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Food Drug Cosmetic Law JOURNAL

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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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REPORTS

TO THE READER

Product Liability Problems.—*Rodney R. Munsey,* an attorney with the Pharmaceutical Manufacturers Association, discussed the problem of generic vs. trade-name in the prescription of drugs at the Pharmacy Management Seminar in Tampa, Florida, on April 25, 1965. The heart of the product liability problem, he feels, is the different pharmacologic actions of various products having the same intended active ingredient. Many examples of a pharmacist's potential product liability problems relating to filling prescriptions with generic or trade-name drugs are given in the article which starts at page 308.

Developments in International Food Standards.—In the article beginning on page 317, *Nathan Koenig,* Chairman of the U. N. Food and Agricultural Association's Interagency Subcommittee on Codex Alimentarius and Special Assistant to the Administrator, Consumer and Marketing Service, U. S. Department of Agriculture, traces the development of international food standards. Specifically, he outlines the work done by the Codex Alimentarius Commission composed of members from the World Health Organization and the U. N. Food and Agriculture Organization.

He believes that agreement and understanding reached through the commission provide a basis for developing realistic standards to facilitate international trade and to safeguard consumer interests in wholesome food and identifiable quantities.

Product Liability—The Ethical Drug Manufacturer's Liability.—An article by *Paul D. Rheingold,* a member of the District of Columbia and Massachusetts Bars, concerns the ethical drug manufacturer's liability when a consumer is injured through the use of a drug.

Part I of Mr. Rheingold's three-part article relating to this problem appears in this issue beginning on page 328. The extra-legal material on medicine, administration, and economics which forms the background for civil liability is described in this first part. The succeeding two sections are legal discussions on "Injury Caused by Established Drugs," and "Injury Caused by a Drug in the Experimental Stage." These will be contained in a future issue.

Food Laws in the European Economic Community.—The harmonization of national food laws within the European Economic Community (EEC) is the topic of the article beginning on page 356. The author, *Warren S. Adams, II,* a member of the New York Bar, in association with *Paul M. Karl,* a member of the German Bar, describes the legislative machinery of the EEC and the process of adopting directives in the food law field. Criticism of accomplishments to-date is made, but the authors conclude that an astonishing amount of work has been done, considering the initial difficulties and understaffing of the various divisions.

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Product Liability Problems— Nonproprietary Names

By RODNEY R. MUNSEY

Mr. Munsey, an Attorney with the Pharmaceutical Manufacturers Association, Presented This Paper at the Pharmacy Management Seminar in Tampa, Florida, April 25, 1965.

THE SUBJECT OF GENERIC VS. TRADE-NAME PRESCRIBING and bulk purchasing of prescription drugs, is undoubtedly one of the most talked about drug topics today in government circles, and in and among the general public. Indeed, discussion of this topic within the health team itself has been long and heated for many years. The reasons for the widespread interest and deep concern are clear and can be summed up in two words: economics and health. Marked cost savings can be enjoyed by purchasing prescription drugs with certain active ingredients by nonproprietary names. On the other hand, two drugs with the same active ingredients may have substantially different effects. Today, we are not going to talk about the various arguments advanced favoring generic or favoring brand names in drug prescribing. The volume of literature on that topic and the widespread availability of the divergent viewpoints would make our attempts to come to any conclusions in a few minutes fruitless. At any rate, our concern this afternoon is with product liability. Product liability problems are involved in generic prescribing because there are meaningful differences between two drugs containing identical active ingredients but prepared by different manufacturers utilizing different manufacturing procedures and containing different excipients, fillers and binders.[1]

[1] Sadove, Rosenberg, Heller, Shulman, "What is a Generic Equivalent?" *American Professional Pharmacist,* February 1965.

As you all know, considerable confusion exists as to the terminology employed in the nomenclature of drugs. For the purpose of this session, I will use the following definitions. Drug means the intended active ingredient or ingredients. Drug product refers to the finished dosage form. The chemical name of a drug is the series of names depicting each of the molecules contained in that drug. The generic name is one word referring to the combination of molecules in a drug. A generic product is a drug product not identifying the source of production or the name of the manufacturer on the label or labeling. As you know, the Federal Food, Drug and Cosmetic Act does not require that the manufacturer's name appear in the labeling. Manufactured for ..... or distributed by ..... is sufficient.[2] A brand-name product is a drug product which identifies the manufacturer by such means as trade-name, trademark, or other proprietary name. Our discussion will center around the product liability aspects of generic products versus brand-name products.

Differences in Pharmacologic Action of Generic Equivalents

The heart of the product liability problem in the area of generic products is the different pharmacologic action of various such products having identical quantities of the same intended active ingredient. These variations are caused in some cases by the difference in quality control between different manufacturers.[3] However, an equally important cause of the marked differences between the effects of two so-called generic equivalents is the difference in the end product caused by different procedures and substances being used by the two manufacturers in transforming the generic drug into the generic product.

Let me refer to an article in the *American Professional Pharmacist* (February 1965) written by three M.D.s, one of whom also holds a degree in pharmacy. These men are active in medical practice, teaching and research and development. They are affiliated with universities and Veterans Administration hospitals. They state that 24 factors other than the active ingredients of a drug can have marked effects on its pharmacologic action. They are: size of crystal or particle; form of the agent (solution vs. salt); vehicle; coatings; degree of hydration of crystal or addition of dehydrating substances to the package; diluent, purity (type and number of impurities);

[2] 21 U. S. C. 352 (b), FOOD DRUG COSMETIC LAW REPORTS ¶ 70,133.

[3] Testimony of Commissioner of Food and Drugs before Senate Subcommittee on Antitrust and Monopoly, June 1960.

viscosity; pH, sustained release forms; enteric coating; solubility; base, container (stopper, type of glass, whether glass is pre-heated or impervious); package dating; contaminants; allergenic substances; irritation; melting point; toxicity, surface tension; storage factors; flavoring; and coloring agents. They gave many examples of varying pharmacologic activities resulting from slight variations of the 24 factors. One such example related to use of the drug erythromycin. It was found that when the drug was utilized in one salt base, it was extremely irritating. A change in the salt immediately reduced the irritancy to a satisfactory level. Examples of a far more serious nature could be given. They concluded "generic equivalency is frequently a fable without basis in fact; chemical equivalency of the primary agent or agents is not necessarily clinical nor pharmacologic equivalency." There is an abundance of other scientific literature describing the difference in pharmacological effects between two supposedly generic equivalents.[4] There have been Food and Drug Administration (FDA) pronouncements on the topic.[5]

Quality control is the sum of all the planning, testing, and supervision which guarantees the consistent production of a product with the purity, potency, uniformity and physical characteristics best suited to obtain a favorable therapeutic response. One out of five production employees in our larger and more respected drug manufacturing firms is engaged in quality control duties.[6] These are the brand-name product manufacturers. The *United States Pharmacopeia* (USP) and *National Formulary* (NF) provide only a limited amount of information on the nature of ingredients other than the active substances. For example, neither publication establishes standards for long range stability tests of the finished product. And yet, even the pressure used to compress the tablet can be as important as its content; for it is not unusual for poorly made tablets to disintegrate too rapidly, too slowly, or even, not at all! Companies conscious of quality control and jealous of the reputation they hold, label their products with their own name. This points out, among other things, that they conduct step-by-step testing in the manufacturing process as well as finished products testing.

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[4] Levy and Nelson, *Journal of the American Medical Association*, September 9, 1961.

[5] Letter dated March 15, 1963, from W. B. Rankin, Assistant Commissioner, Food and Drug Administration, to K. Bambach, Pharmaceutical Manufacturers Association.

[6] Pharmaceutical Manufacturers Association.

Now lets get to the heart of the matter. What is the difference in the responsibility assumed by a pharmacist in filling a generic as opposed to a brand-name prescription? If the physician has prescribed a drug designated by a proprietary name, he has left the pharmacist with little discretionary authority. The physician, himself, has selected the drug product. When such a medical practitioner has written an order for a generic product, he has, in effect, placed the responsibility upon the pharmacist to select any wholesome drug having the requested amount of that active ingredient. He has probably not increased your responsibility for any pharmacologic differences between generic products due to different excipients, fillers and/or manufacturing practices not affecting wholesomeness. He is aware of such differences and has, impliedly stated in his prescription order that any wholesome brand is suitable for the patient's needs. He has transferred to the pharmacist the duty to pick a wholesome, properly manufactured product. What does this mean legally?

Consider three drug products. Products A and B are generic. Product C is a brand-name product. Assume that all would be pharmacologic equivalents if properly compounded by the manufacturer according to his own standards. We'll ignore any differences caused by different excipients and fillers or created by different manufacturing processes. Assume that all three drugs are defective because of contamination by penicillin. A patron comes into your store with a prescription to be filled. You fill it; the customer has severe adverse reactions and of course sues. If the physician had prescribed brand-name product C, a drug he had prescribed with success on previous occasions, and the pharmacist supplied that drug product, it is the manufacturer who may be liable in strict liability breach of warranty and negligence. There would be no negligence problem for the pharmacist. His standard of care in selecting his stock is not relevant since the defect was caused by the manufacturer and the pharmacist was ordered by the physician to dispense that manufacturer's product. The pharmacist most likely would not be liable in implied warranty of merchantability since he had no choice but to supply that product. The physician is not liable because the drug he prescribed, if manufactured properly, would not have caused injury.

If the physician had prescribed a generic name product, and you had filled it with generic name product B, the manufacturer would still be liable but now you may be also. The physician is probably "off-the-hook" because implicit in his prescription is the implied order

to dispense a generic name product of suitable quality. Why may you be liable? It depends upon the standard of care you used in selecting your drug sources. If, in spite of your professional knowledge of the potential differences in various generic name products, your conception that the due care required of a pharmacist in selecting a drug is fulfilled by basing your choice solely on price, *Watch Out!* Not only may you be liable, but as a practical matter you, alone, without the manufacturer, may have to face the suit. The label of the bottle you received said; "Distributed by ..... or Manufactured for ....." It is common knowledge that the company for whom the drug was manufactured may have more than one firm manufacturing the drug for it. Perhaps the drug has been repacked by two successive jobbers after manufacture. Perhaps you place all your generic equivalents in the same dispensing bottle. I recall a case I had a couple of years ago when I was with the FDA. A druggist had unknowingly purchased a counterfeit drug product from a traveling salesman. He had poured the tablets in the same dispensing bottle in which he had placed his genuine product which he had obtained from his usual wholesaler. We couldn't prove a counterfeit case against the traveling salesman because we were unable to prove which tablets in fact he had sold the drugstore. Luckily we had other counts and cases against him. At any rate, for one of several reasons, you may not be able to bring in the manufacturer. An implied warranty of merchantability of wholesomeness may also be brought against you. You and you alone have selected the drug product to dispense to the patron.

Again, going back to our example, let us presume that the prescription called for a generic name product. We'll assume you filled it with generic product A and made the first refill with generic product B, and refilled the prescription a second time with brand-name drug C. Plaintiff was injured. You may have the product liability problems mentioned above plus some additional ones. As you can see, the problem of which manufacturer was involved is more complex. Probably no manufacturer will be brought into the case. Your using different drug products for each refill may present opportunities for liability other than that involved in the due-care standard in selecting your stock generally. The physician ordered you to select the generic name product of suitable quality. As a side light, it's worthy of note that a few years ago, some eastern pharmacy groups were campaigning for physicians to place ARB on their generic product prescriptions. These initials stand for Appropriate Reliable

Brand. I don't think they realized that, in effect, the pharmacist in such case may be considered to have warranted the reliability of the drug that he dispensed pursuant to that prescription. Back to our example, you filled the prescription each time with different products you felt were of suitable quality. Depending upon how you store your drug products, you may or may not have known you were now dispensing different drug products on each occasion. Take the simple case where you did in fact know. Were you so authorized by the prescription? You and the physician both were aware of the potential differences in "generic equivalents". Did the physician contemplate your switching drug products from refill to refill? It is possible the courts would find that the physician in writing a generic product prescription saw no reason to prescribe a particular brand, and that if any adverse reactions developed from the prescription the patient would inform him and appropriate action would then be taken. He would not contemplate that the pharmacist would switch from refill to refill regardless of how well the drug product was working and without informing either him or the patient. Does the due care required of a professional pharmacist require that you call the physician and inform him and request permission to switch? I submit that some courts may so hold and find negligence. In a situation where you don't know whether you are switching or not, the possibility of negligence liability is, of course, greater.

Before leaving the area of potential liability in sub-quality, generic name products, a further point should be mentioned. Bearing in mind the impossibility in most cases, of tracing such products back to the manufacturer, envision a situation where a lot or lots of generic products have been contaminated with hormones. Either an FDA instituted, or a voluntary recall of that lot or lots has been instituted by the company. You don't know whether, in fact, you have any on hand so, of course, you can't send them back. If you do have some, and you sell them, you're probably liable in implied warranty.

Some of you are probably thinking, what I'm saying about sub-quality products may be true, but in your experience, the quality difficulty has not existed and you feel that 99% of generic name products are in fact "generic equivalents". Now let us see what the FDA has said about this. In his testimony before a Congressional subcommittee, FDA Commissioner George P. Larrick reported[7] that, in the ten year period between 1950 and 1960, his agency had to take

[7] See footnote 3.

action a total of four times against the output of 28 well known drug manufacturers who produce 87% of the nation's drugs. During the same period FDA had had to act against 235 firms, out of the remaining 1,200 or so companies who produced the balance of 13% of drug output. This means that more than 98% of FDA's enforcement actions taken during that period were against the group which includes the predominantly anonymous generic drug producers. A former medical director of FDA commented a few years ago at an American Pharmaceutical Association (A. Ph. A.) convention:[8] "The naive belief that, if a drug was not good, the FDA would prohibit its sale, is just not realistic. FDA labors long and diligently to protect the public, but the fact of the matter is that it is completely impossible for FDA to check every batch of every product of every manufacturer that is marketed. Hence, the integrity and reputation of the manufacturer assume unusual significance when drugs and health products are concerned." The Drug Amendments of 1962 have not changed the situation. They require only that a drug establishment be inspected at least once during every two-year period.[9] And there is no batch certification for drug products except in the area of antibiotics.[10]

Leaving aside the quality-control problems as regards unintentional departures from the manufacturer's own standards, that is, manufacturing defects; and considering the differences in pharmacologic effect, between "generic equivalents" resulting from use of ingredients other than the intended active ingredients and different manufacturing processes, we still find possible product liability problems that are not existent in the brand-name product situation. These are primarily in the area of prescription refills. The potential liability in the intentional or unintentional "switching" of "generic equivalents" from refill to refill leave the pharmacist open to the same potential liability described a few moments ago. Negligence may lie in selection of your drug source. If a product recall is instituted because of newly discovered side-effects or the FDA has ordered the drug off the market, there is the same problem if you have a stock of that drug product on hand.

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[8] Annual Meeting of American Pharmaceutical Association, 1959. Dr. Albert H. Holland, Jr., M.D.

[9] 21 U. S. C. 360 (h), FOOD DRUG COSMETIC LAW REPORTS ¶ 71,081.

[10] 21 U. S. C. 357, FOOD DRUG COSMETIC LAW REPORTS ¶ 74,041—¶ 74,059.

Safest Course to Follow

In short, from a product liability point of view, the safest course to follow is to carry only drug products which identify the manufacturer, that is those firms that stand behind their products and are conscious of their reputations. If you do dispense generic products, you should charge a higher price commensurate with the increased risk of liability. I would strongly recommend that any generic name product you purchase be kept in its original container until dispensed. A record of the date of receipt of such product should be maintained. Your records should be devised so that you know from what bottle each generic name products prescription was filled. Refills of particular generic name prescription should be from the same source as near as can be accomplished. Make every attempt to know the identity of your manufacturer. Of course, even these steps will have little effect upon the potential liability arising from use of sub-quality generic name products or those that have been repacked several times or are from sources that distribute identical drug products that are manufactured for them by several different companies.

There are additional potential product liability problems for the pharmacist in the framework of some of the states welfare prescription programs. For instance, for some drugs, Louisiana will allow the pharmacist to charge the state and/or the welfare patient an amount not to exceed the state's generic price list. What is the situation when a physician prescribes a brand-name drug product whose price is higher than the generic list price? Certainly, the pharmacist cannot, without danger of liability in the event of injury, substitute a generic drug product without contacting the physician. There is ample case law holding liability in that situation.[11] The pharmacist has a duty to follow the prescription order. Suppose you call the physician and he refuses to give you authority to substitute? If you tell the patron you cannot fill the prescription, you lose this customer in the future, and perhaps good will in the community. Depending upon the urgency of his need for the drug, you may have negligence problems. If you substitute, you are in the hot seat, if anything goes wrong because you have in the face of a direct refusal, contradicted the physician's order. From a liability standpoint your only safe course is to fill the prescription as written and charge the generic

[11] *Jones v. Walgreen Co.* 265 Ill. App. 308 (1932).

name drug price. Depending upon price difference, a real economic hardship could result to the pharmacist if this happens very often.

