LAW JOURNAL 219 (1963).

[46] See footnote 8, Vol. 2 at pp. 181-183.

[47] 132 *Journal of the American Medical Association* 1090 (1946).

[48] Rule 1 of the *Nuremberg Code* provides for voluntary consent, elaborately defined so as to mean informed consent.

not refer to medical practice or the treatment of patients. Consequently, there is no reason to believe that their scope extends beyond the use of investigational drugs in volunteers.

Unfortunately, investigators who do not clearly differentiate between experimentation and legitimate investigational procedures may attempt to apply to their own patients the requirement that "voluntary consent" must be obtained. The absence of any provision for exceptions, as in the FDC Act, is confusing. The failure to recognize the frequent impossibility of obtaining an informed consent is still more confusing.[49] The AMA's principles of medical ethics are badly in need of revision.

The Need for an Applicable Code of Ethics

The lack of a United States professional code of ethics covering the use of investigational drugs presents an unfortunate void. The first court called upon to make a decision on whether the use of an investigational drug is malpractice per se will have no simple, authoritative guide.

Fortunately, the FDC Act now provides the sanction of federal government for the use of investigational drugs in patients[50] and provides a framework upon which a detailed code of ethics may be built. A step in this direction has already been taken by the National Conference on the Legal Environment of Medical Science held in May, 1959. As a result of this Conference, the Committee on Norms for Testing New Drugs in Human Subjects adopted the following report:

> The evaluation of most drugs, devices and techniques may be carried out completely within the physician-patient relationship as generally understood. In this relationship, the physician has always employed what he believes to be the best available treatment or preventive measure for his patient. When no known therapeutic or prophylactic measure has proved effective either against the disease or for his particular patient, the physician may employ a new measure that offers reasonable promise of success without undue risk to the patient, bear-

[49] The impossibility arises (1) where the patient has insufficient knowledge and comprehension of the possible benefits and risks involved in the use of the drug to make an enlightened decision and (2) where the effects of the drug upon the patient's health cannot be predicted. Beecher, "Some Fallacies and Errors in the Application of the Principle of Consent in Human Experimentation," 3 *Clinical Pharmacology and Therapeutics*, 141, 142 (1962).

[50] The FDC Act, as amended in 1962, provides for the patient's consent. But consent is futile where the physician is engaged in malpractice. Therefore, the Act by implication legitimates the use of investigational drugs.

ing in mind the severity of the patient's condition. When a therapeutic or preventive measure of some known effectiveness exists, the physician may employ a new measure that offers reasonable promise of significant advantage over the known measures without presenting undue risk to the patient. The physician must bear in mind not only the patient's condition but also the risks attendant upon the use of the known measure as well as those attendant upon withholding the known measure.

When the evaluation of a new measure, falls outside the classic physician-patient relationship, the medical investigator is bound by the code of ethics covering human experimentation.[51]

The above is an excellent statement but it fails to cover the problem of consents. In 1964 the World Medical Association, by its Declaration of Helsinki, adopted a code which covered consents and clearly recognized the difference between clinical research for therapeutic purposes and research without therapeutic value to the subject. This code provides in part as follows:[52]

In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation.

For use in the United States the wording of the code should be brought into line with the language of the Food, Drug and Cosmetic Act. However, its approach is basically sound. If such a statement were adopted by a body like the American Medical Association, the American Federation of Clinical Investigation or the American Society of Clinical Investigation, it would constitute a badly needed code of ethics for the use of investigational drugs in the physician-patient relationship. [The End]

[51] Ladimer and Newman, *Clinical Investigation in Medicine*, at p. 139 (Boston University Law Medicine Research Institute 1963).

[52] 189 *Journal of the American Medical Association* 33, 34 (Sept. 1964).

Investigational New Drugs and the Army

By MAURICE LEVIN

Colonel Levin Is Retired from the United States Army and Is a Member of the New York Bar.

SCIENTIFIC PROGRAMS OF THE ARMED SERVICES include provision for research in the creation and study of new drugs[1] useful for military purposes.[2] Some of this research is performed "in house" by scientists of the Armed Services. Some of it is performed through outside grants or contracts. Much of it is "classified" for reasons of national security.

The Armed Forces prefer to work with a minimum of interference from governmental agencies outside the Department of Defense (DOD). This preference rests upon strong foundations in those areas which concern military medical research—special military needs as well as military security require that new drug research for military purposes should be conducted with deference to the best judgment of the military, and without fear of slow-downs that might result from "red tape" in non-military portions of the government.

Thus, when the Drug Amendments of 1962[3] were enacted, there was some feeling in military circles that military drug research might

[1] Pursuant to section 201 (p) of the Food, Drug and Cosmetic Act (21 U.S.C. 321 (p), FOOD DRUG COSMETIC LAW REPORTER ¶ 71,021), the term "new drug" means (1) "Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested . . ." or (2) "any drug the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." Compare ¶ 2, *Army Regulations* 40-7.

[2] Drugs useful for military purposes are also usually of benefit to the civilian population. If new drugs can be perfected for military use, it is possible to create not only a military but also a civilian market for them.

[3] 76 Stat. 780 (1962). Codified in Title 21, U.S. Code. See "Finding Lists," FOOD DRUG COSMETIC LAW REPORTER, p. 2062.

be harmed if it were to be treated as if subject to regulations of the Food and Drug Administration (FDA).

Accordingly, the Secretary of Defense approached the Secretary of Health Education and Welfare (HEW), and they agreed that, at least as regards the clinical use of investigational new drugs in military medical research,[4] the military would have primary responsibility. This became the basis for DOD *Instruction* No. 5030.29, dated May 12, 1964, on the subject: "Investigational Use of Drugs by the Department of Defense."

The DOD *Instruction* is applicable "to all DOD components and their contractors or grantees engaged in the investigational use of drugs." Moreover, the DOD assumed "full responsibility for the protection of humans involved in research under its sponsorship whether this involves investigational drugs or other hazards."

After describing, in general terms, procedures to be implemented by the military departments, the *Instruction* provides for information reports to HEW, and adds that "when the Department of Defense performs clinical tests upon new drugs being sponsored by the pharmaceutical industry, the ordinary claim for exemption (Form 1571 of the Investigational Drug Regulations) will be filed with the FDA."

