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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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Where Is Industry's Voice in Food Regulation?—The article by *Bernard L. Oser*, Ph.D., which begins on page 317 examines the increasingly stringent regulatory measures taken by the Food and Drug Administration. Although he notes that controls are often necessary in a free society because of "the ignorance, carelessness or the misfeasance of a few," Dr. Oser strongly supports the FDA's efforts toward voluntary compliance and self-certification. The article was originally presented as a speech before the Food Technology Conference held at the University of Missouri, March 8, 1968. Dr. Oser is this magazine's Scientific Editor, President of the Food and Drug Research Laboratories, Inc., Maspeth, New York and has recently taken office as President of the Institute of Food Technologists.

International Drug Pharmacopeia.—The article which begins on page 322 reflects the aims of the International Drug Symposium on Pharmacopeias and International Cooperation on Drug Standardization held in Washington, D. C. during the 81st annual meeting of the Association of Official Analytical Chemists. The article is reprinted from the *FDA Papers* (April 1968, p. 11). Dr. Banes joined FDA in 1939 as a chemist and was recently appointed Acting Associate Commissioner for Science.

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Ethical and Legal Implications of Drug Substitution

By SIDNEY H. WILLIG

The Following Article Was Presented at the 64th Annual Conference of the National Association of Boards of Pharmacy on May 6, 1968 at Miami Beach, Florida. Professor Willig, a Member of the New York Bar, Is the Director of the Drug Law Unit at the Institute for Law and the Health Sciences of Temple Law School, Pharmacy and Dental Schools in Philadelphia, Pennsylvania.

THE PHARMACIST'S POSITION in society and in his dealings with patients requires that he adopt a fiduciary position in their behalf. He is the knowing one, they the unknowing insofar as ingredients and products are concerned. They look to him to insulate them against subpotency or deterioration and it is his integrity that guides the dispensing act. This is an obligation in the ethical as well as the legal sense.

Substitution is a complete departure from the principle of *secundem artem* and is by definitions in state enactments, illicit and unauthorized. It represents the replacement of the written or orally specified needs of a patient with any other commodity and without notice, authority or consent.

In examining the ethical considerations, it would be pointless to cite the language of every pharmaceutical group in this regard, but the versions are much the same in tone and spirit:

"The pharmacist must not substitute one article for another without the consent of the physician who wrote the prescription. No change shall be made in a physician's prescription except such as is warranted by correct pharma-

ceutical procedure provided it will not interfere with the obvious intent of the prescriber as regards therapeutic action."[1]

There is no valid argument to excuse substitution in its oldest sense. That is where products or ingredients of particular chemical or biological identity are replaced in the dispensing act by products or ingredients of different chemical or biological structure. It is clear that only the prescribing physician can authorize such a switch.

However, with modern technologic advances, the greater reliance on newer and more potent medicaments and the growth of pharmaceutical consumption, it soon appeared that the traditional significance of substitution had now to encompass greater scientific manufacturing sophistication. Since a manufacturer takes responsibility for his product, he often stands as its innovator, its warrantor, its salesman. Its unique qualities, for better or worse, reflect his skills and abilities, his investment in raw materials, personnel and equipment, his conscience and business attitudes, and everything else that can give an inanimate thing a character that is identifiable. The public recognizes this in automobiles, household appliances, cigars and beverages. It is not unusual that they should recognize it with products designed to maintain their health or benefit them in illness.

As a result, most enlightened jurisdictions added to the old definition of substitution the traditional yet modern concept that where a drug is identified by the prescriber, according to a particular trade name, then that exactly is the drug he and his patient are placing confidence in, and to dispense another drug or ingredient in its place without authority is substitution.

The Pharmacy Act of the Commonwealth of Pennsylvania like most others, states[2] that the Board shall have the power to revoke or suspend the license of any pharmacist upon proof that "he had compounded, dispensed, sold or caused the compounding, dispensing, sale of any drug . . . of a brand or trade name other than that specified by the person prescribing such brand or trade name product or which contains an ingredient or ingredients of a brand or trade name other than that specified by the person prescribing such drug or device, unless the consent of the prescriber is first obtained to each such specific prescription;"

The New Mexico Drug and Cosmetic Act, Section 3(i) lists as a prohibited Act: ". . . dispensing or causing to be dispensed a different drug or brand of drug in place of the drug or brand of drug ordered or

[1] Code of Ethics, Me., Pharmacy Association.

[2] § 5(8).

prescribed without the express permission in each case of the person ordering or prescribing." For this the state can take measures to enjoin and/or prosecute as a misdemeanor.[3]

We should examine the federal and local law for any reference they make to the pattern of action termed "substitution."

While Section 502 of the Federal Food, Drug and Cosmetic Act has long been utilized as a protection for the public, regulations issued under 502(f)(1) have been especially important in preventing distribution of drugs inadequately labeled for safe human use.

It was by regulation under this subsection for instance that a distinction was sought to be made and enforced as to what drugs the pharmacist could sell over-the-counter and those which could be sold only via prescription. Indeed, prior to passage of the Durham Humphrey Amendment, the courts upheld criminal prosecution of pharmacists and others for selling potent drugs without a prescription.

Problems in uniformity of labeling between manufacturers of the same drug, and the desire for clear statutory determination finally laid the ground for enactment of Section 503(b) of the Act, the Durham Humphrey Amendment.

In this same period of legislative and administrative activity an important Supreme Court decision also dealt with the issues. That was *U. S. v. Sullivan*[4] which emphasized the criminal nature of an act which violated the safety objectives of Section 502(f) of the Act and "the doing of any other act with respect to a food, drug, device or cosmetic, if such act is done while such article is held for sale after shipment in interstate commerce and results in such article being misbranded."[5]

"Drug Substitution" in the Federal Act

There was not, nor is there now, a definition of "substitution" in the Federal Act. If you follow the line of reasoning through the legislative, administrative and judicial interpretation and intent expressed in the foregoing, then you must conclude that the pharmacist's inventory of drugs that are only suitable for use pursuant to a physician's direction, is to be inflexibly defined in the interest of the public.

Further, regardless of lack of criminal intent or accident or negligence, he is to be held to strict accountability for that inventory of prescription drug products. His responsibility being, to dispense or

[3] § 26.
[4] 332 U. S. 689 (1948).
[5] 21 USCA 331(k).

distribute such drugs only when, how and as specified on a legitimate prescription.

Therefore, if a pharmacist dispenses a legend drug that is not ordered by a physician, it makes no difference that he uses a prescription label and follows the format in Section 503(b)(1)(c). The *substituted drug* is the seizable matter, of an act of dispensing a drug contrary to its provisions, and is therefore deemed to result in a misbranding. Since it does not qualify for the 503(b) exemption as to the labeling requirements of 502(f), it is also misbranded as dispensed for violation of that section. Also, having tumbled from grace in Chapter Five of the Federal Act, the procedure becomes a Sullivan style violation in terms of 301(k) of the Act.

In short, since a substituted drug is itself immediately misbranded on dispensing, according to the Federal Act, the latter leaves the semantics of substitution to state legislatures and pharmacy boards.

As the Supreme Court pointed out in *U. S. v. Sullivan*,[6] the governmental agency "is given no power to exempt on the ground that compliance is impracticable." It "cannot weigh business convenience against protection of the public health."

In this case the Supreme Court resisted the argument that enforcement had rested upon an overly technical and literal use of the language in the Act and concluded:

"Given the meaning that we have found the literal language of Section 301 (k) to have, it is thoroughly consistent with the general aims and purposes of the Act. For the act as a whole was designed primarily to protect consumers from dangerous products . . . Its purpose was to safeguard the consumer by applying the Act to articles from the moment of their delivery to the ultimate consumer."

Counterfeits and Imitations

"Substitutes" may be "imitations" or "counterfeits" but this is not necessarily so. A counterfeit is always intended for substitution. An imitation simulates the original article without attempting to duplicate its appearance as does the counterfeit. However, the act of substitution may use a non-imitative, non-duplicative and recognizedly non-equivalent product to present in place of the article requested.

Where the substituter is using counterfeits or imitations for his substitution, he must recognize that morally, as well as legally, he is possibly abetting a criminal act or a fraud.

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[6] 332 U. S. 689 (1948).

There are those who feel that the language of Section 301(i)(3) of the Federal Act[7] is capable of judicial interpretation, if we divorce it from the preliminary legislative discussions that preceded its enactment, to include the act of substitution under proper fact patterns.

"The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug."

Consider it in the light of this criminal law definition:[8] "To copy or imitate without authority or right and with a view to deceive or defraud by passing the thing forged for that which is the original or genuine."

Many drugs used by substituters, where the physician's order for a specific brand of drug product is dishonored, physically resemble in color, size or shape the original designated article. It is the dispensing act which qualifies them as a successful counterfeit since at that point they are passed for the original, and only a consumer with the expertise and training of a pharmacist or physician might betray imprudence in its acceptance.

For this reason some drug manufacturers, physicians and pharmacists have recommended that state pharmacy acts or board regulations extend the prescription label's requirements to include along with the date, sequential number, patient's name, directions, doctor's name, etc., the name of the drug specified on the doctor's prescriptive order. A substituter then would leave little doubt of vulnerability to civil and criminal charges on various counts, from patient, from governmental agencies, and from the named drug's manufacturer. Putting solely the established name thereon, would serve only to militate against substitution of patently chemical non-equivalents.[9]

Obviously, to many who have practiced pharmacy for years, this might have an undesirable effect on the interrelationship between pharmacist and patient and physician since it may act to disclose when disclosure is unwanted, may encourage autotherapy by patients along with transfers of medication between lay persons.

As a matter of law and practice however, any physician who wishes the name of the drug included on the prescription label need merely indicate such wish on the written or oral prescription.

Fundamental to the form of our government is federal supremacy in accordance with constitutional parameters, which binds all lesser

[7] Federal Food, Drug and Cosmetic Act.

[8] Black's Law Dictionary, 4th Ed.

[9] Senate Bill No. 3290, Senator Nelson, Spring, 1968.

governmental units to observe that federal laws and treaties are the supreme law of the land. However, where the locality responds to the need for public protection by adding more stringent regulations to those generally set by the federal government, the licentiate and his agents or employees must adhere to the stricter rules.