A brief word about hospital formulary systems as approved by the American Hospital Association, the American Medical Association, the American Pharmaceutical Association and the American Association of Hospital Pharmacists.[12] Basically, the Pharmacy and Therapeutics Committee decides what drugs shall be stocked in the hospital formulary. The medical staff adopts a policy of including drugs in the formulary by their nonproprietary names. Prescription blanks may include authorization of the pharmacist to fill the prescription with "generic equivalents."

The pharmacist may not substitute a "generic equivalent" unless so authorized. The following is a quotation from the statement of guiding principles on the operation of the hospital formulary system as approved by the above listed organizations.[12] "The pharmacists, with the advice and guidance of the Pharmacy and Therapeutics Committee shall be responsible for specifications as to quality, quantity, and source of supply of all drugs, chemicals, and biologicals and pharmaceutical preparations used in the diagnosis and treatment of patients and for ensuring that quality is not compromised for economic considerations." Assuming that directive is adopted by the hospital, the pharmacist bears the final authority for selecting the manufacturer of the drug. Can he safely select a drug product from an unknown manufacturing source on the basis of price when he is by directive, not permitted to compromise for economic considerations?" If he did, and an injury resulted, I would like the opportunity to be a plaintiff's lawyer to question the pharmacist as to the professional due care exhibited in his purchase of the subject drug product. Since control is exercised by the Pharmacy and Therapeutics Committee, and consent for substitution is placed on the prescription blank, the pharmacist's potential liability would be primarily in the area of due care in selecting wholesome drug products. In addition, the recall problem mentioned before could apply. The wording on the physician's consent form on the prescription blank would be the prime determinant of liability if succeeding refills were of different "generic equivalents." **[The End]**

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[12] "Statement of Guiding Principles on the Operation of the Hospital Formulary System," *American Journal of Hospital Pharmacy*, January 1964.

Developments in International Food Standards

By NATHAN KOENIG

This Paper Was Presented at the Symposium on Carbohydrates in Food Industry, 149th National Meeting of the American Chemical Society in Detroit, Michigan, April 8, 1965. Mr. Koenig Is Chairman, U. N. Food and Agricultural Association's Interagency Subcommittee on Codex Alimentarius, and Special Assistant to the Administrator, Consumer and Marketing Service, U. S. Department of Agriculture, Washington, D. C.

A COMMON LANGUAGE IN THE WORLD OF FOOD is beginning to emerge through the cooperative efforts of countries around the globe. The objective is to develop food standards that will safeguard the interests of consumers in wholesome foods and also facilitate international trade. The work is being done through the food standards program jointly undertaken by the Food and Agriculture Organization (FAO) of the United Nations and the United Nations World Health Organization (WHO).

The instrumentality for this international food standards activity is the Codex Alimentarius Commission in which members of FAO or WHO are eligible to participate. Now in its third year of operation, the commission is charting a new course in an area in which there has long functioned a multitude of international and regional bodies and other organizations in various parts of the world.

In fact, the number of organizations and other groups working in the field of food standards throughout the globe is still a matter of conjecture. An admittedly incomplete list developed by FAO in 1962 showed that 135 organizations and instrumentalities, other than governments, were working on international food standards and related problems.

The work of these groups alone covers the entire food spectrum and includes the development of standards governing additives, pesticide residues, sampling, and analysis, and ranges into standards of identity and quality.

With the growing importance of standards in safeguarding the consumer interest in wholesome foods, as well as facilitating international trade, there has been an increasing realization of the need for simplifying and harmonizing the food standards work, and thus eliminate much of the confusion and conflict that has arisen. Moreover, in addition to the scientific aspects of the problem, there was the need to correct the misuse of food standards by countries establishing internal limitations or requirements which protect their products from the competition of imports and thus restrict international trade.

Beginning of Harmonization of International Standards

It was little more than a decade ago that the concept of an international body that would assume leadership in simplifying and harmonizing international food standards first came into being. This was expounded by Dr. Hans Frenzel, a former Minister in the Austrian Government. It eventually led to the establishment in 1958 of the European Council of the Codex Alimentarius. At that time it was also foreseen that food standards development work should ultimately be on a broader international basis, perhaps under the auspices of FAO and WHO. Thus, it was that the Statutes of the European Council were drafted in such a manner as to permit the Council's activities to be absorbed at some future time by one or more general international organizations.

It is against this background that the food standards program was undertaken jointly by FAO and WHO. Both of these United Nations organizations in 1962 sponsored a meeting of government representatives in Geneva to consider a proposal for establishing a Codex Alimentarius Commission. The commission would concern itself with the development of international food standards to overcome the confusion and conflict that was widespread in this field.

That historic joint meeting, held in the fall of 1962, was attended by representatives of 44 countries and 24 international organizations. Following extensive discussions, the meeting endorsed the proposal for joint establishment by FAO and WHO of a Codex Alimentarius Commission which would be responsible for work in the field of

international food standards. The meeting also developed guidelines for the work of the commission and established priorities designed to govern its activities. The food standards to be promulgated were to be both practical and meaningful from the standpoint of both trade and consumer interests.

The Codex Alimentarius Commission actually came into being in mid-1963 when its first session was held in Rome. Representatives of 30 countries and observers from 16 international organizations attended. Using the guidelines developed at the Geneva meeting the year before, the first session shaped the Commission's *Rules of Procedure* and its general program of work.

The basic purpose of the Codex Alimentarius Commission is to simplify and harmonize international food standards work by (1) allocating priorities in the development of standards, (2) coordinating and supplementing the work of other bodies in this field, and (3) providing for finalization of draft standards at the government level and their publication in a consolidated Codex Alimentarius.

The commission's objective is to facilitate trade and at the same time protect the interests of consumers. From the standpoint of the commission, an international food standard aims at insuring the market of a sound, wholesome product, correctly labeled and presented. It does not intend to affect consumer preference. It's primary purpose is to insure that the consumer can know what he is buying.

Most of the work of the commission is carried out through committees—each chaired by an individual country. The work of the commission may also be done on a joint basis with other organizations, such as the Economic Commission for Europe, or it may request other bodies, usually an international organization, to carry on a particular assignment in its own specialized field.

First Session of Codex Commission

The program of work launched by the commission at its first session covers the development of a wide range of international standards relating to foods. These include standards for fish and fishery products, fats and oils, nutritional sweeteners, fruit juices, processed fruits and vegetables, meat carcasses and cuts and processed meat products, milk and milk products, cocoa products and chocolate, food additives, pesticide residues, food hygiene, methods of sampling, and methods of analysis.

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Two of the committees established by the commission to develop food standards are chaired by the United States. One involves standards for processed fruits and vegetables and the other concerns the development of food hygiene standards.

Participation in the standards development work of the Codex committees is open to all countries who are members of FAO or WHO.

Second Session of Codex Commission

The second session of the Codex Alimentarius Commission held in Geneva in the fall of 1964 provided an opportunity for the various Codex committees and organizations to report on the progress of the work that the commission assigned at its First Session. Additional work undertaken as a result of the second session includes the establishment of a Codex Committee on Food Labelling, which is being chaired by Canada, and the development of standards for frozen foods, dried prunes, and edible fungi (mushrooms) on a joint basis by the Codex Alimentarius Commission and the Economic Commission for Europe (ECE). The development of standards for fruit juices is already being carried on jointly with ECE, which has been engaged in a rather extensive program of food standards promulgation. The purpose of working jointly with ECE is to avoid duplication between the two bodies and to afford fuller participation on an international basis.

Under the procedure that has been developed, standards may be formulated on a worldwide or regional basis. In practice, regional standards would be promulgated primarily in those situations where no other alternative was available (chiefly in the case of highly perishable commodities). Recognition would have to be given to equivalency of products coming from outside the region.

Also under the procedure that has been established, countries are given the opportunity to participate, in one way or another, in the promulgation of standards. This feature is most important from the standpoint of safeguarding the interests of all concerned, either directly or indirectly.

When a draft standard is developed by a Codex committee or other body to which the assignment has been made, it is first circulated to governments for comments. It may then be modified by the originating group in the light of these comments. Ultimately, the proposed draft on which agreement may be reached is submitted to

the commission for further consideration and as the basis for producing a draft provisional standard.

The resulting draft provisional standard is then sent to all government members of the commission for comments. In the light of comments received, which are in turn considered by the Codex committee or other body, as the case may be, the commission reconsiders the draft as it may have been revised on the basis of comments from governments. The reconsidered draft may then be adopted by the commission as a provisional standard. This is then sent to governments for acceptance and when, as determined by the commission, a sufficient number have accepted it, the provisional standard is printed in the Codex Alimentarius as a standard.

Although this procedure for the elaboration of standards may seem somewhat complex, it is logical and necessary. This becomes apparent when consideration is given to the importance of providing all government members of the commission an opportunity to comment on any standard that is proposed. This step is most essential in protecting the interests of all governments, including those who may not have participated directly in the work of the group that developed the particular proposed standard. The real safeguard is in the fact that both in the case of any international or regional standard, the adoption of the standard and its subsequent publication in the Codex Alimentarius may take place only after the commission has submitted the draft text to all governments for comments. This affords all an opportunity for review that is not provided by any other instrumentality in the field of food standards.

The legal basis for the work of the Commission was established by FAO under Article VI of its constitution, and through the promulgation of the Statutes of the Codex Alimentarius Commission which subsequently received the endorsement of WHO. The statutes prescribe the responsibilities and functions of the Codex Alimentarius Commission and provide for its operation and financing.

There is no compulsion to the use of a food standard developed through the commission's procedure and published in the Codex Alimentarius. However, any country may adopt the standard and incorporate it as part of its own regulations. In such circumstances, the standard would have the same force and effect commercially and legally as any other legal requirement of the country. Countries can, however, if they so desire, recommend for voluntary use the standard published in the Codex Alimentarius instead of incorporating that

particular standard in its mandatory regulations. In no instance, however, can the Codex Commission standard supersede a standard of any country unless the country itself wants to have it that way by its own action.

Since any Codex Commission standard is entirely voluntary, it cannot restrict trade in non-standardized items. Such restriction can only be imposed by individual governments with respect to their own trade. This is no different from the situation that presently prevails with governments having the right to impose their own regulations governing their trade.

The work being done by the various Codex committees and other bodies in developing food standards under the auspices of the commission is centered, for the present at least, on the promulgation of a minimum standard for each product being dealt with. The objective is to formulate minimum standards acceptable on as wide a basis as possible, but with the understanding that this in no way limits the existence or establishment of higher standards in any country that may accept the minimum standard.

However, the development of minimum food standards for international use as is now being done does not preclude the possibility, if there is real need, of the commission subsequently formulating additional realistic higher international standards.

It must be recognized that there are many countries in the world, particularly among the developing nations, that have practically no standards, while the fully developed countries have many standards ranging upward from the minimum. Through the work of the commission, the developing countries are able to obtain assistance and guidance for bringing into being at least minimum food standards which would be helpful to them. On the other hand, to the fully developed countries the work of the Commission offers the opportunity for simplifying and bringing into closer harmony food standards of international concern. This removes a great deal of the confusion and conflict that has prevailed in this field with benefits accruing both to advancement of international trade and to consumer protection.

Codex Work in Field of Sweeteners

The work being done by the Codex Alimentarius Commission in the field of nutritional sweeteners is, of course, of particular interest

to this symposium which is concerned with carbohydrates in food industry. At its first session in 1963, the commission established the Codex Committee on Sugars charged with the responsibility of preparing international standards for carbohydrate sweeteners. The United Kingdom accepted the chairmanship of this committee which held its first meeting March 3-5, 1964, in London. That meeting was attended by 28 representatives and observers from ten governments and four international organizations. The United States had a representative who participated in that meeting and he was accompanied by two advisors from industry.

After considering the need for standards, including hygiene and other aspects, for the different nutritional sweeteners involved in international trade and establishing a list of priorities among the products, the committee developed draft standards for eight of the more important nutritional sweeteners. These included extra white sugar, white sugar, powdered sugar (icing sugar), soft sugars and brown sugars, glucose syrup, dried glucose syrup, dextrose monohydrate, and dextrose anhydrous.

The job done at the first meeting of the Codex Committee on Sugars was generally regarded as a considerable achievement, considering the fact that this was the first time any such group had been brought together from so many countries for the purpose of promulgating draft standards. Following the meeting, the draft standards were submitted to governments by the committee for comment. Although it was hoped that, after this review by governments, the draft standards could be submitted to the second session of the commission held in the fall of 1964, the volume and detail of the comments received from participating countries made it desirable for the draft standards to be considered further by the committee at the next meeting. This meeting, the second for the Codex Committee on Sugars, was held in London only a few weeks ago, March 2-4, 1965. It was attended by 33 representatives and observers from thirteen governments and four international organizations. The United States participated in that meeting, as it did in the first session that was held in the previous year.

The second meeting of the Codex Committee on Sugars reached agreement on seven standards which are to be submitted to the Codex Alimentarius Commission as draft provisional standards. It is intended that, following consideration by the commission, they will be submitted for comment to governments.

The sugars for which draft standards were agreed upon were the same as those considered at the first meeting of the committee except for the fact that there now are seven draft standards instead of eight. This is because of a decision made by the committee that there should be a single standard for white sugar identified as "white sugar" instead of the separate standards for extra white sugar and white sugar drafted at the committee's first meeting. In general, the specifications for the single white sugar standard is the mean of those originally established for extra white sugar and white sugar.

Thus, in addition to the proposed draft provisional standard for white sugar, the Codex Alimentarius Commission is to receive for consideration, at its next meeting this coming fall in Rome, draft standards proposed by the Codex Committee on Sugars for powdered sugar (icing sugar), soft sugars and brown sugar, glucose syrup, dried glucose syrup, dextrose monohydrate, and dextrose anhydrous. The standards for these sweeteners will come before the commission as minimum standards.

After considering further proposals for standards, the committee also decided that it would undertake to develop standards for lactose and fructose. In connection with its standards development work, the committee also gave consideration to other aspects—such as sampling procedures, methods of analysis, and health or hygienic criteria. Proposals in these and related fields are to be developed for consideration at the committee's next meeting.

The use of sweeteners of one kind or another in foods is, of course, universal. Many wholesome food sweeteners are used as important ingredients in the modern diet. Commercially, they are used in many forms, as liquids, dry crystals, and many degrees of purity and refinement. As is well known, each has its place as a food ingredient and the uses to which various food sweeteners may be put are changing rapidly as advancement is made in chemistry and food technology.

As is generally known, food standards have often been used for impeding or restricting international trade. This is often done, for instance, through incorporating into food standards limitations or prohibitions on the use of additives or other ingredients. For example, United States exporters of canned fruits and juices have encountered difficulties because of restrictions placed on the use of nutritional sweeteners, specifically glucose or corn syrup.

Food standards that impede or restrict international trade are, of course, contrary to the United States interest in such trade. The Codex Alimentarius Commission affords an opportunity for developing acceptable food standards and thereby combating the use of standards for purposes of impeding or restricting international trade, while providing essential safeguards for both buyers and sellers as well as consumers.

United States Participation

The United States has given full support to, and participated actively in, the work of the Codex Alimentarius Commission. As a matter of course, the United States has sent representatives to take part in the work of practically all Codex committees and, in this way, has had an opportunity to use its extensive experience to help in the establishment of workable definitive standards.

The importance of United States participation in the development of international food standards is well illustrated by what is being done in the promulgation of standards for fruit juices. The original work on standardization of fruit juices was started by the Economic Commission for Europe, which set up a group of experts. Recognizing the importance of fruit juices in international trade, the Codex Alimentarius Commission arranged with ECE to have standards for fruit juices developed on a joint basis. This is now being carried out through the Joint ECE/Codex Alimentarius Group of Experts on Standardization of Fruit Juices. The first meeting of this joint group was held in Geneva, April 6-10, 1964, with 15 countries, including the United States, participating. Out of this first joint meeting came a draft minimum standard for orange juice which, among other things, proposed to set up a requirement that only sucrose in dried form in a specified amount would be permitted to be used as a sweetener. Such a restriction in the standard would, of course, close the door to the use of any other nutritive sweetening ingredient commonly used in the United States. In effect, the restriction would be a barrier to United States exports.