This Instruction has been implemented by the Army in *Army Regulations* No. 40-7, dated November 13, 1964, on the subject: "Clinical Use of Investigational Drugs." The regulations provide, in general, as follows:

a. The clinical use of an investigational drug under the auspices of the Department of the Army requires written approval of the Army Surgeon General. Procedurally, each potential clinical investigator of an investigational drug for the Army, whether he be a government employee, a grantee or the employee of an Army contractor, must send a statement giving his own background and justification for the study to the Army Investigational Drug Review Board (AIDRB), a board composed of officers professionally qualified to

[4] There were some good legal arguments to support this. In the first place the military does not ship drugs in interstate *commerce,* so it is arguable that the law does not apply to drugs shipped by the military. Furthermore, the FDA forms relating to Investigational New Drugs did not quite fit "in house" situations sponsored by the military. See Forms FD 1571 and 1573, particularly. (21 CFR 130.3, FOOD DRUG COSMETIC LAW REPORTER ¶ 71,303).

consider drugs and research plans. The investigator's statement[5] must be in the following form:

I. Background Data.

A. Name of investigator.

B. Date of request.

C. Name or other clear identification of drug.

D. Name of manufacturer or other source of drug.

E. Qualifications of investigator in detail or by reference to details already on file in Army records.

F. Name and address of facility or facilities where investigations will be conducted.

G. All known relevant information about past use or pertinent reference thereto available to both the investigator and the drug supplier, including all preclinical data, and all other information justifying the clinical investigation (that is, the safety and rationale of the proposed study).

II. Plan and Conduct of Proposed Clinical Investigation.

A. Specific purpose and military need for or urgency of proposed clinical investigation.

B. Approximate number of subjects, their age, sex, condition, and other pertinent information relevant to the conditions of the investigation.

C. Number of subjects to be employed as controls (if any) and same information as in B above for such controls.

D. An outline of the phases of the investigation already on file in Army records. This outline may include reasonable alternates and variations, and will be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.

E. Description or copies of forms used to record data.

b. If the drug involves a classified investigation or is to be studied by the Army under the sponsorship of a member of the pharmaceutical industry, a Form FD 1571, FDA's usual form of claim for exemption, also will be completed and forwarded.

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[5] Compare with Form FD 1573 in 21 CFR 130.3, FOOD DRUG COSMETIC LAW REPORTER ¶ 71,303.

c. The AIDRB will either approve or reject the proposal and, if it approves, will send it on to the Surgeon General for his approval or rejection. The Surgeon General or the AIDRB may withhold approval to study an investigational drug clinically if it is determined:

1. That there is substantial evidence to show the drug to be too dangerous for use for the purposes and in the manner for which it is proposed for investigational use.
2. That the manufacturing methods are inadequate to maintain appropriate standards of quality needed to assure safety and give significance to the clinical investigation of the drug.
3. That the overall plan for clinical investigation does not appear reasonable or otherwise worthy of support.

d. In an emergency situation, the Surgeon General may approve the short term use of an investigational drug that is being sponsored by a pharmaceutical firm on an individual patient in a military facility without the need for an investigator's statement, if a military hospital commander requests this approval. The request is required, however, to include at least the following information: the patient's name, the diagnosis, the name and quantity of the drug proposed for use, the medical officer responsible for the patient, and the nature of the medical emergency. When emergency use is approved, the responsible investigator will be required to furnish completed copies of Form FD 1573 (Statement of Investigator) both to the pharmaceutical firm and to the Surgeon General.

e. In the case of unclassified clinical studies of investigational drugs, the Surgeon General is required to transmit to FDA copies of the investigator's statement, and signed copies of the AIDRB's and the Surgeon General's evaluation and approvals. These papers need not be submitted to FDA in the case of classified investigations or where the investigational drug is being sponsored by the pharmaceutical industry, but, instead, the Form FD 1571 is to be forwarded to FDA.

f. Each investigator must keep a record of clinical investigation which will include, minimally, a list of patients receiving the drug, the name, lot number, date and quantity of drug prescribed, case his-

tories, and the details of clinical observations, tests and laboratory procedures carried out on each subject before, during and after administration of the drug in question.

g. In addition, the following records will be kept by the Army facility concerned, if the investigational drug is being used in such a facility, or will be kept by or for the investigator, when the drug is used under an Army grant or contract outside of an Army facility:

1. The name of the drug.
2. The manufacturer, or other source of the drug.
3. The amount and date received.
4. The expiration date, if any.
5. The lot or control number.
6. The date of authority to use.
7. The names of individuals authorized to prescribe the drug.
8. The name of the prescribing physician or dentist.
9. The date on which use of the drug is terminated, if applicable.
10. The date on which use of the drug is approved for general use as a safe and efficacious drug, if this occurs during the course of an investigation.

h. Progress reports must be submitted to the AIDRB at least once a year. Final reports also must be furnished. In addition, unusual or important observations of adverse effects must be reported promptly, and alarming effects must be reported immediately. Reports of adverse effects are to be forwarded to the FDA when received.

i. The regulations also contain cautions to investigators to assure the avoidance of harm to persons who will be subjects of use of the drugs. Thus, the investigator must make certain that the drug is administered to subjects only under his personal supervision or under the supervision of other qualified persons. The investigator also must be sure that he has an informed consent from each subject, except where this would not be feasible or, in the professional judgment of the investigator, would be contrary to the best interest of the subjects. In some instances, the use of volunteer subjects is further restricted by a requirement for specific approval from the Surgeon General; this

would be the case where use of the drug on the individual subject would not really be for his personal benefit, that is, the administration of the drug would not be expected to result in the diagnosis, mitigation, treatment, cure or prevention of disease or injury in the individual.[6]

The regulations also set out, at length, a clause required to be included in Army research and development contracts which involve the clinical testing of investigational drugs. This clause includes most of the requirements of the regulations. On the other hand, there is no specific clause to be included in grants—the regulations merely provide that grants will include clauses which require the grantee to submit an investigator's statement, keep necessary records, provide necessary reports, and conform to conditions as to supervision of the testing and obtaining consents.[7]

It will be noted that the understanding between DOD and HEW, the DOD *Instructions* and *Army Regulations* provide an exceptional procedure only as regards the clinical investigation of new drugs under Department of the Army auspices. They do not cover New Drug Applications (NDA's), or exempt Army sponsored investigational new drugs from provisions relating to NDA's.[8] On the contrary, it would appear that even an Army sponsored new drug would require approval by the FDA[9] before it could be shipped in interstate *commerce,* even if shipped to the Army. **[The End]**

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[6] See ¶ 6, *Army Regulations* 70-25 and Levin, "Malpractice and Assault and the Drug Amendments of 1962," *Military Medicine*, November, 1964.