Licensure of Pharmacists

While the national government has undertaken many activities that are essentially local in effect through its constitutional control of interstate commerce, its taxing powers, etc., the licensure of professional practitioners has remained a state function, and the ability to grant it, suspend it or revoke it is an important enforcement weapon in professional discipline.

In pharmacy we have mandatory licensure. In general, a license is a legal document that permits a person to offer to the public his skills and knowledge in a particular jurisdiction where such practice would otherwise be unlawful without a license.

A license to a pharmacist is granted by the appropriate authority to applicants who have fulfilled certain established requirements of education and experience along with meeting the requirements for character consonant with practice of a profession. Therefore, the licensed pharmacist recognizes that his license depends on ethical as well as legal considerations.

The licensure operation is based on delegation of authority by the state via its "police powers."[10]

Police powers are inherent sovereignty which the state government exercises whenever regulations are demanded by public policy for the benefit of the society at large in order to guard its safety, morals, health, order and the like within the needs of its social, economic and political structure, its mores and traditions.

Pharmacy boards and practitioners are concerned with the ethical implications of substitution. The courts are more concerned with the legal consequences that flow therefrom, so that if harm befalls the patient and the substitution is its proximate cause, *that* is their interest.

John J. Galbally, a decade ago in a comprehensive analysis of substitution,[11] saw it as a growing problem, ethical and economic, and felt it was equatable with the charge of "gross immorality" which could sustain the board's prerogative in revoking or suspending licensure in the absence of specific anti-substitution laws. Now, some

[10] *Fuhs v. Barber,* 36 Pac. 2nd 962 (1934).

[11] 12 Food Drug and Cosmetic Law Journal 758 (December, 1957).

pharmacists are asking whether pharmacists who substitute are qualified not only ethically to satisfy state licensure, but academically so that they can afford justification for substitution on a scientific basis. Are they confusing license with privilege?

Much has been said of the risk of substitution to the patient under treatment or on maintenance therapy.

The Danger of Substitution to the Physician

That there are risks for the prescriber in substitution are well known also. Medicine is not an exact science and the physician is not a guarantor of results. He is deemed negligent where he does not act with the ordinary prudence of his peers or with the average foresight and care of lay persons. He becomes a malpractitioner only when, within his professional sphere of activity, he fails to maintain the standards of care, or to exhibit the quantum of skill and knowledge, that the public has a right to expect from a practitioner in that locality, again as compared to other practitioners of like training and activities in the same general area. Non-success or accident is, in short, not necessarily equatable with negligence or malpractice, and the burden of proof which a plaintiff must make and support with expert testimony is considerable.

So a physician for example, whose patient becomes pregnant after he has prescribed birth control pills, does not stand liable for the failure of the pills or the accident of conception.[12]

This does not, however, mean that patients who have adverse reactions or unsuccessful results are not inclined to litigate. The fact is that they do, and although the likelihood of success is not great, suits are expensive in terms of actual costs of litigation, time, reputation and patient relations.

For that reason, physicians eye askance any procedure that by civil or criminal infraction, or through color of misconceived authority, may militate against the desired and anticipated results of prescription.

In the usual patient physician relationship, there is so much of the subjective in comparison to the objective, that organized medicine has constantly striven to ensure the objective structure of diagnosis and therapy by better equipment, reliable and standardized reagents, and drugs whose chemical, pharmacological and other characteristics are known and standardized in their experience. If they are defrauded

[12] *Maley v. Armstrong*, Sup. Ct., Iowa (1967).

in any of these areas through subterfuge or through ignorance, then an outside force is decreasing certainties for them, and is increasing the likelihood of a patient's therapeutic failure and subsequent legal harassment.

The courts have recognized that the doctor is the patient's agent for getting and evaluating prescription advice and individual product characteristics.

Judge Steuer in *Marcus v. Specific Pharmaceuticals, Inc.*[13] said of of a drug supplier in establishing the doctor as agent recipient of medical information for the patient, "to physicians it did make representations, and should any of these be false, it might be claimed with propriety that they were made for the benefit of the ultimate consumers."

Physicians however, are not expected to delegate away to others parts of their responsibility and prerogatives as to medical practice, prescribing drugs being so included. They have resisted as might be expected. "The physician is one whose relations to life and health are of the most intimate character. It is fitting not merely that he should possess a knowledge of diseases and their remedies but also that he should be one who may safely be trusted to apply these remedies. Character is as important a qualification as knowledge."[14]

Authority to Substitute

There are three instances where substitution may occur with color of authority although it does not become knowledge before the fact to the prescriber.

There is the circumstance where the state seeks to authorize the dispensing pharmacist to substitute a less costly equivalent drug after advising the patient and gaining the latter's permission. I know of no method more patently divisive of the cooperation and understanding between pharmacy and medicine, than such an ill-advised determination. The skilled practitioner, the ethical practitioner, the physician who recognizes the intent and the language of the medical practice act, neither delegates to his patient, a pharmacist, or any other, his responsibility to prescribe in accordance with his knowledge, responsibility and reckoning.

As to the patient's ability to consent to substitution, or as a member of the electorate discard anti-substitution restrictions, we

[13] *Markovich v. McKesson & Robbins, Inc.* 149 NE 2nd 181 (1958).

[14] *Hawker v. New York,* 170 U. S. 194 (1897).

should consider Dr. James L. Goddard's statement to the subcommittee on Consumer Interests.

"The same may be said about our supply of medicine. In the last 20 years the science of therapeutics has changed radically. In turn, the science of medicine itself has changed. *It is far more difficult to be an intelligent patient today than it was a generation ago.* Yet, Mr. Chairman, with the great advances in medical care recently enacted by the Congress, it is clear that our elderly citizens are taking increased advantage of the "new medicine." *And, while we may all take comfort in the fact that our parents do have better care, we may be somewhat discomforted to learn that they are generally unaware of the significance of the care they receive, of the drugs prescribed for them,* of the devices that are used for their health—and *of the many medical frauds and cheats that are directed at their ignorance of this "new medicine."*[15]

There is a second circumstance where the state is perhaps even bolder and less wise, in determining that either a central pharmacist in authority, or individual dispensing pharmacists, should have the right to substitute less costly equivalents, where the state is paying the bill. What the state loses sight of here is that the public is paying the bill. Further that they are paying the bill because they are well meaning and well intentioned and are of the opinion that economic station should not militate against the right of the ill or infirm to get medical and dental and pharmaceutic assistance just as those more fortunate, who can pay their own way.

But when Congress realizes the cost and begins frantically to look for economies, who will be asked to subsidize all of this care? The drug industry, the hospitals, and the medical profession, of course. Fee schedules will be established, generic prescribing will be mandated, and profit statements will be scanned with a jaundiced eye. Already, legislation has been proposed in New York requiring that only generically prescribed drugs be authorized for the state's Medicaid Program.

I note incidentally that I have surveyed the feelings of a number of doctors on this point. Although the thinking is not unanimous it is to this effect: "Most of us prefer to prescribe by brand name, especially where we feel that quality control is important. At any rate, we all want the freedom to choose either generic or brand name drugs depending on the circumstances that prevail at the time we write the prescription." This was the point of view expressed by a prominent medical spokesman a year ago. I am sure he would agree to add pharmacists to the volunteers enlisted in subsidization.[16]

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[15] U. S. Senate, January 18, 1967. (Italics supplied.)

[16] Schlossman, Ralph, E., M. D., Secretary, Queens County Medical Society Annual Pharmacy Congress, St. John's University, New York, March 17, 1967.

There is a third circumstance where under color of authority in some states, and through frustration or indifference in others, physicians practicing in institutional environments, agree completely in advance to accept for their patients any drug stocked by the institution as an equivalent to any drug they may specify.

Such a stock of drugs is ordered, maintained and authorized through the medium of a formulary committee or other such named group that sorts out from among various brands what represents to them the best buy for the money. Observations of such activities lead many to the conclusion that the possibilities are wherever feasible dictated by pricing information made available to and by the pharmacist and/or the purchasing agent. Also, the criteria for scientific evaluation are in many cases either sadly minimized or not completely understood by those that make the infrequent judgments.

In a series of articles dealing with the "Battle of Drug Costs", Dr. J. H. Cooper reported opinions expressed by a group whose membership has done much to educate themselves to the scientific and legal realities of plaintiff's claims and expressed interest in "substitution" under formulary systems.

"Lawyers participating in a convention of the American Trial Lawyers Association in September, 1966, seemed generally to agree that through legal discovery procedures it would be possible to ascertain specific responsibility either for the authorization of substitution or the assumption of such responsibility, and that a finding of substitution could lead to a law suit."[17]

I would say as to this third form of substitution, as well as of the second form as it affects the physician, he should be well advised to take measures to protect himself from the effects of decisions which he has cloaked with apparent delegation and authority. Doctors, therefore, who participate in state programs which permit substitution without their prior knowledge or consultation, and doctors who waive normal prescriptive and selective prerogatives in institutional contracts or other understandings, should seek through their societies or medical boards to have a "save harmless" agreement signed by the system's sponsors that will insure the doctor's economic protection from any and all suits where he may be named as defendant or co-defendant, such suits being predicated upon patient's claims arising from such programs of dispensing drugs.

In the main, substitution arises in four classes of circumstance:

1. Through ignorance or accident of the dispenser of the drugs;[18]

[17] *Medical News,* June 5, 1967.

[18] Names that look or sound alike. *Vulesza v. Mayfield*, 1966 Tenn. CA, Flavil dispensed in place of Enovid.

2. Through the intentional act of the dispenser of the drug based on consideration for his advantage;

3. Through the authority of the patient;

4. Through the authority or persuasion of persons other than the prescriber or the patient.

Substitution authorized by the prescriber is not substitution in this sense. It is an amended prescription or a novation.

Breach of Warranty

The first type of action I have indicated, generally sound in tort, as negligence or malpractice, but in today's product liability atmosphere they would be breach of warranty actions as well. Differing strengths between syrups, tinctures, elixirs of the same active ingredient, used to account for many of these. There is a plentitude of cases of this type.