Moreover, the adoption of such a restriction would undoubtedly set a precedent which could be followed in the promulgation of international standards for other foods in which nutritional sweeteners may be utilized. This probably would not bother countries that are self-sufficient through their own production of sucrose derived from either sugar beets or sugar cane, but for a country such as the United

States, and others that utilize a wide range of nutritional sweeteners, such a restriction to one kind of sugar would indeed be detrimental to trade. Moreover, limiting the use of nutritional sweeteners to one kind of sugar and thus prohibiting the use of any others, as proposed in the draft standard for orange juice that resulted from the first meeting of the Joint ECE/Codex Alimentarius Group of Experts, is inconsistent with the United States Government's approach to the establishment of United States standards.

As a leading exporter ($43.6 million in fiscal year 1962) and producer of over 80% of the world's fruit juices, the United States has a great interest in regulations adopted for international trade pertaining to these products. This country, therefore, has a vital stake in the recommendations made by the Joint ECE/Codex Alimentarius Group of Experts. That is why at the second session of this joint group of experts held in Geneva, March 29—April 2, 1965, the United States took a firm stand against the proposal which would limit the nutritional sweetener to one kind of sugar in orange juice.

Since this was the first international standards proposal which involved the use of sweeteners, the United States delegate to the joint session stated the official United States position with respect to the use of nutritional sweeteners as follows:

> International food standards should not be tools of trade restriction and should permit the use of wholesome food ingredients, including suitable types of nutritional sweeteners. International food standards must permit the use of any nutritive sweeteners in quantities consistent with the physical and organoleptic characteristics desired for the food to which they are added.

Having encountered restrictions in the past, it is clear that the problem of nutritional sweeteners in foods is an important one. The restriction of sweeteners in international food standards to one nutritive sweetener, such as sucrose in the case of the proposed orange juice standard, is quite out of keeping with both the stated aims of the Codex Alimentarius Commission's work and also the United States' policy and interest. In this light, the United States cannot accept any unwarranted restriction on the use of wholesome additives in international food standards, including restrictions on nutritive sweeteners.

In the case of the proposed orange juice standard, the sweetener was limited to sucrose. But if a proposal were made to limit the use of sweeteners in an international food standard to glucose or any other sweetener, this would also be out of place as is the suggestion to limit the permitted sweetener to sucrose.

It must be kept in mind that the goal of international food standards is both to serve consumers and to facilitate trade. Therefore, international food standards must not be a tool for trade restriction. The restriction of nutritive sweeteners to sucrose as suggested in the proposed orange juice standard would deny consumers other sweeteners which may be more suitable in some foods and which would also create a major restriction on trade.

The food standards development work of the Codex Alimentarius Commission brings together, for discussion and mutual appraisal, experts from producing and consuming countries around the world. While in the work of its various committees and other groups, differences in points of view are bound to come to the fore, substantial agreement is ultimately reached on the many aspects considered.

The fact that agreement can be reached is most significant when it is recognized that the approach for promulgating food standards through the instrumentality of the Codex Alimentarius Commission represents the blazing of a new trail in international cooperation. Agreement and understanding thus derived provide the basis for developing standards that are realistic both from the standpoint of facilitating international trade and from the standpoint of safeguarding the interests of consumers in wholesome food of identifiable quality. Standards that serve the interests of consumers and also facilitate and boost international trade in food commodities will do so if they can be made to reflect only factors that are of substantial importance to the identity, quality, and wholesomeness of the products defined. They should not include provisions designed merely to serve the economic advantage of one country or region over any other.

The United States has, of course, a vital interest in international trade—both as an exporter and importer. As an exporter, international standards could have a marked impact on the volume of United States shipments to other countries. Thus, it is important for the United States to participate actively in the standards development work of the Codex Alimentarius Commission, seeking wherever possible to have the standards reflect sound marketing and manufacturing practices and also good food law regulations, as the United States has come to learn the practical importance of these elements through many years of experience in this general area. **[The End]**

Products Liability— The Ethical Drug Manufacturer's Liability

By PAUL D. RHEINGOLD

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FROM A MEDICAL STANDPOINT, this has been called "the era of the drug." The physician of the sixties has an armamentarium of ethical drugs[1] of a type and quantity never before known. New drugs appear on the market at an unprecedented rate, faster than the medical profession can learn about their properties. At the same time drugs are being withdrawn from the market in unprecedented numbers because of undesirable side effects which are deemed to outweigh whatever therapeutic value the drugs may have. It has been estimated, for example, that in the United States there are annually over one million adverse reactions to drugs and related substances.[2]

[1] As used herein, *ethical drugs* refers to prescription drugs as distinguished from those proprietary or patent drugs sold over the counter. The term *drug* is defined in § 201(g) of the Federal Food, Drug and Cosmetic Act of 1938 to include both ethical and proprietary drugs. 52 Stat. 1041 (1938), 21 U. S. C. § 321(g) (1958). A *prescription drug* is defined by § 503(b) of the Act as one which "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary for its use, is not safe for use except under the supervision of a practitioner. . . ." 52 Stat. 1050 (1938), 21 U. S. C. § 353(b) (1958).

[2] The United States Public Health Service estimate of 1.3 million drug reactions per year requiring medical attention or resulting in lost work includes reactions to blood transfusions and vaccinations. See *Drug News Weekly*, Jan. 30, 1963, p. 8, col. 2.

In this same recent period, ethical drugs have become one of the most increasingly common products involved in tort litigation against manufacturers and suppliers. Chloromycetin,[3] MER/29,[4] Salk polio vaccine,[5] and thalidomide[6] prove this point only too well. In determin-

[3] Chloromycetin (chloramphenicol) is a broad-spectrum antibiotic which has been on the market since 1949 and has frequently demonstrated its life-saving ability. It has caused numerous adverse effects upon the formation of blood, however, and successively stricter warning statements have been required on its labeling, as described in footnote 99. For a thorough medical review, see Hartman, "Chloramphenicol and the Code of Hammurabi," 13 *Am. Practitioner,* 497 (1962). Litigation involving the manufacturer, Parke, Davis & Co., doctors who have prescribed it, and pharmacists who have filled it has been frequent. A verdict for both doctor and manufacturer was recently reported in *Stottlemire v. Cawood,* 213 F. Supp. 897 (D. D. C. 1963). *Dawson v. Lindsey,* 143 So. 2d 150 (La. App. 1962), represents preliminary skirmishings, involving interrogatories. A $334,046 verdict awarded in 1962 in a California action was reversed on appeal due to misconduct of counsel, *Love v. Wolf,* — Cal. App. 2d —, 38 Cal. Rptr. 183 (1964).

[4] MER/29 (triparanol) was marketed in 1960 to reduce high cholesterol. It was used by about 500,000 persons for a two-year period before it was withdrawn from the market by the Wm. S. Merrell Co. because of its association with cataracts, hair loss, dermatitis and other effects. Some 300 to 400 suits have reportedly been filed for injuries allegedly due to the use of this drug. See *Medical Tribune,* Aug. 26, 1963, p. 1; *New York Herald Tribune,* Sept. 3, 1963, p. 12.

[5] The story of the Salk polio vaccine, a batch of which contained live rather than killed virus, is well recounted in Note, "The Cutter Polio Vaccine Incident: A Case Study of Manufacturers' Liability without Fault in Tort and Warranty," 65 *Yale L. J.* 262 (1955). The civil litigation which followed, involving children in California who were administered vaccine from this defective batch, produced *Gottsdanker v. Cutter Laboratories,* 182 Cal. App. 2d 606, 6 Cal. Rptr. 320 (1960), an important opinion discussed in several places in this paper. A subsequent case involving a child left totally paralyzed was the occasion of a $675,000 verdict, eventually settled for $500,000. 28 *NACCA L. J.* 518 (1962). The president of the company, Robert K. Cutter, is reported to have said that virtually all of the actions, 54 in number, were settled, for a total of $3 million. *TAPA Bulletin,* Aug. 1962, p. 5.

[6] Thalidomide was a sleeping pill which was being used abroad and studied in the United States at the time when it was discovered that it was teratogenic, that is, that it could harm a fetus when taken by a pregnant woman. So great was the impact of this discovery and the harm which it caused that in a review of the year in medicine it was stated, "1962 was the year of the thalidomide." *Medical World Tribune,* Jan. 4, 1963, p. 46. See also Note, "The Drug Amendments of 1962: How Much Regulation?," 18 *Rutgers L. Rev.* 101, 113-15 (1963) [hereinafter cited as Note, "Drug Amendments of 1962"]. For a comprehensive medical review, see Taussig, "A Study of the German Outbreak of Phocomelia," 180 *J. A. M. A.* 1106 (1962). The American company which was using the drug investigationally was Wm. S. Merrell Co. Reports on its activities in seeking approval for marketing and in the role of the FDA appear in Lear, "Some Unanswered Questions on Thalidomide, *Saturday Review,* Sept. 1, 1962, p. 35. Fortunately the number of infants injured in the United States was very low, although the injuries have led to civil actions, none of which has been tried as of this writing.

ing the remedies of the consumer who is injured through the use of a drug, the developing law of products liability must be consulted. Equally important to a proper evaluation of a civil action is a knowledge of the relevant medical practices, the business patterns of the drug industry, and the role of governmental supervision.

Ethical drugs are distinguished among the various classes of products involved in litigation by the degree of regulation and control that is exercised by the government. The Federal Food, Drug and Cosmetic Act[7] as it relates to drugs has only recently been greatly modified by the Kefauver-Harris Drug Amendments of 1962.[8] Day-to-day control is exercised by the Food and Drug Administration (FDA), which has recently promulgated new regulations dealing with both experimental and established drugs.[9] Congressional committees, headed by the late Senator Kefauver and former Senator Humphrey, have investigated many phases of the industry.[10]

[7] 52 Stat. 1040 (1938), as amended, 76 Stat. 780 (1962), 21 U. S. C. §§ 301-92 (Supp. IV, 1963) [hereinafter referred to as the Drug Act]. Generally on the Drug Act and the FDA, see Fisher, "Procedural Techniques in Food and Drug Administration Proceedings," 17 FOOD DRUG COSMETIC LAW JOURNAL 724 (1962); Kerlan, "Federal Food, Drug, and Cosmetic Act—20 Years of Health Protection," 8 *Clev.-Mar. L. Rev.* 89 (1959); "Developments in the Law—The Federal Food, Drug, and Cosmetic Act," 67 *Harv. L. Rev.* 632 (1954).

There are, of course, drug laws in every state, which laws are often not as comprehensive or as strict as the federal law, although some states have adopted a model bill patterned after the federal law. See, *e.g.*, Pettit, *Manual of Pharmaceutical Law* 112-13 (3d ed. 1962).

[8] 76 Stat. 780, 21 U. S. C. §§ 301-92 (Supp. IV, 1963). The new laws took effect upon approval by the President except for certain sections which were deferred in operation until May 1, 1963. See generally Kelly, "The Drug Amendments of 1962," 18 FOOD DRUG COSMETIC LAW JOURNAL 145 (1963); Note, "Drug Amendments of 1962." See also on the new amendments Harris, *The Real Voice* (1964).

[9] Regulations relating to new drugs [hereinafter cited as the new drugs regulations], 21 C. F. R. § 130 (Supp. IV, 1963), are discussed in detail in the text following footnote 43. These were proposed August 10, 1962, and became effective Feb. 7, 1963. Numerous revisions of the regulations relating to established drugs were made in 1963 to reflect the sweeping changes made by the 1962 Kefauver amendments. These are discussed, where relevant to civil liability, in footnotes 46, 96 and 103.

[10] See, for example, *Hearing Before the Subcommittee on Reorganization and International Organization of the Senate Committee on Government Operations*, 87th Cong., 2d Sess. (1962) [hereinafter referred to as *Hearings, Senator Humphrey Subcommittee*]; McMurray, "Congress and the Drug Industry," 17 FOOD DRUG COSMETIC LAW JOURNAL 15 (1962).

An interim report of the Senate Judiciary Committee's Subcommittee on Antitrust and Monopoly of value in civil liability situations is S. Rep. No. 448, 87th Cong., 1st Sess. (1961) [hereinafter referred to as *Kefauver Report*]. See also Note, "Drug Amendments of 1962."

The extra-legal material on medicine, administration, and economics which forms the background for civil liability is described in Part I of this article. This part may either be read as an introduction to the succeeding legal sections, Parts II and III, or may be bypassed for the legal discussions, which refer back to sections of Part I where germane. Legal sources drawn upon for this study include the reported and unreported products liability cases which have involved ethical drugs, commentaries,[11] and pleadings and briefs used in a number of recent drug actions.[12] Manufacturer liability in relation to other products is satisfactorily covered elsewhere, and is referred to in this article only by analogy.[13]

I. Medical and Administrative Background of Ethical Drug Practice

As no legal question is free of the fact situation in which it arises, to evaluate drug manufacturer liability it is necessary to know what harm drugs can cause, how a drug is made, what experiments go into

[11] See 2 Frumer & Friedman, *Products Liability* § 33 (1960) [hereinafter cited as Frumer]; 2 Hursh, *American Law of Products Liability* (1961) [hereinafter cited as Hursh]; Annot. 79 A. L. R. 2d 301 (1961); "Symposium—Pharmaceuticals and Products Liability Law," 29 *Tenn. L. Rev.* 231 (1962). More generally see Dickerson, The Basis of Strict Products Liability, 1962 INSURANCE LAW JOURNAL 7 (1962) [hereinafter cited as Dickerson, Strict Liability]; Dickerson, "Recent Developments in Food Products Liability," 8 *Prac. Law.*, April, 1962, p. 17 [hereinafter cited as Dickerson, "Recent Developments"]; Note, "The Cutter Polio Incident: A Case Study of Manufacturers' Liability Without Fault in Tort and Warranty," 65 *Yale L. J.* 262 (1955); Comment, "Cigarettes and Vaccines: Unforeseeable Risks in Manufacturers' Liability under Implied Warranty," 63 *Colum. L. Rev.* 515 (1963).

Treatises on law written primarily for doctors and pharmacists include Arthur, *Drugs and Druggists* (4th ed. 1955); Dewar, *A Textbook of Forensic Pharmacy* (1946) (British); Pettit, *Manual of Pharmaceutical Law* (3d ed. 1962); Price & Pannall, *A Manual of Pharmacy Law* (1956) (African); Wright, *Prescription Writing and Medical Jurisprudence* (1951).

[12] The author wishes to acknowledge the kind help of the following attorneys in supplying such material: David I. Sindell, Cleveland, Ohio; E. B. Sahlstrom, Eugene, Ore.; T. Terrell Sessums, Tampa, Fla.; Irving Gaines, Milwaukee, Wis.; J. D. Lee, Madisonville, Tenn.; James Markle, Detroit, Mich.; J. Minos Simon, Lafayette, La.; Donald J. Farage, Philadelphia, Pa.; Samuel A. McCray, Dayton, Ohio; Lou Ashe, San Francisco, Calif.; and numerous other practitioners, particularly with regard to the MER/29 litigation.

[13] On manufacturer liability for proprietary drugs, see cases gathered in 2 Frumer § 33; 2 Hursh § 15. As to liability of the pharmacist or others who compound and retail drugs, see King, "Liability for Negligence of Pharmacists," 12 *Vand. L. Rev.* 695 (1959), reprinted, *Professional Negligence* 158 (Roady & Anderson ed. 1960); 2 Frumer § 32; 2 Hursh § 15. On malpractice actions against doctors arising out of reactions to prescribed or administered drugs, see Louisell &

(Footnote continued on next page.)

the development of a new drug, how the FDA controls and supervises these processes, how it approves new drugs, and how ethical drugs are sold and prescribed.

A. Operation of Drugs; Toxic Reactions and Side Effects

Pharmacology is the scientific study of the interaction of chemicals and living material, whether for good or ill.[14] Drugs can be used for diagnosis of conditions, prevention or cure of disease and sickness, alleviation of symptoms, and promotion of health. While it is known that drugs operate in a general way by altering the body environment—the cells—little is actually understood about the specific way they operate. Factors influencing the effect of drugs upon the body include: (a) the body's ability to absorb, distribute, metabolize, detoxify, and excrete drugs; (b) the selectivity of drugs as to site of action; and (c) the mode of action of drugs. Given this complex, multiple effects are the rule rather than the exception.

Pharmacological agents either occur naturally or are synthesized, the latter being by far the more important today. Many drugs on the market are actually combinations of several separate drugs or therapeutic chemicals. If when taken together one drug enhances the potency of the other, the action is synergistic; if it tends to prevent the operation of the other, it is antagonistic in effect. The synergistic effect of mixed or compounded drugs and the potentiation effect of some other substance upon a drug, such as alcohol upon barbiturates, is of medicolegal significance.

The desired effects of drugs, as well as toxic and side effects, are due primarily to the inherent variables, already referred to, in the action of drugs. These variations may be grouped into qualitative and

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(Footnote 13 continued.)
Williams, *Trial of Medical Malpractice Cases* (1960). It is also worthy of note that due to the increased presence of the FDA in drug clearance and regulation, the government itself might be a legitimate defendant. See Note, "Drug Amendments of 1962," at 135-60.