[7] It is interesting to speculate whether, in the event of negligent injury to a subject, the government might not be joined as a party under the Federal Tort Claims Act (28 U.S.C. 2671 and following). This possibility is not without foundation in view of the statement in DOD *Instruction* 5030.29, May 12, 1964, subject: "Investigational Use of Drugs by the Department of Defense" that "The Department of Defense assumes full responsibility for the protection of humans involved in research under its sponsorship whether this involves investigational drugs or other hazards." It would, moreover, be difficult for the government to avoid liability under the Federal Tort Claims Act if damage resulting from an Army sponsored drug could be attributed to failure of the Army to have performed required functions, such as the forwarding of reports of side effects to FDA.

[8] 21 U.S.C. 355a, FOOD DRUG COSMETIC LAW REPORTER ¶ 71,051.

[9] It is by no means certain that the Army would be barred from shipping a new drug not subject to an approved NDA across state lines. Such a shipment would not be one in interstate commerce, particularly if the drug had been manufactured by the Army in its own facility.

Food Law in the Europe of Tomorrow

By PAUL M. KARL

Dr. Karl, of Hamburg, Reports on This International Symposium Held at Brussels University on November 13, 1964.

IT IS NOT ONLY THE ESTABLISHMENT OF THE COMMON MARKET (European Economic Community, EEC) but also the manifest gradual integration of the all-European economy including the European Free Trade Area, which makes the need for the harmonization of European food law ever more urgent. In the Common Market this harmonization of laws will be brought about according to the Articles of the Treaty of Rome of March 1957, in order to abolish, in addition to existing customs barriers, the often considerably greater trade obstacles resulting from different food laws. However, all the European countries have worked for many years towards the harmonization of laws in this field. The work of the Codex Alimentarius Europaeus (which resulted from the initiative of the former Austrian Federal Minister Ing. Chem. PhM. Dr. jur. Hans Frenzel) has been continued by the Joint FAO/WHO Codex Alimentarius Commission which at its second plenary session in September/October 1964 in Geneva, upon motion by several European states, set up a European Group which enjoys a certain independence.

Europe is faced today with the problem of vast discrepancies, even of flat contradictions, in the various national food laws. This divergency of laws becomes apparent not only in certain provisions related to products but also in numerous questions of the legal system and certain fundamental definitions. As a matter of fact, these disparate laws are in direct opposition to the main goal of the Common Market, which is the broadening and integration of the markets in Europe. They also distort the role of competition on the international food market. For example, the production or sale of a particular biscuit or jam is authorized in one country and forbidden in another, and this for questions of components or their amount in a given product,

which, from a scientific point of view, are unanimously accepted as safe for human consumption. Frequently, reasons other than food law principles (namely historical, agricultural and political interests) have hindered the legal acceptance of such components.

Symposium Held on European Food Law Problems

In order to discuss the fundamental problems to be solved in bringing about the indispensable harmonization of laws and to throw light on them from all angles, the Institute for European Studies of the Free University of Brussels, Belgium, held a full day discussion on November 13, 1964, under the title "Food Law in the Europe of Tomorrow," in which more than two hundred profiled representatives of the EEC Commission, national ministries, industry, consumers, food control officials, as well as representatives of science and technology participated.

The purpose of the symposium was to show the various legal techniques on which food laws are based in the EEC countries, to demonstrate the attitude of different groups towards these techniques, and to emphasize the problems created for Europe's integration by divergent legislation and the necessity of arriving at an adequate harmonization in this field as soon as possible.

Prominent speakers guaranteed an outstanding program:

Morning Session

Welcoming address by Professor N. J. Ganshof van der Meersch, President of the Institute for European Studies, followed by an introduction by Professor E. J. Bigwood, President of the Symposium, Hon. Rector of the Free University of Brussels, Member of the Belgian High Council of Hygiene.

General survey and groundwork paper "Basic Principles of Food Laws—Divergencies and Harmonization Problems" by Ing. Chem. PhM. Dr. jur. Hans Frenzel, Vienna, former Austrian Federal Minister, President of the Austrian Codex Alimentarius Commission.

Afternoon Session

A panel discussion of the attitude of various groups directly interested in food laws by the following personalities:

Food Industry: M. G. Jumel, France, Secretary General of the French Federation of Preserved Food Industries.

Consumers: Dr. I. Landegrebe-Wolff, Germany, Division Head of the German Association of Nutrition.

Public Health: Professor E. J. Bigwood, Belgium.

Food Technology: Professor D'Ambrosio, Italy, former government official, food technology expert.

Government: Dr. M. J. L. Dols, Netherlands, Council Adviser in General Services, Dutch Ministry of Agriculture and Fisheries, Chairman of the Council of Nutrition and Chairman of the Advisory Committee Food Law.

A closing paper "Efforts Towards Harmonization—The Work of the EEC Commission" was presented by Dr. H. Steiger, Head of the Division, Harmonization of Legislation, Directorate General Agriculture, EEC Commission, and Mr. M. Ventura, Division Harmonization of the Legislation, Directorate General Agriculture, EEC Commission.

This was followed by an open discussion and conclusion by Professor E. J. Bigwood.

Legal Possibilities of European Food Law

With his general paper on the legal systematic possibilities of establishing a food law and his commentary in which he made legal comparisons, Dr. Frenzel set the frame of the discussion. Dr. Frenzel, who is often called the "father of the European Food Codex," began his paper by stating that each well-developed food law in Europe and many outer-European food laws firmly establish in a general skeleton law the legal goals, that is, the protection of the consumer against damage to health and misleading claims. Both principles which may simply be described by the terms "health" and "honesty" can be traced back to the 3500 year old culture of the Hittites who on the present territory of the Turkish Republic had established a highly developed state. These terms can be found in the European legal history in a more or less similar form to the present time.