In the *Gault* case,[19] at the hospital the saline solution prepared for the patient's use during a gastric cytology test was Na OH, rather than Na Cl, and resultant burns created a painful, long term injury, and a jury verdict of $162,500. This was negligent and unintentional substitution which creates its own impetus for discovery. These are essentially compounding and dispensing errors. For example, the physician prescribes a rhinitis capsule with .4 mg of atropine sulfate per capsule, and the pharmacist erroneously makes each up to contain 40 mg of atropine sulfate.[20]

The prescription is the basis of a sale. The druggist warrants the good quality of the drug sold, that the article is of the kind he contracted to sell, that he used due and proper care and skill. [21] [22]

Any description of the goods which is made part of the basis of the sale creates an express warranty that the goods shall conform to the description, and the doctor's specification on the prescription provides such a description exactly. In a Georgia case, a pharmacist gave, in place of the prescription drug, what he declared to be an equivalent drug to a patient, and the patient was burned. Even though he had informed the patient, the court found him liable in tort as negligent, and liable for breach of warranty.[23]

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[19] *Gault v. Poor Sisters of St. Francis* 375 F. 2nd 539 (1967).

[20] *McKeithan v. DeLuca,* Sup Ct, Fairfield County.

[21] Docket No. 122716, Conn., May 24, 1967, 28CJS, Druggists, 6C.

[22] *Kruger v. Knutson,* 261 Minn. 144 (1961).

[23] *Gipson v. Jacobs Pharmacy,* Ga. CA-43, 154, November 16, 1967.

In a somewhat similar case in Massachusetts, *Andreopalla v. Gaeta,*[24] the pharmacist recommended a packaged drug in place of filling the patient's prescription. The substitute drug caused injury. The court easily found a basis for breach of warranty.[25] In such an action a defense of contributory negligence is inapplicable.

The pharmacist who dispenses willfully, without color of authority from the patient or the state, and without the actual authority of the prescriber, is a misdemeanant at that point, technically and practically, in federal and state law. He has committed the misdemeanor of misbranding on the one hand and the misdemeanor of substitution on the other. These carry penalties of fine, imprisonment or both.

If he is prosecuted criminally therefore or has been the subject of preliminary disciplinary hearings at which his guilt has been established, he has laid the basis for revocation or suspension of licensure as well.

In addition, he is open to civil suit by the manufacturer of the prescribed drug whose product was the subject of the substitution.

He is open to civil suit by the patient who was defrauded in that the ordered prescription was dishonored by substitution. Some of these circumstances do smack of fraud which is a false statement or misstatement of material facts, by one who knows them to be false, to an innocent party, who relies on it and is damaged. It can also arise out of ignorance with a pretense of knowledge.

Negligent use of language can create liability—especially where there is a duty of care to the other party.

If the patient claims injury, pain, suffering or loss of earning power from failure to achieve therapeutic results contemplated by the physician, then the pharmacist's infraction of the regulation may serve to make out a *prima facie* case on the grounds of negligence, since an enacted or promulgated means of public protection was violated. This helps get the case before a jury which will hear and decide the facts.[26]

Where a patient's consent to substitution has been obtained, it should be an informed consent.[27] Therefore, the pharmacist must be willing to undertake sufficient explanatory responsibility, preferably written or witnessed, to sustain him against a patient's later

[24] *Andreopalla v. Gaeta* 260 Mass. 105 (1927).

[25] See also P. D. for exposition of warranty principles, 257 F. Supp 991.

[26] *Donaldson v. A & P,* 186 Ga. 870, Statutory negligence.

[27] *Salgo v. Stanford* 154 Cal. App. 2nd 560, (1957).

charge that the consent was induced by fraud or lack of information. A defense of contributory negligence, for either a pharmacist or a physician, based on the patient's role in selection of the drug of treatment, would have to withstand close scrutiny in a courtroom.

Where the pharmacist has undertaken to make this unauthorized substitution on his own, he has chosen as his co-defendant,[28] if any,[29] in this suit, the manufacturer of the drug he substituted. There are many reasons why this may be unsatisfactory. A major reason is that *if* he is insured for product liability, his carrier may not be willing to assume obligations for defense and reimbursement where an illegal act has been the acorn from which this trouble has grown.[30]

The pharmacist who, unauthorized at the time of substitution by the prescriber, substitutes nonetheless with color of authority in terms of state reimbursement systems, formularial agreements or a patient's consent as previously described—has to foresee certain other legal possibilities. He must satisfy himself that he has not broken the law, or regulations which have the force of law, federal or state. These have pre-emptive right over his business agreements. Within each state the opinion of pharmacy board counsel, pharmacy association counsel, the state attorney general's office and if necessary private counsel should be secured and be the bases for action.

Methods employed in any trade, business or profession, however long continued, cannot avail to establish as safe in law that which is dangerous in fact.[31]

The pharmacist must in addition, evaluate his position as the selector, and possibly warrantor, of drugs which he will dispense as equivalents, and be prepared to justify his choice on the basis of an average man's prudence, and the special pharmacy knowledge, care and judgment that is common to the usual pharmaceutical practitioner in his locale of practice. Here a review of his insurance coverage and a candid discussion with his broker or carrier would be of importance. The same would be true for institutional practice, to determine the type of coverage the hospital has in the event the employee is named co-defendant in the types of suits that could arise from this action.

The Uniform Commercial Code[32] has had a widening influence on product liability, so that service plus sale combinations of action are

[28] *Farley v. S. P. C.*, 271 Mass. 230 (1930).

[29] *Willson v. Faxon, Williams and Faxon*, 208 N. Y. 108 (1913).

[30] *Gray v. Zurich Insurance Company*, 54 Cal. Rptr. 104 (1966).

[31] *Ault v. Hall*, 119 Ohio St. 423 (1928).

[32] § 2—106, 2—105.

now covered and susceptible to breach of warranty. The prescription blank is the contract and the dispensing act is its execution. Even the entrenched doctrine of *Perlmutter v. Beth David,*[33] that would not allow a breach of warranty suit, for example, in hospital sales of blood to a patient and made it necessary that the injured patient who contracted hepatitis from the infected blood transfused prove negligence, is now being renounced.[34] So the choice of treatment gives the physician latitude, but the product dispensed to the patient carries express and implied warranties the breach of which is actionable, with or without a show of negligence.

A pattern of systematic substitution often occurs in circumstances where the pharmacist is following orders. Even were he to do this on his own with the apparent authority of his principal, the institution could be held liable on the principles of "agency" and "respondeat superior."[35] As to this, the Supreme Court, New York County, a few years ago held the City of New York liable for the negligent acts of its employees in treating a patient at a city hospital without the necessity of the patient introducing expert medical testimony to show want of care or improper procedure on the part of said employees.[36]

Generic Equivalents

For the medical practitioner and governmental officials, where drug entities are unprotected by patent, generic drugs that are truly products of current good manufacturing practice may be of growing significance. The availability of these is presently limited to products of most of the major pharmaceutical concerns and several of the smaller houses, many of whom are making conscientious efforts to meet Food and Drug Administration (FDA) criteria and stay clear of injunctions, seizures, recalls and the like.

However good or poor, "generics" do not in themselves absolve or incriminate the act of substitution. When a "branded" specialty drug is prescribed, and that prescription is not amended or "open ended" by the prescriber's authority, only that "branded" specialty may be dispensed. Substitution *per se* is wrongful under the present state of drug control as contrary to the public's interests. While

[33] *Perlmutter v. Beth David* 308 N. Y. 100 (1954).

[34] *Jackson v. Muhlenberg Hospital,* 96 N. J. Super. 314, 315 (1967).

[35] *O'Mara v. California State Board of Pharmacy,* 54 Cal. Rptr. 862 (1966).

[36] "Editorial on *Reeder v. City of New York,*" *N. Y. S. J. of Medicine,* May 1, 1960, p. 1411.

such protection motivates law, rather than preservation of special interests, anti-substitution laws must continue to be enforced.

For the purposes of this paper we need not dwell too long upon the issues, scientific or economic, that surround the concept of generic equivalency. We are here concerned with the ethical and legal implications of substitution and consider "genericism" only as it evolves to defend or mitigate the presently illegal act of substitution.

Suffice it to say, that in what essentially must be a debate of scientific issues, many of those who have come forward for validity of the usefulness of generic equivalency procedure, are for the most part educated and oriented in the social science areas, while those who oppose seemingly are associated with the health professions and drug research and manufacture. The intent of both groups is to help the general public but these disciplines must rely on one another, or conclusions are in the end untenable.

In all fairness it should be noted that there are many in this latter group who hope that at some time in the future, the state of knowledge, the technical advances and increased budgetary aid to governmental services may bring about some degree of standardization in manufacture, material, personnel, and control measures to allow for products of uniformly high quality and proven therapeutic equivalency. That day, however, is not here, nor is the arrival time susceptible of prophecy. The recent prompt de-certification of antibiotic products made with well intentioned conformity to the government's own monograph, on the finding that the finished products were not in vivo equivalents of the innovator's branded product, is but one example.

New Drug Approval

The New Drug Amendments, as we all know, enlarged the concept of a new drug to include more than safety effectiveness in use. A physician who prescribes new drugs for patients does so in reliance upon the FDA's approval of the labels and labeling of the drug as well as its acceptance of proof of clinical effectiveness in the light of such advice to prescribers for patient use.

Part and parcel of the new drug regulations[37] and procedures, and you can read these as simply on the New Drug Approval (NDA) Form supplied by the FDA as anywhere else, is not only to satisfy the government that they can approve a drug product that is safe and

[37] 21 CFR 1.130 and following.

effective when used pursuant to its approved labeling. It is also to prove to the Government that the selfsame manufacturer can make the same drug all the time, so that its therapeutic effectiveness will be identical and consistent. That is, to enable the user to predict with some reasonable degree of success, anticipated results within variances established only by the patient or the patient's illness. For this reason, the manufacturer of a new drug is constantly in the business of making equivalents, for every package of his finished dosage form is the chemical and therapeutic equivalent of any other. That's a hard enough job for insiders—let alone outsiders!

Dr. Earl L. Meyers of the FDA recently put the matter briefly and succinctly in its present perspective:

"Regulations and guidelines do not establish product quality . . . Control methods applicable to the whole process must be worked out to maintain the strength, quality, and purity of each batch. This applies not only to the synthesis of an active ingredient but to the complete manufacture of the final product including packaging, labeling and identification of each lot.