[14] See generally Beckman, *Pharmacology: the Nature, Action and Use of Drugs* (2d ed. 1961); Goth, *Medical Pharmacology* (1961); Grollman, *Pharmacology and Therapeutics* (5th ed. 1962); Krantz & Carr, *Pharmacological Principles of Medical Practice* (5th ed. 1961); Sice, *General Pharmacology* (1962); Emerson & Archer, "Some Medicolegal Aspects of Pharmacology," 3 *J. Pub. L.* 393 (1954); Leake, "The Scientific Status of Pharmacology," 134 *Science* 2069 (1961).

A note about terminology: A pharmacologist is a trained expert in biochemistry or physiology and often is a physician; a pharmacist is a registered or licensed technician who compounds and prepares drugs; a druggist sells previously prepared drugs. The term *contra-indication* as used throughout refers to an undesirable influence which a drug may have upon one suffering from a pathological state.

quantitative elements.[15] The *quantitative* variations are the differences of responses to known characteristics of drugs—the dose-effect relationship. A given dosage is too weak for some persons, proper for some, and too potent for others. The individual reactions thus can be charted along the familiar bell-shaped curve and are statistically predictable. For those for whom the dosage is too potent, the effect is described as toxic—that is, having a poisonous effect upon living tissue. This toxic reaction is affected directly by biological variation.[16] The *qualitative* variations, or side effects of a drug, are the individual reactions of persons to drugs. Side effects have been divided into: (a) the predictable ones in which all or most people have the reaction but where the effect cannot be described as a toxic reaction in the sense that it is due only to too much (an overdosage) of the drug; and (b) the unpredictable effects, which comprise the area of primary interest in drug litigation. This latter category, which is the one most often called to mind when side effects are mentioned, is generally further divided into: (a) *hypersusceptible* effects (also called intolerance and hyperergic reactions), which are non-allergic, toxic-like reactions occurring at the level of the usual or common dosage; and (b) *allergic* or true idiosyncratic reactions, where the effect is qualitatively different from the usual effects associated with the drug.[17]

"Allergy" is used loosely both to cover all those idiosyncratic reactions and, more specifically and accurately, to refer to those reactions in which an antigen-antibody relation can be found. In this latter sense allergy is the specifically acquired (or inherited) alteration in the capacity of the cells of the body to react to a drug as a result of previous exposure to the same drug or to one chemically similar.[18] The exact mechanism of acquiring or inheriting a propensity for allergic responses, however, is not yet known.[19] Given this strict definition of allergy, it is often extremely difficult for an internist or aller-

[15] See authorities cited at footnote 14.

[16] See authorities cited at footnote 14. See also Pfeiffer, "Exploratory Trials of New Drugs in Man," 3 *Clin. Pharm. Therap.* 397 (1962).

[17] See references cited at footnote 14. In addition, there is also the so-called "true idiosyncratic" reaction based upon inherent qualitative differences, often racial or national. See *Merck Manual* 25 (10th ed. 1961).

[18] See generally on allergy and other types of drug reactions, Alexander, *Reactions With Drug Therapy* (1955); Meyler & Peck, *Drug-Induced Diseases* (1962); Rosenheim & Moulton, *Sensitivity Reactions to Drugs* (1958); Schindel, *Unexpected Reactions to Modern Therapeutics: Antibiotics* (1957); Feinberg, "Allergy from Therapeutic Products," 178 *J. A. M. A.* 815 (1961); Harris, "Allergy," 2 *Trauma,* April 1961, p. 75; Lindberg & Newcomer, "Adverse Drug Reactions," 1 *Trauma,* Oct. 1959, p. 3.

[19] See references cited in footnote 14.

genist to demonstrate that there has been in fact an allergic reaction. Thus, the diagnosis of allergy is often made clinically upon the experience of others or upon the reoccurence of the same reaction upon readministration of the drug and its disappearance when the chemical is withdrawn.

Whether a given new drug will produce allergic sensitivity in man is usually impossible to predict before it has been tried, although in some instances its chemical similarity to other drugs which are known producers of allergic reactions may be relevant. Some side effects are so unusual and rare in incidence that they do not, as a matter of fact, turn up until the drug has long been on the market and thousands of patients have used it. Even when the allergy-producing effect of a drug is well documented, whether an individual will react to it in an undesired manner is still often difficult to predict. Some relatively reliable indicators, however, are available to the practitioner. The physician is greatly aided, for example, if there has been a past history of reaction to the same drug or one chemically similar, or if there is a history of prior allergic reactions to other substances, such as food, and of such disease as hay fever or asthma. On the other hand, use of a skin test or similar device in which a very small amount of the drug is administered in order to determine sensitivity has not proven of much value in pharmacological practice both because false negative determinations are common and because reactions often occur only upon full strength internal administration.[20]

Not only are there no adequate means today for determining in advance whether some untoward reaction will occur, but there are also no practical means of preventing a reaction after administration of the drug by desensitizing the patient or altering his allergic potential. Once a reaction has been detected, however, there are a number of drugs which have a therapeutic effect upon the course of the reaction, such as the antihistimines and the corticosteroids. In addition the simplest treatment is invariably followed, that of taking the patient off the drug. Although removal of the drug often leads to complete recovery, permanent, irreversible reaction is an all to common phenomenon. Because of these great dangers and the relative absence of a means of detection and control, it has become routine in the medical profession to adhere to the following rules: a drug should be administered only when absolutely necessary and only in the

[20] See references cited in footnote 14. However, in the case of penicillin, one of the most serious offenders, recent reports indicate that a fairly dependable skin test has been developed. *Medical World News,* Jan. 4, 1963, p. 75.

minimally necessary amount; the doctor should be constantly alert for incipient reactions, through the frequent use of modern examining devices; and the patient should be cautioned to watch for a reaction. The good doctor, thus, must have a high index of suspicion about new drugs and new symptoms.[21]

The types of allergic reactions commonly encountered in medicine and in the legal cases considered hereafter[22] are often classified on the basis of onset and duration:[23]

(a) Immediate reactions. This class includes the most evanescent and minor reactions, such as urticaria (hives) and angioneurotic edema, and also the deadly anaphylactic or anaphylactoid reactions, all too common in legal cases.[24]

(b) Serum sickness type reactions. This class is characterized by appearance only a week or more after administration but may be similar in symptoms to those immediately experienced.[25]

(c) Chronic reactions. Included here are the often fatal blood dyscrasias, such as aplastic anemia, thrombocytopenia, and agranulocytosis.[26]

(d) Contact dermatitis. This is reaction to a drug applied topically (locally, to one external spot).

Just which reactions are to be characterized as allergic rather than as toxic or the product of hypersensitivity is today often a matter of medical dispute, anaphylactic shock from penicillin being a good ex-

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[21] Lindberg & Newcomer, see footnote 18, at page 7.

[22] There are a number of sources available to the doctor and the lawyer to determine what side effects have been associated with particular drugs. See, *e.g.*, Modell, *Drugs in Current Use* (issued annually); *New and Nonofficial Drugs* (issued annually); *Physicians Desk Reference* (issued annually, containing approved statements of the manufacturers). It is of interest to note that a drug may produce an adverse reaction or side effect in at least two different ways. First, the active ingredients may produce exactly the result desired, but in the wrong organ or tissue of the body. For example, a drug designed to reduce cholesterol in one part of the body, say the blood, might unexpectedly and undesirably have the same effect on another part of the body. Second, and more commonly, the active ingredient may have an action or effect completely different from that intended in any part of the body. Thus, an antibiotic which is intended to destroy bacteria might have a toxic effect upon the marrow of the bone or upon a cranial nerve.

[23] This classification is based on Goth, cited at footnote 14, at pages 29-30.

[24] As in penicillin, a common cause of anaphylactic shock. See Kern, "Anaphylactic Drug Reactions," 179 *J. A. M. A.* 19 (1962).

[25] See Schick, "Serum Sickness and Serum Sickness-like Reactions" in *Fundamentals of Modern Allergy* 475 (Prigal ed. 1960).

[26] As in Chloromycetin (aplastic anemia and other dyscrasias).

ample.[27] In jurisdictions which make a distinction between the normal and abnormal plaintiff, this absence of medical certainty is a significant factor in litigation.[28]

B. Development of New Drugs; Role of Manufacturer and FDA

The development of new drugs in the United States is primarily the product of the initiative of private manufacturers.[29] While a new drug may be conceived in some academic surrounding, or while an established drug may be imported, the drug houses perform the extensive and costly research which is necessary to bring a drug to market.[30] At the same time, governmental supervision must be reckoned with in the developmental process. Accordingly, new drugs must be cleared by the FDA before marketing. The recent amendments to the Drug Act and the FDA regulations detailing the amendments have further extended the concern of the public to the testing phases of the drug before it is proposed by the manufacturer for marketing.[31] The fact nevertheless remains that the company which expects to profit eventually from sales of a drug is in charge of and closest to its testing and production.

1. *Stages of Development*

Today, once a new drug has been conceived, that is, once the potential beneficial effect of a chemical compound is suspected, the research and development which follow proceed along a fairly common pattern:[32] The first step, screening, involves laboratory tests upon animals or human tissue in vitro, to determine basic aspects of toxicity and therapeutics and to predict human dosages and tolerances.[33] The work is generally conducted within the drug house. Sec-

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[27] See Goth, cited at footnote 14, at page 29. Compare also the conflicting views of Baum in "Symposium," *Medical Science*, Feb. 25, 1962, p. 328, *with* those of Woodin, *id.* at 338, regarding the cause of bone-marrow depression.

[28] 2 Frumer § 29; 2 Hursh § 8.3; Noel, "The Duty to Warn Allergic Users of Products," 12 *Vand. L. Rev.* 331 (1959); Annot., 26 A. L. R. 2d 963 (1952). The difficulty in analyzing these so-called "allergy" cases arises from (a) uncertainty as to whether the court felt it was deciding an allergy case (cases involving the same product being treated differently); (b) uncertainty as to whether the defendant knew of the allergic potential of the product.

[29] DeHaen, "Drug Development," *Medical Science*, Nov. 1963, p. 19.

[30] In 1961 a spokesman for the Pharmaceutical Manufacturers Association reported that, based upon carefully projected figures, approximately $204 million would be spent in the following year by its members on drug research and $22 million more would be spent by others on such research. 265 *N. Eng. J. Med.* 655 (1961).

[31] See footnotes 8 and 9.

[32] See DeHaen footnote 29.

[33] Animal tests cannot be used to predict precisely how a drug will affect a human, since a drug may have an adverse effect on one animal species and

(Footnote continued on next page.)

ond is clinical testing on normal humans to determine tolerances, metabolism, absorption, elimination, and toxicity for dosage purposes, without direct concern for the side effects or the proper dosage to induce desired effects.[34] This work is again conducted by a clinical investigator under the close supervision of the drug house. This is *Phase 1* of the two clinical pharmacy phases in the new drugs regulations.[35] Third, trials are conducted on the efficacy of the drug in patients suffering from the disease or illness sought to be treated or otherwise affected, with attention to side effects and contra-indications, usually conducted in an institution, or at least somewhat under its control, as well as under the supervision of the primary investigator and the drug house.[36] This is *Phase 2* in the new drugs regulations. Fourth are field trials by doctors in private practice using their own patients as subjects, with a large amount of data, especially on adverse reactions, being funneled back to the drug house.[37] Under the new drugs regulations this is *Phase 3,* the clinical phase. The last step in this process would be submission of a new drug application

(Footnote 33 continued.)
not on another, or on certain animals but not on man. See *Medical World News,* Sept. 14, 1962, p. 59.

[34] Here, normal subjects are used, and there is no treatment per se. These subjects are often paid volunteers, and their legal status is somewhat uncertain. See Part III in future issue. Effort is made to obtain a large enough cross-section of "normal" persons to include those with existing diseases and handicaps, in order that information on contra-indications for a particular class of persons might appear. Terminal cases (persons suffering from an incurable, fatal disease) are also often used.

[35] 21 C. F. R. § 130.3(a)(10)(a) (1963).

[36] There is, of course, no firm distinction between these stages. At this stage comparison is often made with the efficacy and safety of established drugs used for treatment of the same condition. Statistical controls serve to eliminate the introduction of bias into the results and their evaluation. The often-used *double-blind test* requires both that (1) the patient not know whether he is receiving the drug under scrutiny or a placebo, and (2) the administrator not know whether the patient is receiving the drug or a placebo (the fear being that he will unconsciously induce a good patient reaction). See generally Greiner, "Subjective Bias of the Clinical Pharmacologist," 181 *J. A. M. A.* 120 (1962); Ladimer, "Ethical and Legal Aspects of Medical Research on Human Beings," 3 *J. Pub. L.* 467, 474 (1954).

[37] For some representative case histories of clinical trials reported in the literature, see Hammon, "Evaluation of Red Cross Gamma Globulin as a Prophylactic Agent for Poliomyelitis," 151 *J. A. M. A.* 1272 (1953); Roland, "Clinical Trial of Metronidazole," 180 *J. A. M. A.* 242 (1962); Shapiro & Franklin, "Demethylchlortetracycline in Clinical Practice," 176 *J. A. M. A.* 596 (1961). This process of detecting side effects in patients continues after a drug has been marketed, of course. It is considered "new" or "on trial" for at least several years after initial marketing.

(NDA) to the FDA, which requires most of the investigatory steps taken by the drug house while doing its research.[38]

2. *Drug House Control and FDA Regulations*

Every pharmaceutical house has a medical department headed by a medical director, usually a doctor trained in pharmacology.[39] This department controls the development of the new drug, selects the clinical investigators to do the research, sets the standards for experimentation, and interprets the resulting data.[40] The clinical investigator is generally an experienced, established medical researcher not in the employ of the drug house, who can perhaps fairly be regarded as an independent contractor. Because the drug house stands to gain from a favorable investigation (one showing high efficacy and low incidence of reaction), the relationship of drug house and investigator has often come under close scrutiny and has sometimes been the subject of direct criticism.[41] Aside from the possibility of the investigator's loss of independence by drug house influence, there has been concern for the quality and competency of the researchers and for the accuracy of their work. Terms such as "rigged" and "tailored" have been used on occasion to describe the research results submitted with NDA's by the drug houses.[42]

If such problems do exist to a significant extent, a major stride toward improvement has been taken in the recently revised FDA regulations on new drugs.[43] By amending generalized rules for testing which had been untouched since first put forth in 1938, the FDA has for the first time directly intervened in the preliminary stages of

[38] The total number of subjects and patients upon whom the drug is tested in one manner or another can vary from a few hundred to tens of thousands. Four or more years may be consumed in this work, with one year being spent on toxicity studies, two on clinical evaluation, and one for FDA evaluation.

[39] See Fox, "Physicians on the Drug Industry Side of the Prescription: Their Dual Commitment to Medical Science and Business," 25 *J. Health & Human Behavior*, No. 1, p. 3 (1962) (a first-rate attitudinal study by a sociologist of the seven doctors in one pharmaceutical house); Kern, "Legal Problems of the Drug Research Director," 17 Food Drug Cosmetic Law Journal 7 (1962).

[40] According to Fox, see footnote 39, the criteria for the selection of clinical investigators in part involve business motives, since selecting men with influential names is deemed more important than picking skilled investigators.

[41] *Kefauver Report*, Part IV. See also recent reports by Lessing, footnote 345.

[42] See discussions of "rigged research" in "Editorial," 265 *N. Eng. J. Med.* 1116 (1961); *Medical Tribune*, June 4, 1962, p. 3.

[43] 21 C. F. R. § 130 (1963). These regulations operate by exempting a new drug from the FDA clearance requirement of 505(a) of the Act if certain labeling, notice, and other conditions are met. 52 Stat. 1052 (1938), as amended, 76 Stat. 784 (1962), 21 U. S. C. § 355(a) (Supp. IV, 1963).

investigation in an affirmative manner. Whereas its former emphasis was upon reviewing the *results* of all research, the FDA may now interpose itself at the stage when use of an investigational new drug (IND) on humans is proposed by requiring such detailed information as the nature of the drug, the investigators, subject and animal studies to date, and what actually happens as research proceeds.[44] This new FDA authority, it should be noted, extends beyond the drug house to the clinical investigator in the new regulations.[45] It may, thus, be fairly concluded that these new regulations and basic amendments to the Drug Act should have a significant effect in civil litigation as indications of minimal acceptable standards.[46]

It is also worthy of note that there are certain non-FDA, non-drug house elements of control in clinical investigation which are found in the rules and practices of the medical profession[47] and of the institution in which the tests are being carried out (usually a hospital). This is true especially at stage three, outlined above, where sick patients are being treated experimentally under closely controlled conditions. This work, furthermore, is often performed under the guidance of a therapeutics or pharmacology committee of the hospital.[48]

3. Use of Human Subjects; Ethical Considerations

Except for those who decry any use of humans as experimental subjects ("guinea pigs"), it is now well-accepted that in order to determine whether a drug has the usefulness and safeness that merit wide dissemination, it is absolutely necessary to use human sub-

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[44] It should be noted that certain groups, including the pharmaceutical industry and organized medicine, did not and do not regard the new drug regulations as an improvement. A prime objection is that the new regulations will impede new drug research. See, *e.g.*, the statement of Dr. F. J. L. Blasingame, AMA's executive vice president, 182 *J. A. M. A.* 932 (1962); Stetler, "Relation Between AMA and FDA," 18 FOOD DRUG COSMETIC LAW JOURNAL 72, 76 (1963). See also Note, "Drug Amendments of 1962."