These foundation pillars of the food law must remain unassailable parts of legislation, similar to the constitution of a state in miniature. However, in general they are not practicable and must be interpreted by concrete individual provisions related to individual products for the different branches of food manufacturing. It must be the concern of each system of food laws to phrase the individual interpreting provisions as flexibly as possible in fact, and above all, in form, in order to guarantee a quick and smooth adjustment to the progress made in science and technology as well as to the constantly changing eating habits and consumer expectations.

Dr. Frenzel suggested, with great emphasis, that problems of interpretation could be solved through the use of a food manual* with which his home country, Austria, had had the best experience for decades. He considers this to be a desirable solution not only for the national area but also for the whole territory of the Common Market.

* *Codex Alimentarius.*

Such a food manual is a collection of product-related objectivated expertises which outline the principles of assessing the quality of particular foodstuffs or groups of foodstuffs. In their legal character they resemble the Food Standards of the United States Food and Drug Administration (FDA). However, in their form they do not have the effect of an act or even an ordinance. They constitute a written, justified and reasonable consumer expectation and the expression of fair trade usage, and in this, the court is given a standard by which it may proceed to an appropriate and well-founded interpretation of basic food law provisions in individual cases.

The individual chapters of the food manual are worked out by small bodies of independent experts, which guarantee that considerations which are irrelevant from the food law point of view—above all agricultural and economic aspects—are not taken into account. Dr. Frenzel defined the food manual as a kind of voluntary agreement concluded by the interested industries and the consumers, which merely states what is good for eating and what is not good for eating. It may be added that state authority plays the role of an arbiter.

From describing the external form of food law regulation, Dr. Frenzel moved to the systematology of the food law in its basic sense.

Two Methods of Establishing Legal Systems

There are essentially two flatly contradictory methods of setting up a legal system, not only for food law but for any law; these are by the principle of prohibition or by the principle of abuse. Naturally, a number of mixed forms from both systems can be conceived.

According to the principle of prohibition basically everything is forbidden which is not expressly permitted. The burden of proof is on the one subjected to the law who must in each case furnish the proof that a certain not expressly permitted act is unobjectionable and therefore to be included in the list of acts which are expressly permitted.

According to the principle of abuse basically everything is permitted which is not expressly forbidden. The burden of proof is on the state authority which has to furnish the proof in each case that an act which is not expressly forbidden constitutes an "abuse" and must for this reason be prohibited.

Dr. Frenzel pointed out that both systems have their advantages and disadvantages, but that the principle of prohibition is given preference in all those countries where the state rigorously intervenes in the economic life, while the principle of abuse will prevail in countries enjoying greater liberty.

In reality, in the domain of food product law, there are two main groups which can be aligned according to one or the other of these principles: they are the additives and the processing methods, and it is not compulsory to deal with these two groups on the basis of the same principle.

Thus, if one takes as an example the case of the additives, the legislator may, following the principle of prohibition, include in a positive list all additives the use of which involves no danger to health, thus authorizing their utilization in the manufacture of food products. The manufacturer of food products sees his choice limited to the products shown on the positive list, or he must show, by proving the innocuousness of an additive not yet shown on this list, that this additive should be placed on the list which explicitly enumerates the authorized additives. On the other hand, a regulation based on the principle of abuse leads to the composition of a negative list which must comprise all the additives harmful to health. The manufacturer of food products is thus obliged, at his own responsibility, to determine which additives are not expressly forbidden and consequently authorized, which do not present any danger for health, utilization of which does not constitute an abuse and which are most appropriate for his particular product.

While the principle of abuse already forms a practical frame for the creation of a legal system by the simple establishment of a negative list, the principle of prohibition does not supply a similar framework.

The principle of prohibition, in its fundamental, theoretical form, first forbids everything and only authorizes things expressly permitted. If one were to apply the principle in this form, one should immediately and obligatorily forbid by formal prohibition, the use of all products used in the manufacturing of food products, including the basic foods, such as milk, fats, flour and sugar, with the ineluctable consequence of having to authorize expressly these elementary foods. A similar procedure would not, in fact, have any common relation to reality and would be absolutely theoretical in character. This is why

—at least up to now—even legislators haunted by the desire to achieve perfection, have sought solutions which could be practically applied, which under the principle of prohibition would only have the form of a general limitation of the constitutive elements of food products for which an authorization is required. It is for this reason that generally not all staple materials and components used in the manufacture of food products have been submitted to the principle of prohibition, but only the additives, as they are called (that is to say the additional products) or, as in the case of the German Federal Republic, for instance, what has been called, according to a much contested definition, the "foreign matters."

The detailed determination of additives subject to authorization can be made in a positive or in a negative way. That is to say, one can define the group of additives calling for authorization itself, or, one can establish, following general principles, what substances are not to be considered as additives and for this reason are not subject to authorization. From the practical point of view, this distinction does not play an important role, especially since by reversing the definition, it is possible to establish a delimitation of the field which has not been the object of a precise definition.

But one should not be too hasty in drawing conclusions whose falsity is immediately obvious and following which the definition of additives would have to be established by opposition to the concept of food product. This erroneous conclusion is not possible for the simple reason that there is no opposition between food product and additives, but the term "food products" includes the additives whose use is allowed.

Generally speaking, one means by "food products" all substances which are intended for eating or drinking, either alone or combined with other food substances, including the additives. Still, generally speaking, medical products are excepted because their destination differs from that of food products.

In numerous food law systems one also finds incorporated in the idea of food products other materials such as cosmetics, utensils and objects utilized in connection with food products, clothing, tobacco products, and other similar substances.

Adjuvants and Additives

Apart from the additives in the proper sense of the word, one also finds in many food law systems "adjuvants." Additives are utilized in association with a mechanical or chemical process with the food product involved; in other words, to form a combination or a mixture with the said product, which implies that the additive must remain incorporated in the product to which it has been added. The same criteria are not valid for the "adjuvants." These "adjuvants," often designated as "technical or technological adjuvants," are only utilized in the course of manufacturing to facilitate or accelerate the manufacturing process, or else to render possible the realization or the implementation of a process or of certain phases of the process. Examples are the filtering products and those used for clarification, the products utilized to prevent acidification, fullers' earth, and also catalysts such as nickel, petroleum ethers utilized for the extraction of fatty matters contained in raw materials of vegetal origin, and many others of a similar nature.