The active ingredient in a dosage form of a drug is probably not the sole determinant of its pharmacological effectiveness. The physiological response may be a formulation of the dosage form as well as the active component. The rate at which the amount of the active component in the dosage form is physiologically available to the patient upon administration is an important consideration. We have encountered cases of varied clinical response between batches of the same pharmaceutical formulation. Additional study has indicated that differences in physical and chemical properties were caused among other things, by differences in physical properties of the raw materials such as crystalline or amorphous form and particle size, conditions encountered during processing, and contact of the components in the dosage form resulting in complexing, binding, and absorption. Therefore early consideration of these factors is necessary.

It is well known that on occasion apparently minor modifications in the form of a drug may have a profound effect on the absorption of the drug and therefore possibly on its safety and effectiveness. "Then he cited examples to emphasize his points including an anti-cancer drug, an antibiotic and a steroid. Another example is concerned with a patient who was adequately controlled in prednisone but went out of control when substitution of another brand of the drug was made. The substituted tablets contained the labeled quantity of the drug, but dissolved much more slowly than the effective ones."[38]

Interestingly enough in the McLeod case, where a patient claimed injuries because of taking MER 29 on prescription and named the pharmacist as a defendant, the court in dismissing the case against the latter pointed out that the drug had cleared the NDA procedures and had been selected by the physician not the pharmacist. Also that the latter had dispensed it unadulterated and with proper labeling. The patient had no claim against him, therefore, in breach of warranty.

[38] Presented at 3rd National Meeting, Academy of Pharmaceutical Sciences, Nov. 28, 1967, Washington, D. C.

We know also that there are many drugs which represent claimed chemical equivalency to branded new drugs, but which have not cleared the new drug approval system of the federal agency. Where these drugs are substituted for approved new drugs, doesn't this seemingly add another measure of uncertainty? Not only have leading medical educators been concerned with the possibility that chemical equivalency and therapeutic equivalency are not necessarily synonymous in finished drug dosage forms,[39] but the FDA has undertaken major steps in this area to safeguard consumers.

In another case in the West, a cause of action for breach of warranty foundered for lack of proof that the drug was impure or misbranded as it came to the patient. The court held that when a drug gains FDA approval, is properly tested and labeled with appropriate warnings, it is as a matter of law presumptively a reasonably safe product.[40] Might the court view differently a drug which was categorically held to be "new" by the FDA, but which had not gone through the NDA approval procedure?

The best intentioned substituter must therefore be willing, in his own mirror of self analysis, to say "I am absolutely certain that I have not compromised the patient's right to the safe and effective product designated for him. I am certain because I know directly, or have enquired from sources upon which reputable practitioners may rely, that this ingredient or product is equally well made, will achieve the same blood levels for the same duration of time, will be eliminated in the same manner over the same period, will be utilized physiologically and have the identical pharmacological effect on the patient and have no greater toxicity. I am certain because I have carried out or seen the quality controls on this product and it is manufactured with the same raw material specifications, in-line testing, finished product criteria, packaging requirements, as the named drug product." Maybe there is more that the mirror must bear witness to, but that is a start, where the conscience is to be satisfied if not the law.

Recalling McLeod, that's a great deal more exacting than dispensing the drug as prescribed, using due and proper care so that it's not adulterated or misbranded in coming to the patient.[41] Many such cases indicate the advantage of being able to show the original pre-

[39] Letter from Dr. Alfred Gilman, Chairman Pharmacology Dep't, Albert Einstein College of Medicine, to Nelson Committee, U. S. Senate 1967.

[40] *Lewis v. Baker's Pharmacy and Richardson-Merrell, Inc.* 413 Pac. 2nd 400 (1966).

[41] *McLeod v. W. S. Merrell Co.,* 174 So. 2nd 736 (1965).

scription as a means of establishing the liability of the named drug manufacturer should there be untoward reactions to the drug or drugs dispensed.

Pressures to Substitute

Part of the apologia for substitution that has been offered, has suggested that by being allowed to substitute for brand name products, the inventory of the pharmacy can be minimized. Those who would debate this premise point out that since branded articles need to be stocked also for circumstances when substitution is not countenanced, then there is actually wasteful duplication and stocking of "non-movers."

In his advice to community pharmacists beset by economic problems stemming from inventory overload, George F. Slavin, Jr., Editor of Lilly Digest, put the mistakes this way: *First*—The purchase of excessive quantities of merchandise of unproved salability. This is the class of merchandise which later appears on inventories as dead stock. This can be avoided or reduced by buying and featuring goods of known quality and salability and in quantities that can be moved within a period of one to two months' time. Also, establish a buying budget so that purchases will not exceed desired merchandise costs.[42]

Some of the pressures placed upon the pharmacist to substitute are non-subtle and most persuasive. A sometime device is for a governmental unit to undertake reimbursement for prescriptions filled for welfare patients at a price to be determined or preset in accordance with a "generic" price listing. This places the burden upon the pharmacist to locate the practitioner by telephone and get permission to substitute a less costly drug that he has available. The only other alternatives are to ask the patient to pay the difference. That won't work and creates confusion and suspicion. Or, in desperation, the pharmacist substitutes on his own, against his ethics, against the law, and with the possibilities of administrative, criminal and civil penalties.

Federal bills are proposed under similar lines all based on the transfer of some portion of prescriptive prerogative from the physician to those who will establish the availability of drugs by weighing economic as well as scientific factors, and to those who will dispense accordingly.

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[42] Slavin, George F., Jr., Editor, *Lilly Digest*, Eli Lilly & Co., Annual Pharmacy Congress, St. John's University, New York, March 17, 1967.

Recently in presenting a review of the problems inherent in handling professional samples, to the FDA, I pointed out that there are dangers in allowing people unqualified by education and experience to accumulate and dispense from physicians' samples turned in to them by the attending staff or the mail room. While I had in mind the possibilities of diversion, misbranding and adulteration, the additional possibility of substitution should not be overlooked.[43]

Where economic justification provides the rationale for substitution in institutional environments, is it not possible that the drug dispenser, (at least fifty percent of the time a non-pharmacist), will fill the doctor's order for antibiotics with the "mycin" equivalent she or he has in sample packings even though it may not be chemically or therapeutically an equal to that prescribed?

For the pharmacist, there is a special concern when members of his profession indulge in the forms of substitution we have indicated.

We have pondered the overall problem of overkill in legislation aimed at the healing arts this past decade at our Institute for Law and Psychiatry Unit. We think we have the basis for far-reaching and beneficial research in this area and are hopeful that we can undertake it in the near future. One brief indication is that the catabolistic spirit of rebellion that is gnawing at national fibers and spirits, is easily utilized to rally the public to extremes.

The Pharmacist's View

The pharmacist is prejudiced competitively by the actions of substituters and suffers direct economic damage. Will substitution itself, however, be the catalyst to aid the de-professionalization of pharmacy, to estrange supports and loyalties that have helped pharmacy to be firm for centuries? That is what is worrisome apparently to many practicing pharmacists and organization officials and comes through in surveys and interviews we have been making.

A recent questionnaire distributed to the fifty boards of pharmacy by the Temple Drug Law Unit achieved a rapid and complete response that is most revelatory as to the seriousness which boards attach to ethical and legal problems in pharmacy.

A large group showed an attitude about hospital dispensing that requires further study for understanding. Preliminary indications,

[43] Security Seminar, Arlington, Va., Feb. 28, 1968.

however, disclosed a discomfiture, that raised several possibilities. Either they were unsure of their authority in hospitals, or they believed they didn't belong there, or they don't want "to make waves" there.

This might mean, however, that pharmacy boards were concerned with keeping pharmacy practice successful, with not creating antagonisms. Implicit in this is the question then as to whether by inaction or indecision, a privileged group of pharmacy operators and a privileged class of dispensers is being established, to the discriminatory disadvantage of the private and chain retail pharmacies.

The New York State Board of Pharmacy has recognized this lately and sent notice to all pharmacists, including hospital pharmacists, that the anti-substitution regulation[44] bears an exemption clause for hospitals using a formulary system that includes prior consent by its doctors to substitute drugs. They have noted that in many instances, however, the exemption was disqualified by noncompliance with its terms. There is no mention of action taken, then, however, but all other pharmacists are reminded that "all prescriptions for all patients should be filled exactly as written by all pharmacists unless a change has been authorized by the prescriber."

Those responsible for enforcing the law should do so equitably and uniformly. Those who feel that the control is unjust or inequitable or contrary to theirs or the public's interest have their remedy in pre- or post-enforcement review available from our judiciary.[45] When authorities look aside from enforcement of controls designed to benefit all in the honoring, they are adding to dereliction and creating quantitative and qualitative obstacles to enforcement of those portions of the same code that they do choose to enforce.

Some of the questionnaires carried comments that indicated that the Board depends on the manufacturers to do the spade work for substitution violations. Manufacturers do make complaints to the Board based on surveys and investigations that they undertake, but they are interested in violations that affect one particular brand of one particular product generally—and this is too slim an approach for the Board to depend upon for action.

While the manufacturer can take legal actions against his trademark, unfair competitive practices and his property rights, he is more

[44] § 6808, N. Y. S. Pharmacy Law (Handbook 11) and § 6808a.

[45] Art. 78, Prcdg, N. Y. S.; *TGA Inc. v. Gardner*, 387 U. S. 158 (1967).

diligent in his activities against counterfeiters who present a greater drain on his profits.

Therefore, while pharmacy boards and associations may continue to receive support and assistance in anti-substitution activities from manufacturers and manufacturing groups, this should be a "do-it-yourself" operation as well.

There is little doubt that the figures we have received as to prosecution of retail pharmacists for substitution are less than the visible eighth of the iceberg. But is this an iceberg that can sink pharmacy as we know it and bring destructive influences to bear on the institutions and services for the health and welfare of the general public? Estimates have appeared that present claims that 20 million prescriptions are not filled with the brand specified in a given year.[46]

How great the real figure may be, leave to further analysis that must consider that recorded prosecutions are a small percentage of actual derelictions among retail pharmacists. But what of substitution in hospital pharmacies? And what of substitution in the dispensing act by non-pharmacist dispensers of drugs?