[45] The investigator is to agree in writing to maintain complete records on the disposition of the drug, to prepare and maintain complete case histories, and to furnish periodic reports to the drug manufacturer on all cases and immediate reports on any adverse side effects. Any investigator who deliberately fails to keep such records is to be excluded from further supplies of the drug by the manufacturer. The significance of these regulations will lie in their enforcement, however.

[46] The new regulations, 28 *Fed. Reg.* 1459-61 (1963), require a showing of effectiveness as well as safety at the pre-marketing stage. See footnote 9.

[47] See sub-section 3 of text.

[48] See American Hospital Ass'n, *Statement of Principals Involved in the Use of Investigational Drugs in Hospitals* (1957); Friend, "Drug Reaction Committees in Hospitals," 181 *J. A. M. A.* 111 (1962); and Ladimer, footnote 36, at 496.

jects.[49] And, except for the small minority which would freely use human subjects for all types of experiments on the basis of overriding social needs, it is generally conceded that there is a need for controls on the use of human subjects, notwithstanding their apparent willingness to submit.[50] Medicine has attempted to work out its own guidelines for experimentation, both from high scientific motives and because of fear of increased injection of governmental and administrative supervision.[51] These precatory guidelines have taken the form of rules or commandments, the best known of which are the Nuremberg rules[52] and those promulgated by the American Medical Association (AMA).[53]

The FDA, however, was apparently not satisfied with these forms of voluntary policing. Over the strong objection of organized medicine,[54] it promulgated the 1963 regulations, which include requirements that the sponsor supply investigators with full information on preclinical investigations and that the investigator keep full records and administer the drug only to subjects under his personal supervi-

[49] Dr. Chester S. Keefer testified before the House Interstate and Foreign Commerce Committee, August, 1961:

> There is no substitute for the trial of drugs in man. . . . It should be emphasized that the responsibility for the administration of drugs to a patient, whether the drugs are on the market or in an experimental stage, is that of the physician. . . . But there is no such thing as absolute safety or absolute effectiveness. And progress does not come without the payment of some price. . . . Medicine is at best an uncertain science. There is no way of putting a new drug application through a computer and knowing what adverse side effects may occur.

Reported, 4 *New Medical Materia,* Oct. 1962, p. 6. See also footnote 33.

[50] See generally Lear, "Human Guinea Pigs and the Law," *Saturday Review,* Oct. 6, 1962, p. 55.

[51] See generally on ethical problems and moral codes in use or proposed, Bean, "The Ethics of Experimentation on Human Subjects," in *The Clinical Evaluation of New Drugs* 76 (Waife & Shapiro ed. 1959); Beecher, *Experimentation in Man* (1958); Wolf, "Human Beings as Experimental Subjects," in *The Clinical Evaluation of New Drugs* 85 (Waife & Shapiro ed. 1959); Beecher, "Editorial," 3 *Clin. Pharm. Therap.* 141 (1962); Greiner, "The Ethics of Drug Research on Human Subjects," 2 *J. New Drugs* 7 ((1962); Ladimer, footnote 36, at 486-99; Comment, "Legal Implications of Psychological Research With Human Subjects," 1960 *Duke L. J.* 265. See also materials cited *infra* note 347.

[52] 2 *Nuremberg Military Tribunals, Trial of War Criminals* 181 (1947). These rules were promulgated by the Nuremberg court as a result of trial of Nazi doctors in 1947.

[53] A. M. A., *Medicolegal Forms* 37 (1961), especially Form 29, "Authority for Treatment with Drugs under Clinical Investigation," a form of perhaps questionable validity since it does not on its face purport to inform the patient what the actual risks are but only generally that the procedure is experimental. Not only are these guidelines voluntary, but there also is not much evidence that they are subscribed to by a significant section of the medical profession in practice.

[54] See footnote 44.

sion or by investigators responsible to him.[55] On the matter of consent, the investigator must certify that he will inform any patients, subjects, or their representatives that the drugs are investigational in nature and that he will obtain their consent "except where this is not feasible or, in the investigator's professional judgment, it is contrary to the best interests of the subjects."[56]

How much the patient or control subject is to be told about the nature of the study being made has been a particularly thorny problem. While law[57] and medical ethics[58] would seem to dictate full disclosure, scientific circles, organized medicine, and the drug houses have steadfastly maintained that full disclosure can destroy the validity of the study and introduce both doctor and patient bias into the results.[59] Medicine seems to have won the day here in that the new regulations and the Kefauver-Harris Amendments leave a loophole

[56] 21 C. F. R. § 130.3(a)(12) (1963) lists all of the requirements for conducting the clinical phases (1 and 2); subsection (13) spells out similar requirements for clinical trials (phase 3).

[56] 21 C. F. R. § 130.3(13)(12)(6)(g).

[57] There is a body of law in malpractice in which the term *experimentation* is used, opprobriously, to indicate a type of medical fault. In new drug experimentation, however, a doctor is generally investigating a new drug or a new use of an established drug. See generally Stetler & Moritz, *Doctor and Patient and the Law* 326 (1962). In this area of the paper it is better to call the doctor's work *investigation* since he is doing what is proper for studying pre-clearance drugs. Here there would be no automatic malpractice because of *experimentation,* although there is as yet no case law on this point. See footnotes 50—53 on the proper precautions such an investigator is to take. In the final stages of testing, when a physician is using a drug at its recommended dosages upon a private patient, the situation is indistinguishable from ordinary use in practice. On the physician's liability in use of drugs before they are marketed see Hatry, "Editorial," 4 *Clin. Pharm. Therap.* 4 (1963) (perceptive article by a lawyer); Ladimer, "Ethical and Legal Aspects of Medical Research on Human Beings," 3 *J. Pub. L.* 467 (1954); Louisell, "Legal Limits on Human Experimentation," 6 *Arch. Environ. Health* 784 (1963); Markel, "Legal Considerations in Experimental Design in Testing New Drugs on Humans," 18 FOOD DRUG COSMETIC LAW JOURNAL 219 (1963).

[58] See footnote 51.

[59] See, for example, views of Dr. Chauncey D. Leake, presented to the House Interstate and Foreign Commerce Committee, reported in *Medical Tribune,* Oct. 8, 1962, p. 1. Compare the statement of Dr. Frank J. Ayd, Jr., *Medical Tribune,* Sept. 17, 1962, p. 12:

> "An adult has the right to accept or reject a recommended treatment. It is the physician's task to present the facts to the patient objectively and with as little bias as possible. His responsibility in this matter is grave. A doctor must recognize that he does not have the right to urge treatment with a new drug without just cause. However desirous he may be learning, of making progress, or of doing something for the common good, the practitioner must not yield to the temptation to 'sell' his proposal and thus acquire the necessary authorization."

allowing discretion.[60] Since a double-blind experiment is *de rigueur* today, and since that type of test requires that a patient not be told of its nature, it seems that patients will not be informed any more often or in more detail now than before the law stepped in.[61]

4. Adequacy of Tests and Reports

It is no longer an uncommon phenomenon for side effects to turn up only after a drug has been marketed and widely used, and then to be of a serious enough nature to justify either its withdrawal from the market or the imposition of stringent restrictions on its use. The question invariably raised in this situation is whether the clinical trials were adequate in terms of number, type, and depth of investigation.[62] There probably have been some instances in which the FDA relied upon inadequate results or merely failed to prevent a poorly tested drug from entering the market, a danger which has been greatly diminished today.[63] But it is more probable in such a case that research has been shoddily done by the drug houses and their investigators, and, in some cases, that data have been fraudulently created either to enhance efficacy or camouflage adverse reactions.[64] Certain abuses have also been laid at the doorstep of the medical press. Thus, articles which the medical journals carry about new drugs still in their experimental stage, highly influential upon physicians reading them, may at times be more favorable than the intermediate results indicate, or may be the report of but one out of many experiments performed, or one not done according to exacting scientific principles.[65] Even worse, it was recently demonstrated that some medical journals, which by virtue of their ownership are the captives

[60] Section 103(b), 76 Stat. 783 (1962), 21 U. S. C. § 355(i) (Supp. IV, 1963), amending § 505(i), 52 Stat. 1052 (1938).

[61] The National Health Federation has declared that the exceptions leave a loophole through which "human guinea pig" experimentation on unsuspecting subjects is still possible. Reported in *Modern Medicine,* Feb. 4, 1963, p. 14.

[62] On the type of tests which should be made and the scientific controls exercised, see materials cited in footnote 36.

[63] The Kefauver Committee, for instance, cited the instance of Diabinese as an inadequately tested drug. *Kefauver Report* 210. See also Badgley, "An Assessment of Research Methods in 103 Scientific Articles From Two Canadian Medical Journals," 85 *Can. Med. Ass'n J.* 246 (1961).

[64] The manufacturer of MER/29 was convicted of making false statements to the FDA in 1964, *Drug News Weekly,* June 10, 1964, p. 1, and the maker of Dornwal, a tranquilizer, was only recently indicted for concealment of adverse effects associated with that drug, *N. Y. Times,* Aug. 25, 1964, p. 1, col. 3.

[65] See Lasagna, *The Doctors' Dilemma* 144 (1962). See also *Kefauver Report* 189, referring to the subservience of certain medical journals to the drug industry.

of certain drug houses, have opened their pages to inaccurately platitudinous articles on the "miracle" effects of new drugs.[66]

C. Food and Drug Administration Supervision

1. New Drug Applications

We have already considered the scientific stages in the development of a new drug[67] and the role which the FDA plays in these stages, both by direct requirements and indirectly through the requirements for NDA's.[68] As with the requirements for investigation, the requirements for NDA's underwent major revision by the Kefauver-Harris Drug Amendments.[69]

At the heart of the drug law is the requirement that no new ethical drug may be admitted into interstate commerce until the manufacturer has made application to the FDA, providing proof that the drug is safe, and until the application has become effective.[70] The application must contain the following information: (a) full reports on investigations made as to the safety and efficacy of the drug, both on animals and man; (b) a full list of chemicals used as components

[66] Lear, "The Struggle for Control of Drug Prescriptions," *Saturday Review,* March 3, 1962, p. 35. See also "Editorial," 266 *N. Eng. J. Med.* 1280 (1962). Since a major source of finance of these medical journals is advertising, the possibility of influence is undeniably present. Among other factors which tend to prevent complete and accurate dissemination of information to the profession about a new drug, of relevance to civil liability, are (a) the rush to print, resulting in incomplete reports (see DeHaen, Comment, Medical Science, March 10, 1962, p. 474) and (b) puffing and sensationalization by the lay press of reports, sometimes properly released by researchers and sometimes given knowingly for sales purposes (see *Kefauver Report* 183; footnote 51).

[67] A *new drug* is defined in the Drug Act as one not generally recognized as safe or effective by experts for uses intended or one presently being used in investigation experiments. Section 201(p), 52 Stat. 1041 (1938), 21 U. S. C. § 321 (p) (1958). This definition is intended to cover not only true new drugs (those utilizing a new chemical) but also new forms of old established drugs, including combinations of old ones, new dosage forms, new preservatives or even new uses.

[68] The literature on new drug applications and FDA practice is sparce. See Van Winkle, "New Drug Applications," in *Drug Research and Development* c. 13 (Herrick ed. 1948); Leake, Gregory, Ewing & Emerson, "Appraisal of New Drugs," 127 *J.A.M.A.* 244 (1945); Smith, New Drug Applications, 17 FOOD DRUG COSMETIC LAW JOURNAL 497 (1962); Note, "Drug Amendments of 1962," 135-38. See also DeHaen, footnote 29.

[69] See footnote 8. There was a good deal of opposition to the sections of the new law which dealt with new drugs on the part of drug houses and organized medicine. See Stetler, footnote 44, at pages 75-77.

[70] Section 505(a), 52 Stat. 1052 (1938), 21 U. S. C. § 355(a) (1958). Exempted from these requirements are investigational drugs, antibiotics (which are controlled through certification, see note 101 *infra*), and biological products (controlled by the Public Health Service).

in the drug and a full statement as to its composition; (c) a full description of methods and processes used in manufacture of the product and its packaging and a statement as to the facilities and controls used in manufacture; (d) samples of the drug in the dosage and form intended for distribution; and (e) specimens of the proposed labels.[71]

Before the 1962 amendments the Act made an NDA automatically effective if the FDA did not take affirmative steps within 60 days by acting either to accept, deny, postpone, or suspend the application where untrue statements were made or where, after the date of the application, new methods were developed which revealed the drug to be unsafe.[72] Under the 1962 amendments, however, there is no longer any automatic clearance of new drugs by a mere failure of the FDA to act. Under the new law, a drug cannot be marketed until it receives affirmative FDA approval as having met the requirements for both safety and efficacy. The FDA is given a 180-day period for initial consideration of an application, subject to further extension. Final decision, based on a formal hearing, may thus be postponed for half a year or more.[73]

The usual NDA today is a massive document full of animal, pharmaceutical, and clinical trial information collected over a period of years. Chief among the documents are the manufacturer's claims for safety and efficacy and his proposed statements about side effects and contra-indications. Exactly what then transpires within the FDA as far as evaluation of data, testing of the product, and decision-making is not a matter of full disclosure.[74] Certainly all the data submitted by the manufacturer are closely scrutinized, and not infrequently more information is sought. Apparently, however, no independent tests are

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[71] Section 505(b), 52 Stat. 1052 (1938), 21 U.S.C. § 355(b) (1958).

[72] Section 505(c), 52 Stat. 1052 (1938), 21 U.S.C. § 355(c) (1958).

[73] Section 104(b), 76 Stat. 784 (1962), 21 U. S. C. § 355(a) (Supp. IV, 1963), amending § 505(c), 52 Stat. 1052 (1938), 21 U.S.C. § 355(c) (1958). If at the end of the original 180 days the FDA is not satisfied that the drug should be approved, it must give notice of an opportunity for a hearing and the hearing, if requested, must be held within 120 days of the notice. A final determination from the FDA is due within 90 days after the hearing. On the power to suspend an NDA, even after the drug has been marketed, as a device to accomplish removal from the market, see footnote 128.

[74] Note the discussion in *Modern Medicine*, Oct. 15, 1962, p. 26, on the physical arrangements of the FDA's work. New regulations will partially lift the veil of secrecy around FDA activities by providing for publication of reports in the Federal Register of all approvals of NDA's and all withdrawals of previous approvals.

See also Mintz, "New Drugs: Is Government Supervision Adequate?," *The Reporter*, March 28, 1963, p. 46.

performed by the FDA or its agents.[75] The FDA Commissioner has stated that the basic problem is one of balancing the good that a drug can produce against its demonstrated safety.[76]

Whereas formerly only safety was expressly a factor for FDA consideration, and effectiveness was considered only a part of safety,[77] under the 1962 changes the burden is now placed on the proponent of the NDA to show "by substantial evidence" that the drug will have the effect it purports to have.[78] At the moment when an NDA is affirmatively acted upon, the FDA notifies the manufacturer as to those conditions for which the drug may be stated to be useful, what warnings and contra-indications must appear in its literature, what dosages and methods of administration must be stated, and what other material relevant to safe and honest use must be promulgated.[79]

2. Misbranded and Adulterated Drugs; Advertising Control

The primary concern of the FDA with *established* ethical drugs already on the market falls into two statutory provisions covering adulterated and misbranded drugs.[80] The *adulterated* drug provisions cover drugs with impurities or poisons, those consisting of decomposed substances, those of quality or purity differing from that listed in official compendia,[81] and those containing illegal coal tar dyes.[82]

The FDA may also exercise its powers in relation to *misbranded* drugs, defined as: those products with false or misleading labeling, advertising, or any other written, printed or graphic material used to

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[75] Wiley, "The Analysis of Drugs," 16 Food Drug Cosmetic Law Journal 733, 736 (1961).

[76] Testimony of George Larrick before Senate Subcommittee on Antitrust and Monopoly, reported in 4 *New Medical Materia,* Oct. 1962, p. 5.