Essentially, the criterion for defining "adjuvants" is that they are never intended for consumption. They are not destined to remain in the finished product; they are used only to be eliminated completely or, as it is said in the German food law "until there only remains a residue which is technically unavoidable" after they have fulfilled their role. The maximum quantity of "technically unavoidable residue" may be specified by a particular regulation in each case.

If one decides to adopt the concept of adjuvants, the best possible way to do so is to resort to the principle of prohibition, in order to exclude them from the general prohibition of the properly called additives.

Adjuvants do not then require an express authorization and the incorporation in corresponding positive lists, but they can be utilized freely—in as much as their use is not harmful to health. But, if they are not excluded from the principle of prohibition, that is to say, if they are not systematically separated from the properly called additives, there is really no need to make a separate definition of them.

One finds again in a similar form, in the field of manufacturing processes and methods, the same problems as the one discussed above. While, with regard to additives, it is in reality a question of making a preparation by a mechanical mixing of matters or by a chemical

combination, the main aim with regard to processing methods, is to obtain a physical modification of the food products concerned.

This is why the majority of the food law systems are governed, in this sector, by the principle of abuse. The pertinent negative list is limited nearly exclusively to the prohibition of the use of ionization and ultraviolet rays, with occasional exceptions.

American legislation concerning food products has adapted a very simple method; it includes the use of radiation in the domain of additives. This seems quite justifiable and makes superfluous a systematic classification of processing methods, at least at the present stage of technique.

Comparison of National Food Laws

After having given this survey of legal theory, Dr. Frenzel compared the national food laws, starting from the food law of the United States and confining himself to the sector of additives. He came to the conclusion that the system in the United States—above all the Food Additive Amendment of 1958, which is cited as a model by the followers of the principle of prohibition in Europe—was by no means a pure principle of prohibition but constituted a special kind of mixed form. The GRAS lists (substances "generally recognized as safe") worked out by the FDA for additives are by no means complete but leave to every producer—at least theoretically—the choice of using a certain substance in the manufacture of foods which he believes to be "generally recognized as safe." That such action runs the risk of committing the offense of food adulteration in the event that the FDA is of a different opinion, does not change the fact that these are typical characteristics in the principle of abuse. Also under a proper principle of abuse all manufacturers are exposed to the danger of committing an abuse and thus violating the principles of food law.

On the other hand, any manufacturer can learn the opinion of the FDA about a certain additive by means of an "informal petition" to achieve indirectly a kind of authorization or sanction, a possibility which in its effect resembles the principle of prohibition, so that in this case one is fully justified to speak of a genuine mixed form of the system.

Recently, Belgium passed from the principle of abuse to that of prohibition, among other things, referring to the United States food

law. Subjected to the principle of prohibition, that is, defined as additives, are all those substances which are not utilized because of their nutritive value or their natural content of vitamins, aromatic or flavouring components. Criteria for the definition of an additive are consequently the lack of nutritive value and the absence of naturalness of a substance, "natural" probably being the same as "occurring in nature."

An interesting aspect of the Belgian law is the distinction it makes between additives in the genuine sense (intended additives) and adjuvants (technological additives) or indirect or not genuine additives. Both groups are subject to the principle of prohibition and also to the same procedure of admission, so the distinction is of hardly any legal significance.

As Dr. Frenzel stressed, the German food law version of 1958 certainly did not remain without any influence on the Belgian law. The Federal Republic of Germany also adopted in 1958, the principle of prohibition for additives by the so-called "little reform," replacing the principle of abuse which prevailed until that time. Here, too, the definition of additives—they are called "foreign matters"—is on the one hand, oriented towards the lack of nutritive value, and on the other, towards the lack of naturalness, whereby, these synthetic substances are compared to the generally permitted natural substances which in their chemical structure are identical with these synthetics. In Germany, too, distinction is made between "genuine additives" and "not genuine additives" (so-called technical adjuvants), the latter including all those "substances which are used in the production, manufacture and processing of foods but not destined for consumption" and thus may be contained in ready-to-eat foods at the most in "technically unavoidable" maximum quantities. As a consequence, contrary to Belgium's law, "technical adjuvants" were exempted from the principle of prohibition. Their utilization is thus not conditioned upon special authorization. It is, however, limited by the generally codified principles of "health" and "honesty."

Recently (1963), Italy also abandoned the principle of abuse and introduced, at least partly, the principle of prohibition for additives (additivi). These are defined as elements without nutritive value and as substances which are not utilized for the purpose of nutrition but for their typical additive functions which are mentioned in detail. But

not all substances falling under the definition of additives were subjected to the principle of prohibition. This principle was introduced for a number of easily recordable substances or groups of substances in order to facilitate the interpretation of the food law and to arrive at greater safety in applying the law.

This Italian solution, in the view of Dr. Frenzel, may have been decisively influenced by the Swiss food law version of 1936 which is also based on the principle of prohibition and equally abandons the general definition of additives in favour of the more practical enumeration of individual facts.

Finally, Dr. Frenzel pointed out that the French and the Dutch food laws also contain distinct ideas and elements of the principle of prohibition.

In his mother country Austria, Dr. Frenzel said, the principle of abuse continues to prevail and no reason can be seen for abandoning it in the near future. In Germany, too, practical experience with the principle of prohibition was not the best. Furthermore, voices had been heard which demanded a return to the principle of abuse, which should not be feared if it leads to a food law guaranteeing a better practical application.

The most important difference between the systems is that of reversing the burden of proof as to the innocuousness of a certain additive. According to the principle of prohibition, the burden of proof is on the manufacturer, and a free and responsible decision on the part of the producers is made more difficult or even impossible. The development of new and improved foods, the utilization of modern raw materials and scientific knowledge often fails because there is no possibility of putting these innovations to the market test since each new fact requires the explicit authorization by the principle of prohibition. As a rule, this aim cannot be achieved without previously revealing pertinent trade secrets, which in turn often kills the initiative on the part of the producers. It should also be kept in mind what the manifold consumer wishes and that new habits of eating require new additives.