Although in terms of present medical and pharmaceutical relationships, the state of regulatory drug controls, and the attitude of our judiciary, we have deprecated substitution, what the future holds for it is not quite so clear. So many questions. So great a need for attention and equitable solutions in the public's interest.

It is easy to say that those opposed, must oppose harder and those who seek to dilute its significance must exert efforts to re-array it as a reasonable approach, but what are the realities in store for both?

Conclusion

Perhaps in the words of Chief Justice Holmes:

> As law embodies beliefs that have triumphed in the battle of ideas and then have translated themselves into action, while there still is doubt, while opposite convictions still keep a battlefront against each other, the time for law has not come; the notion destined to prevail is not yet entitled to the field.[47]

The public has an interest in the existence of competition that is not unreasonably restricted. It also has an interest in the protection of freedom to contract and in the enforcement of contractual rights and duties.[48]

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[46] Krieg, Margaret, *Black Market Medicine.*

[47] Lerner, Max, *The Mind and Faith of Justice Holmes,* Little Brown & Co., 1943, p. 390.

[48] *Lovelace Clinic v. Murphy* 417 Pac. 2nd 450 (1966).

Do we need to re-examine substitution in terms of newer trends in patient care, in terms of government financed reimbursement programs?

In a recent address to physicians, Dr. M. O. Rouse, President of the American Medical Association (A.M.A.) said: "Physicians must recognize that they have important responsibilities with respect to the cost of health care. The physician must acknowledge in every instance, that what he does for his patient is a matter of money as well as a matter of science." The A. M. A. News of April 8, 1968, further quoted him as urging cooperation as essential with other professionals and institutions in the health field, including government, since it is doubtful that free enterprise alone can provide all the desirable features of the health care system.[49]

"Be that as it may, there can be no question but that the judicial thinking of the vast majority of our courts today is very much pro the rights of the individual.[50] Never in the history of our country have the courts reached out so far, in so many different directions, to protect the individual, sometimes it seems, even against consequences of his own folly."[51]

We have dwelt on the dangers of substitution to the public and to pharmacists and physicians. Does substitution jeopardize our economic institutions as well as our health care traditions?

As to the economic forces involved, however, the courts have held that no person or class of persons or trade or industry or profession may "admit a hazard created for economic reason and then say, as a matter of law, the public must bear the risk."[52]

There is much here that requires in depth study and objective analysis, because past history and the evolution of law and regulation in this area of concern may not have kept pace with the changing political and sociological patterns that must be law—affected and must affect law. Or perhaps government and public have been too ready to compromise principle for expediency?

This is a research objective we are hopeful of undertaking through our Institute for Law and Health Sciences at Temple University in the near future. And we would hope to report our results in a form that will lend itself to some degree of predictability and guidance.

[The End]

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[49] A. M. A. Congress on the Socio-Economics of Health Care, April, 1968.

[50] *See v. City of Seattle,* 387 U. S. 541 (1967); *Camara v. Municipal Court of San Francisco* 387 U. S. 527 (1967).

[51] Dean Prosser, 16 Nev. St. Bar Journal, pp. 51-72.

[52] *Darling v. Charleston Community Memorial Hospital* 211 N. E. 2nd 253 (1965).

Legal Control of Narcotics

By ROBERT KINGSLEY

The Following Article Was Prepared for Delivery on April 18, 1968, as the Charles Wesley Dunn Memorial Lecture at The Law Center, University of Southern California, Under the Auspices of the Food and Drug Law Institute. Mr. Kingsley Is Associate Justice, California Court of Appeal.

FOURTEEN YEARS AGO, the Citizen's Advisory Committee to the (California) Attorney General on Crime Prevention opened its Study Report on Narcotic Addiction with these words:

> While it was the objective of your committee to study all reasonably pertinent matters relating to narcotic addiction, they were ever cognizant of the fact that narcotics and certain other addicting drugs do serve a useful purpose in that they alleviate pain, and even assist in restoring health and their proper use is almost indispensible to modern medicine. We are, therefore, concerned with a substance which may be used correctly or incorrectly, legally or illegally.

As that report proceeds to point out, the problem of control of these potentially dangerous, but frequently essential, products, is further complicated by the fact that some, although not all, of the narcotics in use in California and in the nation are addictive, and all of them are habit-forming. Because the term "addiction" is rather often used as though it were a synonym for "habit-forming," and sometimes as though it were synonymous with "enjoyable" or even "pleasant," I point out that it is, at least for our purposes today, a legal term, defined by the courts of California, and a term of somewhat restrictive meaning.

In *People v. Victor*, 62 Cal. 2d 280 (1965), the California Supreme Court gave us its understanding of the statutory term "addicted," and of the term which accompanies it in the statute of which I shall speak later, "imminent danger of becoming addicted." "Addiction" we are told, is "more a process than an event," and it involves three elements: emotional dependence, tolerance, and physical dependence. "Imminent danger," we are told, is the next to the final step in that "process":

> On the one hand, an individual may not escape an inquiry into his addictive status merely by showing that he is not yet "hooked" in the strict sense of that

word. On the other hand, to be brought within this category it is not enough that the individual be "addiction-prone," or associate with addicts, or even have begun to experiment with drugs; he must have subjected himself to "repeated use of narcotics." . . . The legislation is not vulnerable to defendant's charge that it subjects to narcotics commitment proceedings individuals who simply suffer "personality disturbances" or predisposition towards addiction. The legislation does not reach such persons until by repeated acts of obtaining, preparing and ingesting an addictive drug they demonstrate that they have failed to resolve their problems by socially acceptable methods and that total addiction is just a matter of time.

In our fumbling attempts to control both addictive and non-addictive drugs, we have used three kinds of devices: (1) control of origin; (2) control of possession and sale; and (3) restriction of market.

Control of Origin

We have tried to control the origin of the proscribed drugs, first, by prohibition or regulation of their manufacture, and, secondly, by restriction or prohibition of their importation. Insofar as the derivatives of opium are concerned, the process has worked reasonably well within this country. The processes of treating the opium poppy are sufficiently complex that any wide-scale manufacture outside of the regulated and licensed production facilities has proven impracticable. But for other drugs, especially marijuana and, recently, LSD, the attempt to control origination is almost a total failure. Marijuana can be grown in any backyard or vacant lot; its preparation for market requires only harvesting, drying and packaging; LSD can be made in a home laboratory from materials legally and easily available.

The attempt to control origination by restriction on importation is, I am sorry to say, almost a total failure. Heroin, the most commonly used opium derivative, is small in bulk, easily concealed, and easily procured in many foreign countries. It flows across our southern border and through our ports in a stream broken only by an occasional discovery. I do not say this in any derogation of the honorable men who act as our customs inspectors. The practical problems of search and discovery are so great, and their numbers are so small, that they can but try to sweep back the sea with a very small and worn broom. Efforts have been made to enlist the help of other countries to stop these products before they enter the stream of commerce which brings them to our borders. Many promises, and some actions, have resulted. But the economic problems in the producing countries, and the fact that in many of them the use, possession and sale of narcotics are respectable activities, have made this device an almost useless one. If narcotics in the United States are

to be controlled, it must be by some method which renders it no longer profitable to export them to this country.

Control of Possession and Sale

Frustrated in our efforts to cut off the narcotic traffic at its source, we have turned to attempts to cut it off at the receiving end. Starting, for all practical purposes, with The Harrison Narcotics Act, the Congress and the several state legislatures have made it a criminal offense to possess or to sell narcotics and certain other drugs, except under very strictly controlled and licensed conditions. Our success in this endeavor is immeasurable—immeasurable in the sense that it represents a quantity so small as almost to defy identification.

In the first place, the very processes of discovery of these crimes involves an immense amount of police work. Those engaged in the sale of narcotics do not do so if they fear observation, and their customers, for obvious reasons, do not talk. As a result, we must resort to an elaborate apparatus of under-cover officers and informers who, often after a long period of developing acceptance, finally succeed in arresting a petty peddler of a single marijuana cigarette or of a single "bindle" of highly diluted heroin. Occasionally, it is true, a larger "haul" is made and some intermediate distributor is caught. But the mass of cases are of the most petty nature. And these are the cases which, because of the practical police problems involved, give to the courts their most difficult problems in the areas of search and seizure, reasonableness of arrest, corroboration, entrapment, and other issues of constitutional law and of evidence.

Secondly, for the addictive drugs, the pressure on the addict to replenish his supply as the risk of withdrawal and its physical torment approaches is so great that he will pay any price, and run any risk, to obtain even a small amount. With that kind of market, it is not difficult to find peddlers, distributors and importers who find the high profit an ample counter-balance to the risks of arrest and conviction.

The non-addictive drugs present a different picture, but produce the same result. Both addictive and non-addictive drugs find their attraction in their ability to relieve frustrations and to produce a state of euphoria. To this ability to give release from the pressures and cares of this world we have, in the past few years, found the added inducement that the use of narcotics can be a form of defiance by people—young and old—who prefer to reject society rather than to live within it. While not of the same character as the addict's fear of physical torture in withdrawal, these psychiatric pressures again

produce a willingness to pay a price that makes the supplier's risks worthwhile.

A look at some figures will show the extent of our failure. In spite of a substantial increase in penalties imposed by the 1961 Legislature, and in spite of highly increased effectiveness in police methods, the total of drug arrests in 1966 was 60.2% over that in 1960. In 1966, out of a total of 114,283 adult felony arrests, 19,403 were for drug law violations; out of 41,959 adult felony filings in Superior Court, 8,176 were for drug offenses; of the 40,832 cases determined by the Superior Courts in that year, 7,240 were drug violation cases. In short, about one-fifth of all the law enforcement activity in California is directed to the attempt to control narcotics and related drugs by the process of arrest, conviction and punishment. Although the figures differ from year to year, the relation between narcotic offenses and other cases has remained substantially constant.

In other words, in spite of the most dedicated efforts by law enforcement officers and prosecutors, and in spite of the heaviest penalties ever imposed, the attempt to control narcotic use and sale by the use of criminal prosecution has not reduced its volume by any measurable amount. A mountain of law enforcement brings forth a very small mouse.