[77] Even toward the end of the earlier period an FDA examiner had declared that efficacy of a new drug was material and relevant to NDAs and had ruled that Altafur was not as efficient as other anti-bacterial drugs. Reported in 178 *J.A.M.A.* No. 10, Dec. 9, p. 17, 1961.

[78] Section 102(b), 76 Stat. 781 (1962), amending § 505(b), 52 Stat. 1052 (1938), 21 U. S. C. § 355(b) (1958). This section comprehensively lists the grounds for refusal of application. On the matter of efficacy of new drugs, see Wilson, "How to Establish the Effectiveness of New Drugs," 92 *Drug & Cosmetic Industry* 152 (1963). See also Note, "Drug Amendments of 1962," at 111.

[79] Farren, *New Medical Materia,* April 1962, p. 37.

[80] Sections 501, 502, 52 Stat. 1049-50 (1938), 21 U. S. C. §§ 351, 352 (1958), as amended, § 101, 76 Stat. 780 (1962), 21 U. S. C. § 351(a) (Supp. IV, 1963). See excellent discussion in "Developments in the Law—The Federal Food, Drug and Cosmetic Act," 67 *Harv. L. Rev.* 632, 640-59 (1954).

[81] Section 501(b), 52 Stat. 1049 (1938), 21 U.S.C. § 351(a), (b) (1958).

[82] Section 501(a)(4), 52 Stat. 1049 (1938), 21 U.S.C. § 351(a)(4) (1958). See general discussion of the FDA's powers in relation to misbranded and adulterated drugs in "Developments in the Law," footnote 80, at pages 673-720.

promote drug sales at any level; those lacking required warnings; those with the wrong name; and those with misleading packaging, directions, or warnings.[83] The basic policy is one of full disclosure. Specifically, in the area of labels and labeling, misbranding exists under the statutory scheme if the composition, effectiveness or nature of characteristics of the drug are misrepresented.[84] The label is to be conspicuous and its directions and warnings are to appear prominently.[85] Habit-forming substances are to be warned of,[86] and common names and active ingredients are to be clearly stated.[87] A drug will be deemed misbranded if warnings and adequate directions for use are not given where special pathological conditions or use with children are involved.[88] Further, a drug is considered misbranded if it is dangerous to health if used in the dosage, duration, or frequency prescribed or suggested on the label.[89] A label must also state where required, "Caution: Federal law prohibits dispensing without prescription."[90]

By the terms of the 1962 amendments, *labeling* for prescription drugs must also contain a statement of the names and quantity of all active ingredients, whereas the quantity formerly had to be stated for only certain named drugs.[91] In addition, the scientific or generic name (denominated the "established name") must appear on all labeling in type size at least half as large as that of the brand name.[92]

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[83] Section 502, 52 Stat. 1050 (1938), 21 U.S.C. § 352 (1958).

[84] Section 502(a), 52 Stat. 1050 (1938), 21 U.S.C. §352(a) (1958).

[85] Section 502(c), 52 Stat. 1050 (1938), 21 U.S.C. § 352(c) (1958).

[86] Section 502(d), 52 Stat. 1050 (1938), 21 U.S.C. § 352(d) (1958).

[87] Section 502(e), 52 Stat. 1050-51 (1938), 21 U. S. C. § 352(e) (1958), as amended, § 112(a), 76 Stat. 790 (1962), 21 U.S.C. § 352(e) (Supp. IV, 1963). See footnote 92.

[88] Section 502(f), 52 Stat. 1050 (1938), 21 U.S.C. § 352(f) (1958).

[89] Section 502(j), 52 Stat. 1051 (1938), 21 U.S.C. § 352(j) (1958).

[90] Section 503(b)(4), 65 Stat. 649 (1951), 21 U.S.C. § 353(b)(4) (1958). Exempted from these labeling requirements are drugs which are resold by a pharmacist on a prescription as long as the label of the dispenser is affixed and bears his name, prescription number, the date, and the doctor's directions for use, if any.

Similar requirements exist for labeling of drugs which might be habit forming, § 502(d), 52 Stat. 1050 (1938), as amended 53 Stat. 853-54 (1939), 21 U.S.C. § 352(d) (1958).

[91] Section 112(a), 76 Stat. 790 (1962), 21 U.S.C. § 352(e) (Supp. IV, 1963), amending § 502(e), 52 Stat. 1050-51 (1938), 21 U.S.C. § 352(e) (1958). In addition, in the instance of certain inactive ingredients listing is also required.

[92] Section 112(a), 76 Stat. 790 (1962), 21 U.S.C. § 352(e) (Supp. IV, 1963), amending § 502(e), 52 Stat. 1050-51 (1938), 21 U.S.C. § 352(e) (1958). The term *established drug* is defined as the name designated for it under a new name-standardization authority also created by the same amendment. If there has not been such a designation, the

(Footnote continued on next page.)

And, in the case of a drug previously approved and marketed, where upon FDA re-evaluation in the light of new evidence it appears that the labeling is false or misleading on the basis of a fair evaluation of all material facts, the FDA is empowered to order it withdrawn from the market.[93]

Specifically as to *advertising,* which has been held by case law to fall within the misbranding provisions of the Drug Act,[94] a new Kefauver-Harris revision requires that advertisements and other descriptive printed matter show the formula quantitatively and bear the "established name" of the drug.[95] Moreover, the advertisements must present a true and non-misleading brief summary of information as to adverse side effects, contra-indications, and effectiveness for the guidance of the physician. Regulations promulgated in 1963 also require side effect warnings *if* advertisements present information regarding indications or dosage.[96] These regulations tie in with the so-

(Footnote 92 continued.)
official title in an official compendium is to be used, or, lacking that, its common or usual name, if any. See extensive discussion and evaluation in Note, "Drug Amendments of 1962," at pages 120-35.

The FDA regulations added in 1963 require the use of the established name in every advertisement and on every label. 28 Fed. Reg. 6375 (1963). In unprecedented litigation begun thereafter by 37 drug manufacturers and their trade association, the trial court held that the new statute did not empower the FDA to promulgate this "every time" regulation. *Abbott Labs v. Celebreze,* — F. Supp. — (D. Del. 1964).

[93] Section 102(d), 76 Stat. 781 (1962), 21 U. S. C. § 355(e) (Supp. IV, 1963), amending § 505(e), 52 Stat. 1052 (1938), 21 U.S.C. § 355(e) (1958). Also by new amendment, the FDA is empowered to refuse approval of an NDA if, on the basis of a fair evaluation of all material facts, it is found that the labeling which the manufacturer proposes is false or misleading in any particular respect. Section 102(c), 76 Stat. 781 (1962), 21 U.S.C. § 355(d)(6) (Supp. IV, 1963), amending § 505(d), 52 Stat. 1052 (1938), 21 U.S.C. § 355(d) (1958).

[94] See *Kordel v. United States,* 335 U.S. 345 (1948); *United States v. Urbuteit,* 335 U.S. 355 (1948); *Alberty Food Products v. United States,* 194 F.2d 463 (9th Cir. 1952); *United States v. Research Labs.,* 126 F.2d 42 (9th Cir. 1942); *United States v. 38 Dozen Bottles of Tryptacin,* 114 F. Supp. 461 (D. Minn. 1953). It has also been held that there is no compliance where directions for use are set out in one place and warnings in another, *Colgrove v. United States,* 176 F.2d 614 (9th Cir. 1949), *cert. denied,* 338 U.S. 911 (1950).

[95] Section 131(a), 76 Stat. 791, 21 U.S.C. § 352(n) (Supp. IV, 1963).

[96] 21 C.F.R. §§ 131.15-131.17 (1963). Advertising claims for new drugs are restricted to only those conditions originally approved by the FDA. In instances where there is a serious hazard connected with the drug, advance approval by the FDA of the proposed advertisement may be required. Seriously misleading advertisements under these regulations are grounds for the FDA to order removal of all stocks of the drug from the market. While a full statement of side effects, therefore, need not appear in ads, a complete statement is required for all other classes of information, including mailing pieces, detail man literature, brochures and price lists. The prior approval provision brings the FDA from its

(Footnote continued on next page.)

called "package insert" rules, added in 1961, which, with exceptions for certain common drugs about which it was assumed the medical profession was well-informed, called for more noticeable labels on all inserts accompanying medicines by use of at least eight point type and special location requirements.[97]

FDA authority has been exercised in conditioning an ordered withdrawal of a drug upon the use of special labeling with special warnings which it designates in the case of drugs which are dangerous but of unique therapeutic value.[98] After a series of injuries and deaths in 1952 associated with Chloromycetin, for example, the FDA ordered that the label bear the following warning:

> Certain blood [disorders] . . . have been associated with the administration of Chloromycetin. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloromycetin should not be used indiscriminately or for minor infections.[99]

And when further injury and death were reported, the FDA in 1961 added even stricter labeling requirements for the drug.[100]

3. Certification of Batches of Drugs; Quality Control

Special provisions have been made for certain classes of drugs which Congress has become convinced are hard to manufacture in uniformly high quality. In the case of insulin and certain antibiotics (penicillin, chloramphenicol, streptomycin among them), the FDA is empowered to inspect and certify each batch of the drug as it is manufactured.[101] The Salk and Sabin vaccines were brought under a similar type of control but under the supervision of the Public Health Service.

The general power of the FDA to investigate manufacturing conditions and to insist on quality controls for the production of all phar-

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(Footnote 96 continued.)
traditional rule-making approach into one more accurately called adjudicatory. See generally, Note, "Drug Amendments of 1962."

In addition a section has been added to these regulations, consistent with the requirements of a 1962 amendment, that where a new drug is on the market the manufacturer must submit all advertisements and mailing pieces on a current basis to the FDA to enable it to determine if there is compliance with its original restrictions.

[97] 21 C. F. R. § 131.10 (1963). See description in 177 *J.A.M.A.* No. 11, Sept. 16, 1961, p. 33; *Modern Medicine,* Sept. 18, 1961, p. 7. See, on labeling requirements, Kleinfeld, "Recent Developments in Drug Labeling Regulations and Interpretations," 17 FOOD DRUG COSMETIC LAW JOURNAL 238 (1962).

[98] See HEW Release, Sept. 26, 1961; *Modern Medicine,* Oct. 16, 1961, p. 3.

[99] *Kefauver Report* 194.

[100] 21 C. F. R. § 146d.301(c) (1962).

[101] Section 507, 59 Stat. 463 (1945), 21 U.S.C. § 357 (1958). Regulations on certification are in 21 C. F. R. §§ 146-146e.431 (1963). See Duckworth, "Antibiotic Certification," 17 FOOD DRUG COSMETIC LAW JOURNAL 229 (1962).

maceutical products was greatly expanded under the 1962 amendments and 1963 regulations thereunder, to assure that drugs are safe, pure, and of proper identity, quality, and strength.[102] A further definition is added to "adulterated" to include a drug produced in a plant that is not established, equipped, administered or operated in conformity with "current good manufacturing practices."[103] Additionally, a new drug previously cleared may be ordered removed from the market if, upon re-evaluation in the light of new evidence, it is found that the manufacturing controls, facilities, or methods are inadequate.[104] While these controls indicate that the production of impure drugs is unlikely today, it is still far from impossible.[105]

D. Marketing a Drug; Experience in Use; Withdrawal

1. Inducing the Physician to Prescribe

Of significance to the manufacturer's civil liability are the methods he uses in selling his product—the means he employs to convince the prescribing physician to use his drug rather than another drug or another form of therapy. If the manufacturer misrepresents the safety or efficacy of a drug, or if he conceals or fails to mention side effects, and if either of these actions induces the physician to prescribe where he would not otherwise have done so, these actions will be relevant evidence of the manufacturer's civil liability.

Precise identification of the influential sources of information used by the doctor in his choice of ethical drugs and especially of newly-marketed drugs is a much disputed issue.[106] Sources of information commonly cited include the following:

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[102] Section 201(a), 76 Stat. 792 (1962), 21 U.S.C. § 374(a) (Supp. IV, 1963), amending § 704(a), 67 Stat. 477 (1953), 21 U.S.C. § 374(a) (1958). Consulting laboratories doing work for drug firms are also included in the list of those subject to inspection. Federal courts are expressly given power to issue injunctions against firms which refuse to permit inspections. The 1962 amendment requires that each manufacturer register with the FDA and that FDA inspect each plant as least biennially. Here again a licensing process has been introduced into a previously-used rule-making pattern.

[103] The new regulations of 1963, 28 *Fed. Reg.* 6385 (1963), define "current good manufacturing practices," serving as a guide to the manufacturers.

[104] See footnote 103. Approval may also be withdrawn for failure to establish a system of maintaining the required records, failure to make reports as required, or refusing to allow the FDA access to such records.

[105] See example reported by Weber, "Drug Contamination with Diethylstilbestrol," 268 *N. Eng. J. Med.* 911 (1963) (contamination of drug with hormone).

[106] See generally May, "Selling Drugs by 'Educating' Physicians," 36 *J. Med. Ed.* 1 (1961); Searle, "The Pharmaceutical Industry," 36 *J. Med. Ed.* 24 (1961) (rebuttal to May, above, by eight presidents or managers of drug firms).

(a) The drug house's promotional literature about the product, including advertisements, direct mail, and drug manuals;

(b) Personal statements by detail men who call on the doctor;

(c) The manufacturer's labels, containers, and package inserts;

(d) Articles in medical journals;

(e) Evaluations from unbiased appraisers including drug letters;

(f) Continuing medical education including symposia on new pharmaceuticals; and

(g) Statements from pharmacists.

The answer one receives on the relative influence of these factors depends upon the source of the opinion. Organized medicine, individual physicians,[107] the drug houses,[108] the Kefauver Committee,[109] and even the pharmacists give differing reports. All sides would concede that the ideal is that the medical profession inform itself of the qualities and capabilities of the various new drugs, without direct influence from any outside source. Practice deviates from the ideal, however. Typically, the doctor does not have the time to read all the available material,[110] let alone conduct experiments on drugs before he first uses them on his patients; nor have the various professional and independent commercial services accessible to the doctor been

[107] Compare views of May, footnote 106, and Lasagna, cited at footnote 65, with those of Beckman, "In Defense of Tinkerers," 267 *N. Eng. J. Med.* 72 (1962).

[108] See, for example, the views of Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association in *New Medical Materia,* Oct. 1962, p. 21. The position generally taken is that doctors are doing a proper job of informing themselves.

[109] The majority concluded that the business of advertising and promoting ethical drugs had gotten out of hand and was misleading to the physicians. *Kefauver Report* Part IV. The dissenting view of the minority appears there at 348-50.

[110] The National Library of Medicine has estimated that there are about 200,000 original papers on drugs each year and that there are 726 principal pharmaceutical journals in the world. For one drug alone some 13,000 articles had been written in 11 years. *Drug News Weekly,* March 23, 1963, p. 8, col. 2.

Dr. Walter Modell, a well-known pharmacologist, in referring to rapid technological advances in pharmacology which give a drug house but a short time after the introduction of a new drug to secure a firm share of the market, has stated:

> In this kind of rat race, it is simply good business for industry to attempt to recover a large portion of its investment in a drug immediately after it is introduced . . . [However,] no time is permitted for the physician to learn through a scientific journal or by experience. The drug is promoted as if it were a part of a standard and accepted practice. The physician is besieged by advertisements and elegant brochures. He is spoon-fed information by the detail man.

World Medical News, Jan. 18, 1963, p. 70, 76.

adequate to the task. To fill this breach, the drug companies and their agents have stepped in with information, both as a needed service and as a sales device. While pharmaceutical houses publicly disclaim their influence, it is true that they conceive of their role as one of "educating" the doctor to think of their particular brand-name product. This practice has been widely condemned as a potential source for the dissemination of false and misleading information, concealed under the euphemism of "education."[111]

Specific examples of the dangers which may come from reliance upon drug advertisements and other promotional material are not lacking. In certain notorious and documented cases, for example, cited research had never been performed, or results of research actually done had been exaggerated as to efficacy or safety or had been misapplied and misinterpreted.[112] In other cases, qualifications or limits on the value of the research,[113] as well as know side effects and warnings, have been omitted from advertisements or sugared over with assurances of safety.[114] Full warnings, as favorably passed upon by the FDA, have appeared in places where the statements were not likely to come to the attention of the prescribing physician or have been completely missing from the direct messages to the doctor, which are foreseeably going to be more influential.[115] "Word-smithing" has been indulged in.[116] Detailmen have been shown to have puffed-up results and glossed over reported adverse reactions, whether or not acting under the direction of their employers.[117]

[111] See Lasagna, cited in footnote 65, at 136; testimony of Dr. Harry Dowling before the Kefauver Committee, *Kefauver Report* 155 (misleading advertising said to cause doctors to make mistakes). See also "Editorial," 265 *N. Eng. J. Med.* 910 (1961); Leake, "The Scientific Status of Pharmacology," 139 *Science* 2069, 2078-79 (1961); May, footnote 106.