The afternoon session began with a panel discussion in which the main groups interested in food law were given opportunity to express their opinions on the problem outlined.

Food Industry Representative Speaks

Speaking for the food industries, Mr. G. Jumel, Secretary General of the French Confederation of the Preserved Food Industries, pleaded in favor of legal harmonization as an economic necessity for rationalized production. This harmonization is needed to eliminate the barriers which divide Europe, to ensure balanced trade and fair competition. It is particularly necessary in the food industry because of many divergencies in the conception and application of food laws in the member states of the Common Market. Mr. Jumel proposed a flexible and progressive harmonization, horizontal (general problems, such as additives, questions of plant-hygiene) and vertical (regulations for specific foodstuffs such as chocolate, preserved foods, jams) with a priority for products subject to large scale inter-community trade. Some general principles should deal with a basic directive, namely sampling, labelling, language of importing country, name and specification useful to consumers' full information, indication of producer or brand, indication of country of origin, national food control and penalties.

Mr. Jumel agreed with a pragmatic approach to harmonization, but insisted that legislation in any form whatsoever should be based on the three principles of health, honesty and progress, fully realizing that the ultimate objective of all harmonization work is the creation of a true food law.

Consumers' Representative's Opinion

Frau Dr. Irmgard Landgrebe-Wolff, Departmental Director of the Deutsche Gesellschaft für Ernährung, spoke on behalf of the consumer. She, too, recognized the urgent necessity for the harmonization of food laws and for the free circulation of products. This harmonization, however, should not be achieved at the cost of lowering health standards. For this reason, she suggested that the authorities should stimulate a feeling of personal responsibility among those participating in the processing or handling of food products. Negligence among these people has sometimes ruined the results of a long series of efforts. Food laws concern goods which serve to maintain life, and which are at the same time subject to the instability of all life. To remain up-to-date, these regulations require cooperation on an equal footing between producers, the food industries, trade and

consumers. The firmest foundation for this cooperation is respect for human health, and mutual respect for the work of other people.

Public Health Service's View

The next speaker, Professor Bigwood, represented the Public Health Service. He said that before international regulations are set up, that is, while they are at the stage of preliminary studies, the Public Health Services should be better represented, and especially so in relation to agricultural delegations. Professor Bigwood cited as an example the excessive degree of tolerance practiced at present in connection with the antibiotic treatment of poultry and livestock, a tolerance which, in his opinion, was a source of danger to consumers' health. Generally, Professor Bigwood stressed that in the additive area, originally any additive was permitted, except those explicitly forbidden. Today, when the importance of additives in food is increasing, the common trend in various countries is to reshape the basic system and to provide that all additives are forbidden, except those explicitly authorized.

Professor Bigwood felt the definition of an additive should indicate that a food itself cannot be considered as an additive. If preserved peas contain sugars because the consumer prefers sweet peas, the sugars, although added, cannot be considered as additives. On the other hand, according to Professor Bigwood, certain nutritive elements, as for example vitamins, occurring in agricultural products have to be classified as additives if they are used in their pure isolated form. There is no international definition of the term additive presently, although on certain points agreement has been reached.

Many of the difficulties standing in the way of the harmonization of food laws arise from the fact that the national regulations to be harmonized are in themselves still in the course of development.

Food Technologist Calls for Unified Standards

Professor Angelo D'Ambrosio, the Italian expert on food technology, claimed that his profession aims not only at the realization of a rational production chain, apt to reduce production cost, but at a still improved production with regard to nutritional value and to micro-biological, chemical and organoleptic properties. He called for the unification of scientific standards as well as for the proportioning

of ingredients. What is authorized in one country should not be prohibited in another. To prove his point, he cited the paradox of the free sale in Italy of Danish cheese containing ingredients which are allowed in Denmark and forbidden for Italian cheese processers!

Dr. M. J. L. Dols, President of the Dutch Food Council and the Consultative Committee Food Law, Adviser to the Ministry of Agriculture and Fisheries, spoke mainly about the duties and responsibilities of the public services and the ministries responsible for food law enforcement. In the case of a regulatory system based on the principle of abuse with its negative list of forbidden substances, whenever there is prejudice suffered by the consumer, the responsibility falls on the producer. On the other hand, when the legal system is based on the principle of prohibition with positive lists of authorized ingredients (Dr. Dols is in favor of this latter system), the question is whether in all fairness the public authorities should not shoulder the responsibility for their own decisions and thus free the producer.

Present Achievements in Harmonization of Laws

Presented in the latter part of the afternoon was a paper by Dr. H. Steiger, Head of the Division "Harmonization of Laws" of the Directorate General Agriculture of the EEC Commission and by Mr. Ventura, an official in the same division, describing the actual efforts and practical achievements realized by the EEC Commission in food law harmonization up to now. They mentioned the various EEC directives already issued, concerning the harmonization of national regulations regarding the use of coloring matters and preserving agents. Furthermore, they reported on the present state of affairs regarding EEC directives on cocoa and chocolate, meat products, antioxidants and criteria of purity for preserving agents.

Until now the main efforts of harmonization within the EEC have been concentrated on the additive area. On the other hand, initial work has been started in 1964 in the following fields: flours and pasta products, food extracts and similar products, dairy products, oils and fats, fruit juices and soft drinks. On more general lines the study of a project regarding general questions of labelling and packaging of preserved foodstuffs has been continued. For 1965, Dr. Steiger and Mr. Ventura expected the beginning of harmonization efforts in other sectors including emulsifiers and stabilizers, wrapping material, sugars (dextrose and glucose syrup), wines and instant coffee.

The harmonization procedure is rather lengthy, said Mr. Ventura, and starts normally with the drafting of an initial working document on the specific area in question. This is compiled by the officials of the Directorate General Agriculture, Division "Harmonization of Laws," or submitted by the EEC Industry Association concerned. A specialized sub-group and the coordinating Working Group Food Law, both consisting of government experts under the chairmanship of EEC officials, and if necessary, with the help of the Scientific Committee, draft the proposal for a directive. It is then presented to the UNICE, the EEC umbrella organization of the entire industry, and the EEC Consumer Association for their comments.