Restriction of Market

In the 1954 Report of the Attorney General's committee appeared the suggestion of a third mode of controlling narcotics, namely procedures to reduce the demand by striking at the ultimate source: the psychological pressures which drive men and women to use narcotics and which keep them on that usage in spite of threats of punishment. The concept was revived and expanded in the recommendations, in 1960, of the Special Study Commission on Narcotics. And those recommendations were to result in the adoption, in 1961, of the California Narcotic Rehabilitation Act, originally sections 6399 and following, of the Penal Code and, later, transferred to the Welfare and Institutions Code as sections 3000 and following.

The concept of this Act was that the tendency toward addiction was psychological, that sound psychological and psychiatric techniques existed to enable addicts to resist the pressures toward narcotic usage, but that these techniques could operate with effectiveness only where the addict was under legal compulsion to remain in a treatment program until rehabilitation was accomplished or until failure was clearly demonstrated.

I have discussed on other occasions the details of that procedure. It calls for a three-fold consideration of the individual and his problems, followed by a treatment program, by specialists, for as long a period (up to six years) as is required to determine either success or the impossibility of success. The procedure, with provisions designed to insure recognition of constitutional rights to a fair hearing, is, briefly, as follows:

Following a criminal conviction for any offense, if the possibility of personal narcotic involvement appears, the judge makes a preliminary finding as to narcotic addiction, or the imminent danger thereof, and his own preliminary finding as to the possible value of treatment. Since the judge is not an expert in psychiatric treatment, his determination on that point is phrased as a negative one: the proceedings for commitment must commence unless the trial judge is prepared to find that "defendant's record and probation report indicates such a pattern of criminality that he does not constitute a fit subject for commitment." There follows a judicial hearing, devoted, however, only to the single issue of addiction or of imminent danger of addiction. Once the judge who tried the criminal case has ordered commitment proceedings to start, no further *judicial* inquiry into the possible value of treatment is in order. (*People v. Strickland,* 243 Cal. App. 2d 196, 199 (1966).) If this judicial hearing determines the fact of addiction or of imminent danger of addiction, the individual is committed to the Rehabilitation Center. For a period of not less than 90 days, the professional staff of the Center examines him. If that examination, which includes observation of the person in treatment programs, indicates that his background and attitudes are such that he cannot be treated with any hope of success, he is returned to court for resumption of the criminal case, ordinarily for a prison term. But the technical staff is cautioned, by statute, that it is not to give up easily, and that a mere reluctance to accept treatment is not, itself, a basis for rejection.

Similarly, the public, and law enforcement officials, must remember that the rehabilitation—frequently the habilitation—of the narcotic addict is a slow and difficult problem. It is no easy task to discover the deep-seated reasons for a man's rejection of all hope of meeting the world on equal terms and for his resort to a chemical crutch to enable him to forget his problems. And it is even harder for the man who has come to rely on narcotics to ease the strains of daily life to meet these strains face-to-face without help from anything but his own spirit. The person committed to the Center will go

out on parole, fail, return, be paroled again, fail and return again many times before his "cure" can be said to have been accomplished. If each period of semi-freedom on parole is longer than the one before, if the parolee meets and overcomes more disappointments and frustrations on each parole, then the program is succeeding. But we must have patience. We know that mere imprisonment, "drying out" of the physical dependence, and release, have never accomplished a cure. We have reason to think that this new program may. It is worth a chance, and that means a chance over a substantial period of years.

The past years have brought into focus a different problem, that of the increased use of the non-addictive drugs and the hallucinogens. As I have suggested above, the resort to these drugs grows out of much the same kind of psychological and psychiatric problems as those which lead to addiction. In many cases, the non-addictive drugs, especially marijuana, gradually lose their power to give escape and the user turns to heroin. In the cases where that does not result, the non-addictive drug still has serious effects on the user and on the society in which, with vision both opthalmologically and psychologically distorted, the user attempts to operate. Our present laws deal with these people only by the increasingly ineffective device of criminal prosecution. Mostly, they are young. The median age for marijuana arrestees has dropped since 1965 from 22 to 20 years, and the number of arrestees has increased: the rate per 100,000 of population rose in one year from 125.6 to 226.8. But our therapeutic commitment program operates only for the benefit of those whose frustrations have brought them to the use of heroin and to, or over, the border of addiction. I suggest here that we need thought, study and action to provide on the same compulsory basis for the psychological and psychiatric treatment of the non-addicted users of narcotics and of dangerous drugs. It is true that, to an extent not known or studied, part of the frustrations involved grow out of racial and economic discriminations and that widely based social and economic programs will be needed to eliminate that kind of pressure. But thousands of our young men and women, and men and women no longer young, endure these social problems without resorting to chemical crutches to ease their lives. Along with wars against poverty, we must provide wars against mental rejection of society. That process will, it is true, make all that we have attempted in the past seem child's play, but it is a process we must begin, and we must begin it soon! **[The End]**

The Federal Trade Commission and the Fair Packaging and Labeling Act

By FREDERICK A. CASSIDY

The following article was delivered at the Fair Packaging and Labeling Act Seminar sponsored by the Food and Drug Administration in cooperation with Chemical Specialties Manufacturers Association and the National Paint, Varnish and Lacquer Association on May 28, 1968 at the Department of Commerce Auditorium, Washington, D. C. Mr. Cassidy is with the Division of Special Projects of the Federal Trade Commission.

AFTER SEVERAL YEARS OF ARGUMENT PRO AND CON, the Fair Packaging and Labeling Act (FPLA) became a reality on November 3, 1966. Dedicated to the proposition that an informed body of consumers is essential to a free market economy, it obligates the Federal Trade Commission (FTC) and the Food and Drug Administration to issue regulations to implement the law.

It is my purpose today to offer comment reflecting the views of that part of the FTC staff charged with the duties of implementing the law and of interpreting the regulations which are an essential part of the implementation. In so doing, I speak only as a staff member and not as one whose opinions are binding on the Commission itself.

FPLA recognizes the need for mandatory regulations and also for regulations additional to the mandatory ones. Section 4 of the Act not only specifies the basic requirements and prohibitions which affect the consumer's supplier, but it also directs those who write the regulations along prescribed channels. Section 5, while still restrictive as to the nature of the additional regulations which can be written, does allow more latitude.

When FPLA was enacted, the FTC, after an extremely detailed study of the Act, issued its proposed mandatory regulations on June 27, 1967. As expected, comments were received by the Commission, and these, numbering in the hundreds, provoked another detailed study. I say, as expected, because any regulations affecting so many

commodities and hence so many manufacturers, packers, and distributors, are bound to precipitate comment. In many instances comments were in the nature of objections. Typically, these were of the sort "but surely it doesn't apply to my products, because." Also, informal comment frequently predicted dire consequences of the regulations as related to the economic well being of the manufacturer, packer, distributor and to the consumer as well.

After a detailed study by the staff of the various comments, the Commission did not proceed at that point to issue the regulations in final form. Recognizing the preemption authority contained in Section 12 of the Act, and appreciating that FPLA regulations would have a profound effect on State authorities, the views of the States and the expertise of States officials were desired. Therefore, with the assistance of the National Association of State Departments of Agriculture and aided by State Weights and Measures personnel, the advice of a Committee of State officials was solicited. Six in number, these representatives of the various States met with the staff and the Commission to express their views of the Section 4 regulations. Only after this review of the content of the proposed regulations and of all subsequent comments thereon did the Commission publish the regulations on March 19, 1968. At that time, the Commission took recognition of, but did not rule on, the application of coverage to many commodities. The Commission indicated that it would rule on the points of coverage in the very near future. Such a rule is now imminent.

Not by way of apology, but merely to afford the grounds for an understanding of the complexity of the problem we must deal with, I direct your attention to the types of commodities envisioned by "consumer commodities not foods, drugs, or cosmetics etc." Ammunition to antifreeze, safety flares to shoelaces, fertilizers to plastic table cloths, mops and brooms to toys—these are only a few.

The Spirit of the Law

But let us for a moment go back to the spirit of the mandatory or Section 4 regulations. All of us are shoppers; all of us are consumers. Quite apart from our vocations which take up the major portion of our daily activities, we do have occasions to enter retail stores when we are just shoppers. If we are shopping for a can of paint, a tube of household cement, or a box of soap, are we not reasonable customers when we look for the identity on the label of the item? Is it a latex interior or a varnish stain; is the item a paper glue or an epoxy; did the wife want the soap for the laundry or the electric dishwasher?

Is it unreasonable to expect the manufacturer or distributor to identify himself? If you wish to praise him for his quality or perhaps criticize him for lack thereof, or if you just wish to know for the sake of knowing, do you not look for name and address? And if you do, do you expect to search for it, knowing only it is "somewhere"? If you are satisfied as to identity and manufacturers of competing items, and you have the option of selection, do you not compare price and quantity?

If, then, you concur with the Declaration of Policy of the Act, found in Section 2, "Informed consumers are essential to the fair and efficient functioning of a free market economy," and, "Packages and their labels should enable consumers to obtain accurate information as to quantity of contents and should facilitate value comparisons," it seems to us that the Section 4 regulations are basically only what a reasonable person would expect them to be, and furthermore we suggest that industry will have a rather easy time in living within these regulations.

New Concepts of Label Compliance

I do not attempt to oversimplify the regulations. There are some new concepts. After all, if the status quo had been sought, would there have been the FPLA?

What are some of the new facets of label compliance? Section 500.6 requires the net content statement within the bottom 30 per cent of the principal display panel, excepting those panels of 5 square inches or less. The Act requires the statement "in a uniform location on the principal display panel of that label." Many who had used the upper 30 per cent were unhappy. If the Commission had selected the upper 30 per cent, what would be the state of happiness of those who customarily had used the bottom 30 per cent? The Commission had to strive for uniformity and thus arrived at it.

Another new concept is that of dual declaration of net quantities. This should materially assist consumers to make value comparisons.

The regulations recognize a necessity to specify the actual corporate name, or partnership name in order to comply with the "name" requirement. They also require city, State, and Zip Code (street address, too, if it is not to be found in local city or telephone directory). These requirements are new only to the extent that the actual corporate or partnership name must be specified, and the Zip Code be included. The Commission has had several comments on these matters. Why is it necessary to qualify New York City by the State

name? Doesn't everyone know where New York City is located? It can be agreed that New York City is a well known location. Is Kansas City an adequate location, and if so, which one? Should the regulations not then require the State, without exceptions. The regulations permit standard abbreviations. Is it unreasonable to require "N. Y." to follow "New York." In a similar manner, if your firm name is "John Doe, Incorporated," why not say so? Does "John Doe" the individual mean the same to a consumer as "John Doe, Inc."? Likewise, if a firm merely distributes under private label, isn't it informative to the consumer to know that the firm did not manufacture that which it is distributing?