[112] Such instances are reported in the *Kefauver Report* 165; Lasagna, footnote 65, at 140. Dr. Lasagna also reports a case of an advertisement which referred to 512 cases treated with a certain drug, whereas in fact none were treated. See Lasagna, page 135.

[113] Advertisments have been based, for example, on results obtained from animal experiments alone. *Kefauver Report* 168.

[114] See *Kefauver Report* 165, 192, 198 (warnings regarding Chloromycetin watered down by subtle changes, thereby avoiding reference to or minimizing seriousness of certain adverse effects).

[115] *Kefauver Report* 202 (manufacturer careless in glossing over untoward effects). The subcommittee majority concluded that the manufacturers have apparently believed that it is up to the doctor to inform himself. *Kefauver Report* at 210—17.

[116] FDA Release, HEW-W58, Feb. 13, 1963.

[117] *Kefauver Report* 198 mentions a company's inter-office directions regarding Chloromycetin, partly misinforming the detailmen as to side effects and partly mentioning the need to water

(Footnote continued on next page.)

As to advertising or promotional material aimed directly at the public and the ultimate consumer, an issue of some legal significance, it is fair to say that ethical drug manufacturers make but little effort to inform the public or induce lay sales. Patients, in fact, have little if any knowledge about a prescribed drug except that learned from the treating doctor.[118]

2. Detecting and Disseminating Data on Side Effects

Adverse reactions serious enough to warrant withdrawal of the drug from the market are occasionally found only after several years of general use.[119] It is important, therefore, that one or more organizations deem it their duty to gather information on recurring side effects and to disseminate the data immediately to practitioners so that they may modify their use of the drug. Non-governmental sources for such detection and publication include several bodies within the AMA,[120] a committee of the Pharmaceutical Manufacturers Associa-

(Footnote 117 continued.)
down the strict warnings recently required by the FDA. See also "Editorial," 265 *N. Eng. J. Med.* 910 (1961), acknowledging that sales representatives often exaggerate with the employer's consent. In relation to thalidomide, see Mintz, footnote 74, at 47.

Two other areas of dissatisfaction with drug house practices also have some relevance to civil liability: (1) The use of brand names confusingly similar to other brand names or wrong generic names [see Leake, footnote 111, at 2078; "Editorial," 265 *N. Eng. J. Med.* 755 (1961)]; (2) Marketing a drug substantially similar to one already on the market, either to have a full, competing line or to give the appearance of a new drug by making a slight molecular rearrangement (which usually only increases the side effects) [see Leake, footnote 111, at 2078; *Kefauver Report* 128 (citing the cases of vitamin B-12 and certain corticosteroids)].

[118] It is true, of course, that the American public is knowledgeable about the new "miracle" drugs in a general way by virtue of the lay press. To the extent that the articles are encouraged by or planted by the drug industry, some intentional contact with the public and patients-to-be is created, by a most undesirable route. Doctors often contend that patients come to them asking for currently popular drugs and the profession complains about this popular influence. The noted pharmacologist, Dr. Walter Modell, has stated:

> Here, then, is the pattern for disaster with new drugs: a short-sighted view of all effects; faulty experiments; premature publication; too vigorous promotion; exaggerated claims; and careless use—in brief, a break in the scientific approach somewhere along the line. . . .
>
> . . . Safety with the new drugs, which are both potent and numerous, therefore demands the attitude and skill of the scientists; anything less is clearly dangerous. Events have proved it.

Modell, "Hazards of New Drugs," 139 *Science* 1180-84 (1963).

[119] See footnote 20 and accompanying paragraph of text.

[120] The Council on Drugs publishes new and nonofficial drugs and digests new drugs in the "New Drugs and Developments in Drug Therapy" section of the *Journal of the American Medical Association;* it also maintains the valuable *Registry of Blood Dyscrasias* which reports periodically on adverse

(Footnote continued on next page.)

tion,[121] the various medical journals which carry reports as submitted to them from practitioners who have had untoward experiences with the drug, and the manufacturers themselves in the form of warning letters to the medical profession.[122]

The FDA has not in the past maintained any direct reporting service to physicians on side effects which have been reported to it by manufacturers or others. Nor has it undertaken continuing investigation of possible adverse effects of marketed drugs. The agency does on occasion, however, conduct its own probes or investigations,[123] and has recently begun an "Adverse Reaction Reporting Program" under which a few general mailings on side effects have been made to the whole profession.[124] More important, perhaps, are the changes wrought by the Kefauver-Harris Amendments which will regularize by law what formerly was accomplished only by the good intentions and moral obligations of the manufacturers. The amendments authorize regulations and special orders directed to manufacturers to require them to record side effects and other relevant clinical data as received and to report promptly to the FDA any information which affects the safety or effectiveness of an established drug.[125] Under this system, new drugs will be kept on probation for a number of years. Indeed, it has been urged that all new drugs be considered as on probation for a period of two to three years because of the delay in discovery of reactions.[126]

(Footnote 120 continued.)
drug reactions. See descriptions of its work in *A. M. A. News,* Jan. 21, 1963, p. 8; 178 *J. A. M. A.* 951 (1961). Recently, adverse reaction reporting functions have been increased. See *A.M.A. News,* May 27, 1963, p. 1.

[121] See discussion of Archambault at 95 *Hospital Management* 84 (1963). See also DeHaen, "Comment," *Medical Science,* April 10, 1963, p. 572.

[122] The FDA has at times suggested, and in certain instances may have compelled, that a warning be sent out. Note that a warning letter may serve as a data-gathering device, allowing the FDA and the manufacturers to gather information on reaction incidence by encouraging doctors to report cases under their care.

[123] See letter from FDA Deputy Commissioner, John L. Harvey, to Senator Humphrey, Nov. 6, 1962, reported in *Drug News Weekly,* Dec. 12, 1962, p. 13.

[124] Kerlan, 3 *New Medical Materia,* Dec. 1961, p. 30 (report by director of FDA division of research). See *Drug News Weekly,* June 5, 1963, p. 13, col. 1, for a description of the new FDA warning letter system. A national clearing house for drug reactions to be operated by the Public Health Service has been proposed by the government. *Medical World News,* April 26, 1963, p. 88.

[125] Section 505, 52 Stat. 1052 (1938), as amended, § 103(a) 76 Stat. 782 (1962), 21 U.S.C. § 355(j)(1) (Supp. IV, 1963).

[126] See statement by Dr. Modell in *Medical Tribune,* Jan. 11, 1963, p. 5, urging such probation for a two to three year period because of the delay inherent in the discovery of many adverse reactions.

3. Modification and Withdrawal of Drugs and Labeling

The Kefauver-Harris Amendments place great stress upon the power of the FDA to order removal of an approved, established drug from the market under a variety of circumstances.[127] These include:

(a) Where safety is not established upon re-evaluation of the NDA data in the light of new experience and testing;

(b) Where labeling is found false or misleading upon re-evaluation of the NDA, and is not corrected;

(c) Where a manufacturer's record-keeping or methods and controls are inadequate and not corrected within a reasonable time;

(d) Where a drug, previously passed as efficacious, turns out in the light of new evidence to lack substantial evidence of effectiveness;

(e) Where a drug on the market before the efficacy provisions of the new law became effective and the government can meet the burden of demonstrating that the drug is not efficacious as claimed by its labeling.

The same result can also be accomplished by suspension of an NDA, even after the drug has been marketed.[128]

Withdrawals of established drugs from the market, apparently an increasing phenomenon, have sometimes been wholly voluntary; at other times, they have been the consequence of FDA pressures and drug house appreciation of the need and concern for its reputation. On rare occasion withdrawal has resulted from the direct order of the FDA. The FDA, on the other hand, has been criticized for failure to effect withdrawal promptly enough.[129] Short of actual withdrawal, the agency has long exercised the power to order changes in drug

[127] Section 505(d), 52 Stat. 1052 (1938), as amended, § 102(d), 76 Stat. 781 (1962), 21 U.S.C. § 355(d) (Supp. IV, 1963).

[128] Under the Drug Act before the 1962 amendment, an NDA could be suspended only because false statements were discovered to have been made in the application or because newly developed tests proved the drug to be unsafe. It could not be removed because the FDA had a substantial medical doubt as to the safety of the drug. Under the amendments, however, the Secretary may order the drug's application suspended, as long as it is still in its probationary period though marketed, if there is a substantial doubt as to its safety or efficacy. If the drug presents an imminent public health hazard he can suspend it at once and then hold a hearing; if not, he must order a hearing first before suspension, unless, of course, he can come to an agreement voluntarily with the manufacturer. Section 505(e), 52 Stat. 1052 (1938), as amended, § 102(e), 76 Stat. 781 (1962), 21 U.S.C. 355(e) (Supp. IV, 1963).

[129] See *Hearings, Senator Humphrey Subcommittee,* Part 2, 380, 383.

labeling and accompanying literature to reflect hazards to life and limb more serious than had previously been appreciated.[130] The expansion of the FDA's powers in this area would seem to augur well, by both preventing harm and by providing a better standard for the determination of what omissions and corrections constitute evidence of a failure to use due care. **[To be continued in July issue]**

HEARINGS HELD ON FDA DRUG SURVEILLANCE

Hearings on the Food and Drug Administration's activities for monitoring the continued safety of new drugs after their approval for marketing were held the week of June 7, 1965, by the Subcommittee on Intergovernmental Relations, House Government Operations Committee. The hearings focused on the manner in which the FDA makes decisions with respect to an approved drug if its safety is called into question.

Dr. Joseph F. Sadusk, Jr., Medical Director of the FDA and Director of the Bureau of Medicine, stated the FDA policy for surveillance of approved drugs. He explained that the Kefauver-Harris Drug Amendments of 1962 required new drug applicants to maintain records and submit reports of experience, as found necessary, to facilitate a determination of whether prior approval of a new drug should be withdrawn or amended. In addition to implementing this "records and reports" provision of the Kefauver-Harris Amendments, the FDA maintains surveillance by the operation and expansion of an adverse reaction reporting program. Six hundred hospitals, the American Medical Association, physicians and consumers furnish the FDA with information concerning adverse reactions to drugs. The Medical Literature Branch of the Bureau of Medicine also screens 225 periodicals for reports of adverse reactions.

Dr. Sadusk stated that systematic re-evaluation of all drugs approved since the 1938 Food, Drug and Cosmetic Act will take years of effort, and that in-depth re-evaluation require specialists who need additional training after coming to the FDA. Improvement in the personnel situation should occur with an expected increase in the 1966 budget. While more progress is desirable, he stated that progress has been made, and that, specifically, nine new drug applications have been withdrawn and many labeling changes have been required to disclose newly found hazards since passage of the Kefauver-Harris Amendments.

[130] See footnote 98.

Harmonization of National Food Laws under the Treaty System of the European Economic Community

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ON MARCH 25th, 1957, THE TREATY establishing the European Economic Community (EEC) was signed in Rome. In contrast to the European Coal and Steel Community Treaty (ECSC Treaty) and the European Atomic Energy Community Treaty (Euratom Treaty), the EEC Treaty provides not partial integration but the fully integrated, economic unity of the Common Market by removing the economic barriers in Western Europe and by progressively integrating the national economies of the six Member States: Germany, France, Italy, the Netherlands, Belgium and Luxemburg. The Common Market is to be established in three phases, each of principally four years each—consequently within a transitional period of twelve years, or, under exceptional circumstances, within fifteen years.

The aim of the Common Market is depicted in Article 2 of the Treaty, according to which:

> . . . it shall be the aim of the Community, by establishing a Common Market and progressively approximating the economic policies of Member States, to promote throughout the Community a harmonious development of economic activities, a continuous and balanced expansion, an increased stability, an accelerated raising of the standard of living and closer relations between its Member States.

In order to achieve these aims a customs union between the Member States serves as a basis, that is, the removal of customs barriers, and the consequent abolition of tariffs and quantitative restrictions when importing and exporting goods among the individual Member States. This includes the introduction of a common external tariff against third countries. Apart from a complete liberalization of trade, there is to be established free movement of labor and the self-employed. Furthermore, intra-market movement of capital, payments and services is to be freed from all existing restrictions.

For the creation of a genuine, smoothly working Common Market, equal competitive conditions are indispensable. The Treaty therefore proscribes measures restricting competition and government aid. It mandates harmonization of taxes, wages, social benefits and harmonization of national legislative provisions if they would otherwise hamper the functioning of the Common Market.

Food law of the individual Member States was mainly codified towards the end of the last century. In its origins, however, it traces back into the past and is based fundamentally on roots of Romanic and/or Teutonic legal conception. Although all national food law systems valid within the EEC today are based on the principles of health and full disclosure; cultural and social development, different eating habits, and the effects of two world wars have produced laws which in their system and formal structure differ greatly.

Existing customs barriers may strongly hinder the movement of foodstuffs among the individual Member States within the EEC. A much stronger obstacle to trade is, however, the varying food law regulations which in many cases are almost contrary to each other in substance and which could be an absolute barrier to movement of foodstuffs across national boundaries. The present situation in Europe is well illustrated by the regulations regarding the use of glucose syrup on the one hand in preserves and jams, and on the other in soft drinks.

(a) In Italy the use of glucose syrup in preserves and jams is absolutely prohibited. In France and Belgium it is, however, not absolutely but practically prohibited. Although in these countries glucose is actually permitted for this type of product, a product containing glucose may neither be called a preserve nor a jam. It has to be put on the market under a special name or under the name

"glucose preserve" or "glucose jam." In Austria, glucose syrup may be used up to 5% of the finished product without declaration and up to 12% with declaration. The same regulation is applicable in Germany for preserves, while in jams the maximum of 12% without declaration is permissible. The Netherlands still has another regulation, where glucose syrup is permitted only in so-called "household jams," but in these, to a maximum of 36% of the finished product. Denmark confines itself to requiring a declaration without prescribing a maximum quantity, while Great Britain, Sweden and Switzerland allow glucose syrup in jellies and jams without restriction.

(b) Soft drink standards also demonstrate very clearly the existing division of laws in Europe. Glucose syrup is not permitted in Italy nor in the Netherlands; Belgium permits glucose in soft drinks in addition to sucrose. The situation in Germany is similar, where, however, for the time being a minimum of 7% sucrose and/or dextrose is prescribed, and glucose syrup is allowed only in addition to this. In France glucose is permitted only in carbonated lemonades, while it may be used with a declaration for all soft drinks in Spain. The legal situation in Switzerland is not clear, while Denmark, Great Britain and Sweden permit this type of sugar without restriction.

These two examples only represent hundreds of similar divergencies—in many cases unjustified—which are incoherent in themselves and lack any obvious system. They show clearly the need for legal harmonization within the European Economic Community and, moreover, the practical and psychological difficulties. Differing legal traditions and economic developments of the individual member nations do not render this easier.

According to Article 100 of the Treaty "harmonization of such legislative and administrative provisions of the Member States as have a direct incidence on the establishment of functioning of the Common Market" has to be effected. Strictly interpreted, almost all legislation has an influence on the economic life and functioning of the Common Market. If, however, the contractual aim of Article 100 is taken into consideration, namely, a guarantee of smooth-flowing trade among Member States and harmonization of diverse competitive conditions, the legislative harmonization is necessary only if conflicting statutes hamper the functioning of the Common Market. This effect must be direct and not caused by noneconomic factors as, for example, the effects of conscription on the labor market.

Harmonization under Article 100 of the Treaty is generally effected by so-called "directives" under Article 189, paragraph III of the Treaty. These directives are binding as to substance for every Member State to which they are addressed, while leaving to the competent domestic legislative bodies the choice of form and means. Directives thus create no actual domestic law, but require Member States to adopt appropriate provisions in order to create the same situation for the entire EEC. Before the issuance of these domestic provisions the directives have, therefore, no effect as law. On the other hand, "ordinances" provided in Article 189, paragraph II of the Treaty have a stronger legal effect. They are of general application and binding in every respect in each Member State. The power to enact such ordinances creates a direct right of legislation in the EEC institutions and thereby interposes a far-reaching limitation upon national authority. This was, however, agreed upon by the national parliaments with the ratification of the Treaty in the interest of achieving its goals. In addition, by ordinances (under Article 189, paragraph II of the Treaty) completely new laws may come into existence in the Member States. Directives under Article 100, on the other hand,—according to the prevailing but not undisputed view—may only *harmonize* existing laws of the Member States.

The competent agencies in Brussels soon found that the food laws of the Member States were in many cases hopelessly outdated or followed antiquated conceptions and principles. In order to enable the adoption of creative legislation consonant with modern views in the food field, and yet to avoid dispute about the possibly limited scope of Article 100 (to harmonize existing law), the revision of food laws was in certain instances based on Article 43 of the Treaty, having to do with common agricultural regulations, which permits the use of Article 189, paragraph II, providing for the issuance of ordinances. From this ensued the possibility of harmonizing existing law and, moreover, of adopting new law of general application and binding force.