The EEC Commission adopts the draft after approval by the Directorates General Inner Market and Competition, and proposes it to the EEC Council of Ministers. As a rule, the Council asks the advice of the European Parliament and the Economic and Social Committee. The final stages of this procedure consist of the Council's official adoption, notification to the member states and publication in the official gazette of the Communities.

Dr. Steiger and Mr. Ventura at least partly refuted the criticism frequently uttered about the working methods and their results. One could but appreciate the result achieved so far in spite of the limited number of personnel entrusted with it and the manifold problems. Also the pragmatic working method could not be criticized because doctrination would only lead to further complications. The simultaneous drafting of directives of a general kind (horizontal) and directives for special products (vertical) makes it possible to enrich both areas with the experience gained in each single case. The working out of a skeleton food law for the EEC is considered to be necessary more as the ultimate aim, rather than as a direct task of the harmonization of the food law. Also, for practical reasons, an approach towards the harmonization of methods of analysis and the coordination of food control can only be made at a later date.

Dr. Steiger and Mr. Ventura moreover opposed the view that the future EEC food law should be governed by the principle of prohibition, it should rather be investigated in each case whether this or the contrary and more liberal principle of abuse should be given preference.

Finally, it was pointed out that in some cases one may at least question whether it is really necessary to provide for true legal standards or whether it would not be better to limit oneself to a product-

related interpretation of the basic food law principles of "health" and "honesty" in the form of expertises in a food manual. Even legal standards could, it was said, be effective only if one succeeded in methodically educating the interested circles.

Summary of Results

After an open discussion, Professor Bigwood, President of the Symposium, summarized the results. He underlined first that the state of affairs of the food law in the individual European countries was far from an ideal situation. Two fundamental formal ways towards a future European food law had been indicated: on the one hand, that of a European food manual and on the other hand, that of a true Community law which could at best, for the time being, exist parallel to the national law, but which should be exclusively binding the moment the political integration of Europe had been reached.

Concerning the system of food law, according to Professor Bigwood, there was a trend from the principle of abuse towards that of prohibition, which in some countries was already realized. Also, there is a development towards use of a food manual or to mixed forms of both systems.

This trend towards the principle of prohibition may, Professor Bigwood warned, involve serious obstacles to progress in science and technology on the food sector, and should, therefore, be carefully watched.

The discussions have indicated the intolerable confusion by which definitions as important as those of the "additives" are governed. A common definition and an international vocabulary are indispensable.

For the study of questions of food law, Professor Bigwood suggested the creation of an international body in which not only government experts but also scientists, technologists of the food industry and lawyers participate. There is no objection to calling in more consumers, provided that they organize themselves and are sufficiently informed about the problems in question. The establishment of a European Food and Drug Administration could solve many problems.

Finally, Professor Bigwood expressed the hope that this symposium was only a first step which will be followed by further meetings of a similar kind. The best way to thank the Institute for European Studies for its initiative would be for interested circles to continue to cooperate in its studies. **[The End]**

Planning in the Food and Drug Administration for Regulation of Prescription Drug Advertising

By JOSEPH F. SADUSK, JR., M.D.

Dr. Sadusk, Medical Director of the Food and Drug Administration, Presented This Paper at the Pharmaceutical Advertising Club Meeting on February 11, 1965, in New York City.

THE IMPORTANCE OF THE ADVERTISING INDUSTRY in the economic development of our country is well-recognized and more specifically, in the development of use of new and better drugs. Practicing physicians receive a substantial part of their education concerning drugs through the medium of prescription drug advertising. This, indeed, is basic and underlies the federal law which places responsibility on the advertising industry to present factual and undistorted information to the physician. Furthermore, the prescription drug advertising provision of the law actually is a recognition of the importance of such advertising in the entire area of medical care in the United States.

Let us first establish an important point, namely, that Congress has divided authority for surveillance of medical advertising between two agencies of the government: The Food and Drug Administration (FDA) and the Federal Trade Commission (FTC). The FDA has been made responsible for prescription drug advertising, and the FTC continues to be responsible for over-the-counter drug advertising. Consequently, my discussion with you today will be limited to prescription drug advertising.

Development of Present Drug Laws

Let us very briefly review the development of the present law dealing with drugs. In 1906, over half a century ago, Congress

passed the first Pure Food and Drug Act. Although it was inadequate by today's standards, this law was of landmark importance.

As the years went along, inadequacies were recognized and certain amendments were enacted in the public interest. For example, a 1912 amendment for the first time made it possible for the government to take action on false therapeutic claims for drugs. Unfortunately, it was largely unenforceable because the government had to prove that such claims were made with fraudulent intent. Another fundamental change came in the 1930's when the public was aroused as a result of the marketing of sulfanilamide in liquid form by using diethylene glycol as a dissolving agent for the drug, causing the death of over 100 people before the product could be removed from the market. Congress took prompt action and provided appropriate safeguards in the Federal Food, Drug and Cosmetic Act of 1938. Provisions in the "new drug" section of this law required a manufacturer to not only test a new drug for safety, but also to report his results to the FDA before the drug could be marketed.

In 1951 Congress enacted legislation resulting in the Humphrey-Durham Amendment which specifically placed drugs in two classes:

1. Those drugs safe for use without medical supervision and for which adequate directions for use could be written for the layman and consequently could be sold over the counter; and

2. Those drugs which were not safe for unsupervised use and therefore could be sold only upon prescription of a physician.

Another major step which leads us to the present law came about in 1962 as a result of the passage of the Kefauver-Harris Drug Amendments. These amendments provided a number of additional safeguards over drugs, including the following:

1. Effectiveness as well as safety of a drug had to be demonstrated;

2. The distribution and use of investigational drugs were adequately controlled;

3. Improved procedures for approving and withdrawing approval of new drug applications were outlined;

4. Drugs were required to be produced in accordance with good manufacturing practice;

5. Provisions were made for record keeping and reporting by the manufacturer of experience with approved drugs so that an ineffective or unsafe drug could be removed from the market and its directions for use could be revised; and

6. Prescription drug advertising was placed under control.

These new safeguards were implemented as quickly as the resources of the FDA permitted. During the latter part of fiscal year 1964 and through fiscal 1965, a beginning was made in monitoring drug advertising in order to carry out the intent of Congress. In fiscal year 1966, which begins on July 1, 1965, our anticipated resources should enable us to meet our statutory responsibilities in substantial fashion.