The regulations also relate to the placing of certain information on the "principal display panel." I would suggest you carefully distinguish between "principal display panel" as a part of a label, and the "area of the principal display panel." Thus a principal display panel may occupy only a portion of the side or surface of a package, and yet it is the area of this side or surface which determines the type size to be used on the net quantity statement appearing on the principal display panel.

Another question which we have been asked many times involves "in lines generally parallel to the base." This applies to statements of identity and net quantity. The word "generally" permits deviations from an exact parallel, and now we are being asked the degree of deviation. Surely the Commission is going to apply common sense to opinion-making, but anticipating that it might be asked to stretch the concept of "generally parallel," the Commission will refrain from decisions in the absence of the label itself. Here the so-called grey areas are the difficult ones. At some angle from the base line the Commission may disagree with your opinion.

Another point of possible interest is the necessity to use the term "net weight" in stating the net quantity of contents in terms of weight. However, when expressing units of fluid measure, the use of the terms "net" or "net contents" is optional, that is to say, neither term is mandatory. Here we recognize a potential confusion involving net and gross weight, which potential is lacking in the case of fluid measure.

At this time, it is well to recognize that the existing regulations are directed only to Section 4 of the Act. Perhaps even more significant effects of FPLA will be evidenced when Section 5 regulations are issued.

The authority to issue Section 5 "additional regulations" is limited to four areas:

(1) Standards for characterization of the size of a package.
(2) Label statements regarding lower than usual retail price.
(3) Component identification.
(4) Non-functional slack-fill.

When specifying these four areas, we are referring to additional regulations, rather than exempting regulations. The latter are also issued under the Section 5 authority.

Questions which anticipate Section 5 regulations are being directed to us at an ever-increasing rate. Obviously, it is most difficult to allay the expressed fears of many, and likewise difficult to clarify grey areas when the Section 5 regulations are still in the minds of the regulation writers. I would ask therefore that you anticipate only that such regulations will be written but please do not anticipate the contents and raise theoretical objections to these regulations. If you have basic data which you think we could use in order to formulate the best possible additional regulations, we solicit this data, but only in the form of a letter making the data available. Certainly it should not be an expression of fear of things to come, or a criticism of what may be.

To the degree that FPLA anticipated the need for certain practices to be prohibited or at least regulated, I suppose that there are some who will object to whatever form and content these Section 5 regulations will take. We can assure you that we intend that they will reflect the purpose of FPLA.

Conclusion

When the Commission's public announcement in the Federal Register has clarified its views on product coverage as it applies to the items enumerated in the Federal Register of March 19, 1968, this will not, of course, close out your option to request opinions on still other items, and it will not signal the end to exemption requests. In this regard I would call your attention to Section 6 of FPLA, which states that regulations promulgated by the Commission under Sections 4 and 5 of FPLA shall be in conformity with Section 701(e),(f) and (g) of the Food, Drug, and Cosmetic Act. Since the possibility exists that many firms now subject to FPLA because of items "not foods, drugs, or cosmetics" are not too well acquainted with the Food, Drug, and Cosmetic Act, a study of Section 701 is recommended.

[The End]

Where Is Industry's Voice in Food Regulations?

By BERNARD L. OSER

The Following Article Was Presented at the Food Technology Conference Held at the University Of Missouri on March 8, 1968. Dr. Oser, Who Is the Scientific Editor of This Magazine and President of Food Drug Research Laboratories, Inc., Maspeth, New York, Has Recently Taken Office as President of the Institute of Food Technologists.

THE LAWS AND REGULATIONS which confront the food industry reflect the advances in agricultural production, food distribution, processing, packaging, and marketing. The emphasis with respect to the amendments that have been enacted during the past fifteen years or so is on safety; the need to protect the interests of the consumer, particularly from the health standpoint. Their implication, however, is that the consuming public has not been adequately protected by the manufacturer or the distributor of foods, and that it is necessary for the government to instigate new protective measures. This creates, of course, a somewhat less than complimentary image for the food industry, and the scientists and food technologists that are a major part of it.

The achievements in agriculture, food processing, and the related skills, which have increased our total food supply from the available acreage while reducing the total number employed in achieving this gain, is partly offset by the claims that foods are more expensive and that many foods have lost their natural taste and flavor which characterized grandma's cooking. Food additives are used which jeopardize the safety of foods, and conditions in food plants are such that—well, they just aren't what they ought to be. And so we come to find that consumers demand more protection from unknown hazards and the suspected inferiority which surrounds manufactured foods, and Congress has been giving this kind of protection. The Hon.

John W. Gardner, who recently resigned (regrettably) as Secretary of Health, Education and Welfare, said that the greatest efforts for the protection of the consumer are the efforts of businessmen (and here I would like to add, food technologists) to turn out reliable products.

Regulatory Measures Increased

By and large, the food industry of our country has borne this responsibility well. Nevertheless, it is the ignorance, carelessness, or the misfeasance of a few in a free society that give rise to regulatory control and strict enforcement in the public interest such as we have today. The iron hand of authority of the enforcement agency, the Food and Drug Administration (FDA) however, can be used to lead into righteous paths those whom it governs rather than to wield the policeman's club. The punitive powers of the FDA are like the sword of Damocles of which every food technologist or food manufacturer should be keenly aware. In administering its new responsibilities under the Food, Drug and Cosmetic Act, and the amendments controlling the safe use of pesticides, additives, and drugs, the FDA has not been infallible. Quite the contrary, it has experienced the difficulties and frailties of any organization of men. During the period from 1948 to 1958, the size of the FDA and its budget was relatively constant, the budget being somewhere in the neighborhood of 6 or 7 million dollars per year, and the total personnel being in the order of 1000. During the period from 1956 to about 1966, after the various amendments to the act covering pesticides, additives, colors, and hazardous substances labeling, the size and budget of the Agency has increased. FDA's budget has increased about tenfold, and its size has increased about fivefold, and the curve is still going up, almost perpendicularly.

Priorities of FDA Policing Functions

It is important for food technologists to be aware of the major areas of interest to the FDA during recent performance of its policing functions. A summary of the judgment actions of the FDA for the year 1967 shows 355 such notices. Of this total, 25 are related to the presence of poisonous or deleterious substances; 34 to economic violations, generally misbranding; 5 to vitamin or other dietary foods, that is, vitamin-containing foods which were below potency; 15 to animal feeds; and 245 to contamination or spoilage from insanitary handling.

This illustrates the FDA's principal targets from the standpoint of inspection and control. According to recent information from Washington the FDA has issued an advisory to district directors on a recommended order of priorities for enforcement purposes. At the top of the list is microbial contamination. The chief emphasis here is being placed on *Salmonella.* Now *Salmonellae* are not the easiest type of microorganism to detect and identify, and the conclusive demonstration of its presence involves adequate sampling, enrichment of the innoculum, plating, biochemical identification, and even serotyping in cases where the source of the infestation has to be established.

Next in importance in the FDA list of priorities is non-permitted residues resulting from the excessive or improper use of pesticides on agricultural crops, or the presence of unauthorized pesticides, that is, those not permitted in foods. Here, violations have occurred by reason of barely detectable traces of residues where regulations specify "no residue," or "zero" tolerance. This has created a difficult situation for growers, processors and even for the regulatory agency itself.

Next in order of priority FDA inspectors are advised to consider mycotoxins and other naturally occurring toxic agents in foods. Particular attention is being directed to the aflatoxins derived principally from the ubiquitous fungus, *Aspergillus flavus.* The chemical and biological methods for detecting aflatoxin contamination are characterized by extremely high sensitivity, so much so that, notwithstanding its potent carcinogenicity for most farm and laboratory animals, "unofficial" tolerances have been recognized by control officials here and abroad, of the order of 5 to 30 parts per billion depending upon the country and the particular crop. Frequently impugned as the source of aflatoxin are peanuts and peanut meal, the latter being the poultry feed ingredient that caused thousands of deaths in turkey poults, and in which aflatoxin was first discovered. Whereas it was originally thought that this mycotic infection was found only in African or South American peanuts, harvested or stored under conditions conducive to mold growth, it is now possible, thanks to the ultrasensitive gas chromatographic techniques, to find detectable levels of aflatoxin in an uncomfortably high proportion of the domestic crop of peanuts. Unfortunately, there is no feasible way of removing it, and only improved harvesting, storage and quality control can be relied upon to reduce or eliminate this source of contamination.

It should be noted that not only aflatoxin, but other toxic metabolites of molds are being found in increasing number in corn and

various grains and seed meals which are fed to poultry, swine, and cattle. The effect of these toxins on animals, and on products derived from animals as food for man, are receiving much attention from investigators throughout the world.

Adulteration due to chemical substances used either as direct food additives, or arising indirectly in the course of manufacturing, packaging, or similar steps are currently of lesser significance as public health problems. This may be in part due to the effect of the 1958 Food Additives Law and the plethora of regulations and amendments which have followed its enactment. It may also be due to the probability that the use of food chemicals has not posed such a public health problem as the proponents of highly restrictive legislation believe. Despite the complexity, and the cost of complying with food additive regulations, this aspect of law enforcement seems to be operating satisfactorily.

But problems still remain. One might wonder whether the advantage to be gained from the application of this law to the various classes of indirect additives is real and great enough to justify the effort and cost to both industry and to government. The recent two-day conference in Washington on the subject of indirect food additives was prompted largely by the proposal that the law regulating indirect additives be amended to exclude certain migrants from packaging materials. These are present at very low concentrations in the plastic films, or the lacquered cans, or whatever the food container may be, and which migrate to a very slight extent, if at all, into foods. This proposal is now under consideration by the FDA. It has led to reconsideration of what constitutes a toxicologically insignificant level of a substance in food. This topic has come up several times during the past ten or fifteen years, and is now being reviewed by a National Research Council Committee.