Harmonization by proceeding pursuant to Article 43 and Article 189, paragraph II, of the Treaty, is also facilitated in other ways. While directives pursuant to Article 100 of the Treaty can only be issued by the EEC Council of Ministers acting unanimously during the entire 12-year transitional period of three stages, ordinances

under Article 43 of the Treaty will require only a qualified majority after the present second stage has expired on January 1, 1966. The requirements of a qualified majority are found in Article 148 of the Treaty calling for 12 of the existing total of 17 votes. The votes of the Member States are valued as follows:

Belgium, 2; Germany, 4; France, 4; Italy, 4; Luxemburg, 1; and the Netherlands, 2.

Competent agencies in Brussels have for the most part based their practical work on Article 100. They have, as shown by some still unofficial draft directives, wisely put aside possible disputes about Article 100 of the Treaty and have worked out proposals for individual directives which by modern standards represent in some respects much more than mere harmonization of national law.

Dr. Edmund Forschbach, the director of the Food Division in the German Federal Ministry of Health and Vice President of the European Council of the Codex Alimentarius, however, has stated:

The EEC has no direct concern with the promulgation of the *ideal* food legislation. Its mandate is merely to harmonize *existing* laws to the limited extent necessary to wipe out barriers to intra-EEC trade and to reduce certain flagrant abuses. EEC's job, in short, is to come up with something pragmatic and workable and then get on to other business.

Actual development has—I think I may state—shown that a remaking of food law is the goal in Brussels and nothing is being left untried to achieve this goal.

Through its General Directorate VI (Agriculture), the EEC Commission is the competent authority in this area according to Article 100 as well as Article 43 of the EEC Treaty. Within General Directorate VI, this task falls to Division 3, "Approximation and Harmonization of Legal and Administrative Regulations Regarding Agricultural Products," of Directorate F, "Agricultural Economy and Legislation."

In passing, it should be noted that Division 3 has available for the harmonization of food laws apart from the division head only a so-called A-official and a few assistants. This lack of personnel has understandably led to an official inquiry on the part of the European Parliament as to what importance the EEC Commission ascribes to harmonization of food laws within the Common Market, and whether in view of the present lack of personnel, harmonization could be completed before the transitional period of 12—or 15 years (commencing January 1, 1958) at the most—would expire.

Commission's Importance in the Common Market

Before dealing with the proceedings within the EEC Commission I would like to explain briefly its importance in the Common Market. According to Article 155—163 of the EEC Treaty, the commission consists of nine independent members who are not subject to instructions given by the Member States or other authorities. They are appointed by the Member States by a unanimous vote for a period of four years. It is the function of the commission to supervise the application of the Treaty and the regulations set up on its basis and in this connection to supervise the coordination of the conceptions of the Member States. For the accomplishment of their tasks, the commission has at its disposal the nine General Directorates, among which is General Directorate VI (Agriculture).

Towards the end of the year 1959, General Directorate VI initiated the harmonization of food laws by establishing the Food Law Working Group. For this working group and also for the internal working procedures within the EEC Commission with regard to a harmonization of laws there are no—at least no generally disseminated—rules of proceeding or business. The standing rules contained in Article 100 of the EEC Treaty, concern only the formal treatment of commission drafts. They are not applied until a concrete project has left the scope of the commission. This becomes clear from the wording of Article 100—"on proposal of the commission".

I will trace the adoption of an EEC directive in the food law field on the basis of Article 100 of the EEC Treaty.

Members of the Food Law Working Group are representatives of the governments of the Member States, and this in most cases from the authorities concerned with food law. The working group is presided over by a member of the EEC Commission, that is, one of the two gentlemen of Division 3 (VI, F) mentioned above. The Food Law Working Group generally does not discuss special questions but leaves them to its sub-groups because of the large variety of legal problems at hand and the large number of food law provisions. The sub-groups also work under one of the two presiding officials of the EEC Commission and consist of experts of the six governments of the Member States, who may also be represented in the Food Law Working Group. Luxemburg is in many cases represented by Belgium, which with the Netherlands are members of the BENELUX Economic Union. General Directorate III (Inner Market) and Gen-

eral Directorate IV (Competition) may send representatives into the Food Law Working Group and/or into various sub-groups. These two General Directorates have a right to be heard before passing on any draft directive to the EEC Commission as a whole, without General Directorate VI being bound to their recommendations.

Individual sub-groups are established and meet whenever a specific legal subject is being considered for harmonization. Three different methods for initiating harmonization exist:

a) Government proposal by one of the Member States (either direct or through a government delegation).

b) Proposal by a European industry or consumer association (in practice the industrial associations present detailed proposals).

c) Initiative of the EEC Commission.

The following sub-groups have been established and are working at present: (a) "additives," (b) "fruit and vegetable products," (c) "cocoa and chocolate," (d) "meat products," (e) "feeds," and (f) "general questions regarding preserved foods."

Initially the contents of the relevant national legislation are examined by the competent officials of the commission and the individual sub-group. The commission then works out a first draft. This task is made much simpler if for the sector in question a draft of the appropriate industrial association of the EEC is submitted.

If in the course of this preliminary work, problems concerning public health arise, the sub-group may discuss these problems with the so-called "Scientific Committee". The "Scientific Committee" is a body of experts expressly created for this purpose. One scientist of each Member State belongs to this committee. These members, however, do not function as representatives of their countries, but act as individuals. In Brussels consideration is being given to whether in the future it will be possible to institutionalize this body as a kind of "Consultative Food Law Committee."

Closely interrelated efforts and exchange of thought between the sub-groups and the Food Law Working Group exist in this early stage, so that no sharp dividing line may be drawn. The sub-group deals chiefly with the specific questions under study, whereas the Food Law Working Group in the first instance is concerned with overall and general matters, thus exercising a coordinating function with regard to the sub-groups.

In this stage the main work done is with regard to substance. As a result of the distribution of membership in the sub-groups and the Food Law Working Group, many contributions come from the experts of the national governments, who are in a good position to see all the requirements a future supranational legislation will have to meet. They also have, however, a natural tendency to regard the laws in force in their own countries as the optimum.

The Food Law Working Group having studied a project, it is normally passed on by Division 3 to the interested EEC Industrial Associations, in any event, however, to the UNION DES INDUSTRIES DE LA COMMUNAUTE EUROPEENNE (UNICE),[1] that is, the EEC controlling association of the whole industry. This association has formed a COMMISSION DES INDUSTRIES AGRICOLES ET ALIMENTAIRES (CIAA),[2] safeguarding the interests of the EEC food industry. Representation of the individual branches of the food industry by way of the UNICE is complicated and wearisome; sometimes the opinion is expressed that there should instead be a European Food Law Institute. Beyond that, in this stage each draft of harmonization is submitted to the European Consumers' Association.

The opinions of these groups of interested persons are debated in a final discussion of the working group. After conclusive adjustment with the two interested General Directorates III and IV, the draft is presented to the Commission for decision. This is followed by its submission as "Proposal of the Commission" to the Council of Ministers of the EEC.

Under the provisions of Article 100 of the EEC Treaty, the Council of Ministers is required to obtain the opinion of both the Economic and Social Committee and of the European Parliament if a change of legal regulations in at least one of the Member States will ensue from the project. The practice of the Council is to ask for the opinion of the two bodies in any case without examining in detail its necessity.

European Parliament and The Economic and Social Committee

In this context it is useful to explain briefly the composition and significance of the European Parliament and also of the Economic and Social Committee. The European Parliament exercises

[1] Union of Industries of the European Community.

[2] Commission of Agricultural and Food Industries.

democratic surveillance over the European Economic Community, the European Coal and Steel Community and the European Atomic Energy Community. Under Treaty regulations for the functional scope of the Common Market, it is called the "Assembly" (Article 137—144 of the Treaty). It is composed of 142 members allocated to the individual countries as follows: Germany, France and Italy, 36 each; Belgium and the Netherlands, 14 each; and Luxemburg, 6. At present, the members are elected by and from the national parliaments of the Member States. The Treaty provides, however, for direct universal suffrage in the future. Plans have been drawn up for this purpose and are before the Council of Ministers.

Differing from a real parliament, the European Parliament has no legislative power; it has only an advisory and observing function. The advisory power relates particularly to decisions of the EEC Council of Ministers which have legislative character or are of special political importance. In these cases, which are enumerated in the Treaty, the Council of Ministers may only reach the final conclusions after consulting the European Parliament.

The Economic and Social Committee (Article 193—198 of the Treaty) also has a mere consultative function. It is composed of representatives of all categories of economic and social life: producers, agriculturists, transport operators, workers, merchants, artisans, professionals, and representatives of the public interest. Germany, France and Italy have 24 members each in the committee; Belgium and the Netherlands, 12 each; and Luxemburg, 5. They are appointed for a period of four years by unanimous vote of the Council, and are not bound by any mandatory instructions. Though the committee is not an institution of the Community, great importance is ascribed to its opinions, the members being expected to have a profound knowledge of economic and social problems, which are of special importance within the frame-work of an economic community.

The competent committees of the European Parliament and of the Economic and Social Committee are increasingly intensifying their studies for harmonization of food laws. Competent officials of the EEC Commission may also participate in the meetings of these committees and make their views known. In this stage, too, UNICE and the Consumers' Committee may again present their views.

After receiving the opinions of the European Parliament and of the Economic and Social Committee, each individual project is finally

dealt with by a working group of the Council of Ministers of the EEC. The directive is given its definite text and by way of the Committee of Standing Representatives of the Member States to the EEC it is submitted to the Plenary Assembly of the Council of Ministers for final decision and passage. The directive takes effect upon publication in the Official Gazette of the European Communities. The directives published up to the present have provided, and presumably also the future directives will provide, that their legal contents have to be adopted into national food law systems within one year, and that they must become effective within one further year thereafter.

EEC Council of Ministers

The Council of Ministers of the EEC, commonly referred to as the "Council" in Article 145—154 of the EEC Treaty, is composed of representatives of the governments of the individual Member States. Normally, these are the ministers or their respective state secretaries. The office of the president is held for a term of six months by each Member State in alphabetical rotation. Germany, France and Italy each have four votes; Belgium and the Netherlands, two each; and Luxemburg, one vote. The Council's task is the achievement of the objectives of the Common Market and coordination of the economic policies of the Member States under the provisions of the Treaty. Formally, the Council is the legislative authority of the Community.

Since the beginning of harmonization studies, the following has been accomplished:

1. Directives passed by the Council of Ministers and published in the Official Gazette:

a) Directive of the Council, of October 23, 1962, for the Harmonization of Legal Provisions of the Member States, Regarding Colorants Which May be Used in Food (Official Gazette of the European Communities, No. 115 of November 11, 1962, pages 2645—2662).

b) Directive of the Council of November 5, 1963, for the Harmonization of Legal Provisions of the Member States Regarding Preservatives Which May be Used in Food (Official Gazette of the European Communities, No. 12, of January 27, 1964, pages 161—164).

2. The following proposals for directives submitted to the Council of Ministers, but not yet passed:

a) July 1963—Proposal for a Directive of the Council for the Harmonization of Legal Provisions of the Member States Regarding Cocoa and Chocolate (Ref. No. VI/KOM (63) 219 final).

b) December 1963—Proposal for a Directive of the Council for the Settlement of Questions Concerning Health and Food Legislation, as to Trading Meat Products (Ref. No. VI/KOM (63) 499 final).

c) August 1964—Proposal for a Directive of the Council for the Amendment of the "Directive of the Council for the Harmonization of Legal Provisions of the Member States Regarding Colorants, Which May be Used in Food".

d) August 1964—Proposal for a Directive of the Council for the Harmonization of the Legal Provisions of the Member States Regarding Antioxydants Which May be Used in Food (Ref. No. VI/KOM (64) 289 final).

3. A draft of a proposal for a Directive of the Council regarding "Specific Purity Requirements for Preservatives, Which May be Used in Food" soon to be submitted to the Council of Ministers.

Criticism of Commission's Work

Certain committees of the European Parliament, its Plenary Assembly, and the Economic and Social Committee as well as the Consumers' EEC Contact Committee, have criticized the Commission for not satisfactorily dealing with more regulations—considering the total range of regulations to be harmonized. Furthermore, criticism is expressed that until now, the Commission was only concerned with very much limited parts of food legislation, while its basic problems were completely ignored. Beyond that it was criticized for carrying out harmonization on two levels. The Commission has under simultaneous study so-called "horizontal" and "vertical" parts of food legislation, without first conclusively dealing with one or the other level. In this context, all those provisions are termed "horizontal" which are generally and equally valid for the whole food industry. In the main, this is represented by directives on additives, directives which do not restrict the foods or groups of food in which a certain additive may be used or prescribe what maximum quantities and label declarations must be observed. "Vertical" directives cover specific food items.

If the present process is continued it is doubtful if it will be possible to achieve harmonization of food legislation before the end of the transitional period in 1970. On the other hand, an astonishing amount of work has been done, if the multitudinous difficulties encountered in the beginning, and the understaffing of the various divisions are considered.

In my opinion, much more importance must be ascribed to the criticism that harmonization of the basic problems in food legislation has been ignored. This becomes evident in the difficulties which have

arisen in the domestic domain when trying to apply to existing legal systems the two final directives dealing with additives, such as "colorants" and "preservatives".

Though nowadays all of the national systems of the EEC countries are based on the so-called "positive-list system," as far as additives are concerned, the basic definitions for the term "additives" are still very different. It is only with difficulty that one can compare the structure of the national system of the EEC countries with the system introduced by the 1958 Food Additives Amendment in the United States. The European countries prefer abstract definitions, corresponding more to Roman legal tradition, and thus base their definitions of food additives mainly on the criteria of lacking nutritive value and being artificial.

Nevertheless, present definitions of additives still vary to a considerable extent among the European countries. It is these definitions, however, which determine the range of substances subject to the "positive-list system," substances which expressly require a license for use.

It has been agreed that the two additive directives on colorants and preservatives, would be based throughout on the "positive-list system." There could, however, be exceptions to this principle.

It has been, moreover, planned to amalgamate in one uniform directive the six or eight directives on the main additives decisive for human health. It has been, furthermore planned to include in the first adoption of this general directive a comparatively broad definition of additives. In the second installment, the "principle of prohibition" (positive-list system) is to be introduced for the above-mentioned main additives, which could also be called "special" additives, namely colorants, preservatives and similar substances. The required positive lists are to be added in this second installment. In the third installment, all further additives, in the sense of the definition in the first passage, which could be called "general" additives, are to be subjected only to the "principle of abuse" (negative-list system). Accordingly, every substance that is not prohibited is to be allowed. The hopes of industry that the EEC food laws would mark a return to the more liberal and flexible negative-list system, will in a degree not be realized, but this solution seems to be quite practicable.

From one viewpoint it may seem not to make any difference if a certain substance is classified as an additive as long as it is a permitted additive. However, in Europe, additives (in Germany they are called "foreign substances") are considered artificial substances without nutritive value of their own. As a consequence, the "vertical" regulations on individual food groups in many cases produce important consequences. A lower classification of consumer products may be required if they contain additives, or label declaration may be required. The criticism that in Brussels the EEC is working on two levels seems little justified, provided that the two "levels" ("horizontal" and "vertical") are sufficiently coordinated.

Language Problem in the EEC

This paper would be incomplete without a few words about the language problems within the EEC. In the Common Market there are four languages: German, Dutch, French and Italian; that is, two of Teutonic origin and two of Latin origin. All four are official languages, and all directives are published in each of them. In practice this does not create many difficulties since it has been agreed to consider the French version as conclusive when conflicts in interpretation arise. It is different with the labeling and declaration of foodstuffs. Goods are to be admitted for sale in all EEC countries but it is agreed that labeling cannot be done in four languages. For this reason labeling is considered sufficient if it is in one Romance and one Teutonic language.

The foregoing will give some idea of the necessarily complex program for bringing order out of the chaos of the food laws of the EEC countries. Complex as the matter is, there is hope that the food laws of the EEC Member States, in so many ways outdated, will not only be harmonized but in the course will be brought to the present levels of scientific research and technological progress.

Recently, Dr. Edmund Forschbach expressed his hope for an adjustment of food laws to modern knowledge when in his "Credo for World Food Laws" (February 1963 issue of FOOD DRUG COSMETIC LAW JOURNAL), he called the food laws applicable not only in Europe but also in the whole world "a hodgepodge of archaic patchwork regulations, far behind the times, the technology of food and the needs of consumers." Perhaps the experience and record of the EEC countries will be an inspiration for the future. **[The End]**

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