During the past year, a minimum staff in our Bureau of Medicine has surveyed the situation and has challenged and secured correction of a number of flagrant violations of good medical advertising principles.

On November 3, 1964, Commissioner Larrick announced an FDA-wide plan for the monitoring of prescription drug advertising. His directive defined the agency's responsibilities for medical advertising, set up basic operating guidelines for the review of such advertising, and assigned program responsibilities to the various operating bureaus of the Food and Drug Administration. Objectives were laid out for the present fiscal year, and on a five-year planning basis. During the current year a start was made with corrective measures against those advertisements in urgent need of attention; and by the end of this current fiscal year 1965, June 1965, the bureaus were directed to have prescription drug advertising programs functioning on a routine, though minimal, basis.

Over the next five years, it will be our goal to attempt to completely eliminate prescription drug advertising containing imminent and pressing health hazards and to have a fully developed industry educational program functioning with maximum efficiency. Our intent for the control of prescription drug advertising, if the cooperation of industry can be obtained, will be along the lines of basic FDA philosophy, namely, to secure voluntary compliance and self regulation rather than to force regulatory compliance. It is realized that periodic adjustments will have to be made in our planning to reflect changes dictated by experience.

Control of Medical Advertising

The task for control of medical advertising has been assigned to four of the operating bureaus of the FDA: the Bureau of Medicine, the Bureau of Education and Voluntary Compliance, the Bureau of Scientific Standards and Evaluation and the Bureau of Regulatory Compliance.

The Bureau of Medicine, through its Medical Advertising Branch, will be responsible for the following objectives:

1. Monitoring of journal advertising for three major classes of therapeutic agents: new drugs, not-new drugs, and antibiotic agents;

2. Searching out or receiving advertisements which are most violative along the guidelines established and documenting the nature of the violation; and

3. Forwarding comments on the advertisment in question, with recommendations to the Bureau of Regulatory Compliance and providing medical assistance to that bureau until the regulatory action of the FDA is completed.

The Bureau of Scientific Standards and Evaluation, through its Division of Antibiotics, will be responsible for:

1. Furnishing scientific evaluation to the Bureau of Medicine in matters concerning bacteriology and chemistry, or related disciplines, for antibiotic drug advertising; and

2. Recommending to the Commissioner a course of action involving certification services for improper advertising of antibiotics.

The Bureau of Education and Voluntary Compliance will be responsible for:

1. Continuing to answer, through the Advisory Opinions Branch, specific questions coming from industry regarding prescription drug advertising; and

2. Determining through these questions and through consultation with the Bureau of Medicine, what items and questions are of such general interest that they warrant a formal educational approach either to pharmaceutical companies or advertising agencies, or both.

The Bureau of Regulatory Compliance will be responsible for:

1. Advising the district offices of the FDA of their responsibilities pertaining to the surveillance of drug advertising through the establishment inspection process and other means; and

2. Preparation of guidelines for regulatory action where this is necessary.

Until full resources can be developed within the FDA, priority will be given to those cases which present a serious and dangerous health hazard to the consumer. This does not mean that we shall completely disregard claims which may not involve serious danger to patient health or life, but rather that we shall maintain a balanced program in consonance with our resources in order to accomplish the greatest possible enhancement of the quality and truthfulness on prescription drugs conveyed to the practicing physician by the pharmaceutical industry.

Operating Guidelines for Regulation

What are going to be our operating guidelines? Our present plans call for us to monitor and regulate advertising along the following lines:

1. Prescription drug advertising and other descriptive printed matter will be required to show the established (generic) name in type at least half as large as that used for the brand name. The quantitative formula of the drug to the extent needed is required on the label. A true and non-misleading brief summary of information as to adverse side effects, contraindications and effectiveness of the drug will have to be included in the advertisement for the guidance of physicians; and

2. Careful inspection will be made of the advertisement along the lines of having the advertisement present a fair balance between the information on effectiveness and that on side effects and contraindications. Examples of what we shall consider as false and misleading information will be along the following lines:

An extention or distortion of the claims for usefulness beyond what is approved for the final printed labeling of the drug; selection of poor quality research papers which make statements favorable to the product while ignoring contrary evidence from scientific papers of higher quality; quoting out of context of a seemingly favorable statement but omitting unpleasing data from the same article; quoting from an authoritative source but failing to quote from other differing experts in that field—with the result that properly balanced views are not given; featuring data from papers that report no side effects but failing to quote from other authors who do; and continuing to run advertisements which are constructed from data previously valid but rendered obsolete or false by newer research.

It should be noted that the errors presented above will generally appear in relation to positive claims or omissions concerning the product, and claims which may or may not involve danger to a patient's health or life but in which the selling message can seriously mislead as to the proper place of the drug or antibiotic in the total spectrum of products available to meet a specific disease situation.

With regard to the other types of advertising which may present a potential danger to the patient in varying degrees we might cite the following examples:

Omission of some of the pertinent side effects, precautions or contraindications; improper statements concerning the effectiveness of indications for the drug or antibiotic; and omission of some of the information on dosage form, ingredients, or directions for use where required.

Now, it must be realized that three men are basically involved in the development of advertising for a drug: the advertising director of the pharmaceutical company whose overall knowledge leads management to commit funds for these specific advertising campaigns, the physician in the pharmaceutical company who best knows the characteristics of the drug and who approves the message the advertisement conveys, and the agency copywriter. It has been said that there are about 60 large advertisers who spend $750,000,000 on promotional activities. If so, this means that much of our task should not be too difficult since it should be accomplished through working with a relatively small number of persons.

Let us hope that the pharmaceutical and advertising industries will join forces with the FDA to look upon the primary mission of advertising as that to give truthful, exact, and balanced descriptions of the nature, quality, and properties of the drugs advertised. Let us further hope that this type of ethical advertising will enable our manufacturers to create new demands for better drugs, to serve as a source of information and education of physicians, and that in the long run such factual and informative advertising will be more persuasive to the physician than untrue, distorted, and biased advertising.

It is our hope that the advertising industry will join with the pharmaceutical industry and the FDA in carrying out the intent of Congress for promoting safe and effective drugs for the public. Let us all join together to do this on a voluntary basis rather than a compulsory or regulatory basis. **[The End]**

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