FDA has proposed definitions and requirements for "good manufacturing practice" (sanitation) in the manufacture, processing, packing, or holding of human foods. The proposal goes into considerable detail with respect to the food plant and the grounds on which it is built; construction and design of buildings; equipment, utensils, sanitary equipment and controls; sewage disposal; plumbing; storage facilities; waste disposal; plant maintenance; pesticides; details of the processes; quality control measures; and even into the qualifications of personnel. The proposed regulation applies to personnel cleanliness as well as to their education and training.

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Nevertheless objections have been raised in the food industry to the vague and ill-defined aspects of this proposal, such as those requiring facilities to be "adequate", "suitable", or "appropriate". While they may be "traps for the innocent" it would seem virtually impossible to spell out such requirements in explicit terms.

Self-Certification as Positive Goal

FDA's efforts to promote voluntary compliance on the part of industry has been aided by its sponsorship of workshops and seminars, by the publication of guidelines, and by the encouragement of programs of self-certification. Food technologists have an important stake in these activities and should share their first-hand knowledge and experience in developing such programs rather than leaving the initiative entirely in FDA's hand. **[The End]**

FDA PROPOSES REGULATIONS ON PRE-1962 DRUGS

New regulations reclassifying pre-1962 drugs as effective as well as safe have been proposed by the Food and Drug Administration. All drugs cleared for marketing through the new drug procedures between 1938 and 1962 have been under review by the National Academy of Sciences—National Research Council. The drugs under review had been approved as new drugs on the basis of safety alone. New drugs marketed after 1962 are required, under the Kefauver-Harris Drug Amendments of 1962, to be effective as well as safe for their intended uses.

The proposed regulations would set up a system for carrying out the recommendations of the NAS-NRC with regard to the efficacy of the pre-1962 drugs under review. Drugs reviewed by the Academy and determined by the FDA to be both safe and effective would be classified under the proposed regulations as "not new" or "no longer new." The holder of an approved new-drug application would no longer have to submit routine periodic reports on his product. Each drug listed as not now requiring an approved new-drug application would be covered in the regulation by separate composition and labeling requirements. Any manufacturer could market the listed drug provided he complied with the requirements set forth in the regulations. The FDA said that drugs not involved in the efficacy review could also be listed as "not new drugs" and marketed without submitting new-drug applications and awaiting approval if they meet stated conditions.

The FDA also revoked all its previous opinions that certain drugs were either "not new" or no "longer new." Drugs covered by such opinions will be processed under the new proposed regulations. CCH FOOD DRUG COSMETIC LAW REPORTS ¶ 80-198.

International Drug Pharmacopeia

By DANIEL BANES

The Following Article Is Reprinted from the FDA Papers (April 1968, p. 11). Dr. Banes, Who Joined FDA in 1939 as a Chemist, Was Recently Appointed Acting Associate Commissioner for Science.

EVERY NATION, TO SAFEGUARD PUBLIC HEALTH and refine medical practice within its borders, needs assurance of the identity and purity of its commercial drug products, whether these are made domestically or abroad. It was toward this end that an International Drug Symposium on Pharmacopeias and International Cooperation on Drug Standardization, in which officials of FDA participated, was held recently in Washington during the 81st annual meeting of the Association of Official Analytical Chemists. The symposium* looked at the situation emerging in Western Europe, Japan, the United States and the World Health Organization concerning multi-nation pharmacopeias.

Pharmacopeias—sets of monographs which name the essential physicochemical characteristics of drugs and the means of verifying identity and purity—have been compiled nation by nation as a guide to medical practice and drug control.

At the beginning of the 19th century, Europe had around a hundred "official" pharmacopeias. Upon the unification of various smaller states into larger nations, the number dropped. Nonetheless, the two dozen or so that remained often presented conflicting or incomplete profiles of important drugs.

Only recently have nations collaborated on pharmacopeias. The logic favoring this collaboration is not hard to see. Nations make common use of many drug preparations. The effort required to compile pharmacopeias on a periodic basis in an age of rapid introduction and distribution of drugs consumes a significant part of any nation's scientific energies, often in unfruitful duplication of efforts made elsewhere.

* The papers comprising this symposium have been published in the *Journal of the Association of Official Analytical Chemists*, Vol. 51, pp. 81-113, January 1968.

The growing "internationalization" of the pharmacopeia cannot be ignored by the United States. Because of its own status as importer and exporter of drugs, because it is a center of the development, testing, and manufacture of drugs, and because it is the possessor of a fund of governmental experience in drug regulations, the United States affects and is affected by international pharmacopeial efforts.

The Nordic Pharmacopeia

The experience of four North European nations may serve as an introduction to the legal, administrative, cultural, and policy-making aspects of pharmacopeial collaboration. Sweden, Denmark, Norway, and Finland subscribe to a Nordic Pharmacopeia in lieu of separate national compendiums.

Dr. Hans Hellberg of the National Pharmaceutical Laboratory, Stockholm, described the successes of the venture, the similarities and differences among these countries in control processes, their current problems and their hopes for further "internationalization." These countries are similar in many ways, unalike in others. The languages of Denmark, Norway, and Sweden are mutually understandable, with some attentive effort; and although Finnish is entirely different from the other languages, Swedish is spoken to some extent in Finland. The Nordic countries have abolished passport checks among themselves, have established a common labor market for certain workers in the medical field, have almost eliminated customs duties among themselves, and are on the way to adopting common patent legislation.

The Nordic Pharmacopeia Commission was formed in 1948, and the first edition of its work appeared in 1963 in all four languages. It has been official for all four countries since 1964. Annual loose-leaf supplements are published. A wholly new edition, to be forthcoming, will remedy a number of shortcomings, as the supplements have already begun to do. The makers of the Nordic Pharmacopeia, although they plan the new edition, are watching with some interest the activities of the European Pharmacopeia Commission, a subject to which I shall return.

Although each of the countries concerned has its own legislation regarding drugs and its own control organization, they do cooperate in several ways, for instance, in active control of manufactured drugs. There are limitations in this field. For example, although information is exchanged about deficiencies that may be found through random tests of specialties held in stock, such evidence from one

country cannot be used as a reason for administrative action by another. The information is used by the country receiving it to carry out an investigation of its own.

There are some, Dr. Hellberg said, who believe this cooperation could be extended even further, for example, to a common Nordic registration system. But there are difficulties. Each country has its own traditions in drug legislation and such a registration system would get into legal problems. Moreover, "in some countries there are regulations of a more politico-economic nature which are rather difficult to change."

The Swedish official, after considering future lines of possible international cooperation, including compendiums of prescribing information and data on the safety and efficacy of drugs as well as their identity and purity, summed up his views this way:

> Finally, it is highly desirable that the number of bodies publishing pharmacopeias and pharmacopeia-like monographs should be reduced. Few countries have such resources of their own that they can ignore the pharmacopeias of other countries. In a country like mine where we import almost half of our drugs and, in addition, a lot of substances from which home-produced drugs are prepared, we need to use the pharmacopeias of other countries. This means that we—like industry—have to check the same goods according to several different monographs.
>
> It is therefore highly desirable from the point of view of both the controlling bodies and the industry, in small countries, that the number of pharmacopeias diminishes. The contribution to this reduction which the Nordic countries rendered by combining their four pharmacopeias now appears to be insufficient. The present hopes are directed toward what the coming so-called European Pharmacopeia will achieve.

The history and current status of that pharmacopeia were outlined by G. B. Marini-Bettòlo, Director of the Instituto Superiore di Sanita, Rome. The work is being carried out under the auspices of the Council of Europe. Although the six countries of the Common Market, or European Economic Community (EEC), are members of the Council, it includes other nations. The Common Market countries are France, Italy, West Germany, Belgium, the Netherlands, and Luxembourg. Two non-EEC countries participating in the European Pharmacopeia are Great Britain and Switzerland. Great Britain also is a member of the European Free Trade Area (EFTA) bloc, to which the four Nordic countries belong. Hence, references by European speakers at the symposium to "bridge building" in the pharmacopeia and drug standardization area were hardly exercises in rhetoric.

Although the Common Market countries had expected to embark on their own pharmacopeia, they decided to work through the geo-

graphically broader Council of Europe. In fact, Prof. Marini-Bettòlo noted, the six have agreed to move to ensure that the standards, methods, and monographs of the European Pharmacopeia shall become the official standards applicable in their respective countries. This is the most striking aspect of the European Pharmacopeia effort; it will create common standards binding on participating nations. Other published international pharmacopeias have not been obligatory.

Because the pharmacopeia will affect the legislation of eight countries, decisions on the choice of its monographs must be unanimous, Prof. Marini-Bettòlo noted.

Criteria for Drafting the Text of the European Pharmacopeia

In 3 years, the Commission charged with preparing the European Pharmacopeia has covered considerable ground. It agreed on the general criteria for drafting the text as well as on the general notices concerning nomenclature, atomic weights, percentages of an element in a molecule, solubility, concentration of solutions, methods of assay and tests, storage, units of measurement, and so on. It has agreed on the lists of general methods, both chemical and biological, to be adopted in the pharmacopeia; on the first list of monographs to be prepared; and on a system of following the work itself and of final approval of the texts. Over 700 draft documents have been produced —some representing original work. The general methods of analysis and about 50 monographs have been approved and will form the first volume of the European Pharmacopeia. Work on the second volume is "already well advanced." The Commission has collaborated with the Nordic Pharmacopeia and has corresponded with the U. S. Pharmacopeia.

The European Pharmacopeia, the Italian official said, "will not only be the fulfillment of the obligation undertaken by the Council of Europe with the European Economic Community, but we hope, the beginning of the use of common standards for drugs for the whole of Europe." After ratification of the Pharmacopeia Commission's work by all the signatory countries, participation will be open to all the countries of the Council of Europe. Since there is widespread use in other parts of the world of the standards of the European countries, the European Pharmacopeia "is bound to have worldwide significance," as Prof. Marini-Bettòlo put it. What kind of common drug regulation if any might result from adoption of common pharmacopeial standards? Dr. P. Siderius of the Netherlands noted that all the Common Market countries but West Germany

have premarketing clearance systems for efficacy, safety, and conformity with labeling. But there are considerable differences among them in ways of enforcing legislative prerequisites for marketing of drugs. The goal for coordinating Common Market legislation aims at allowing a drug which receives premarketing clearance in one country to qualify automatically for marketing in the others.

Dr. Siderius had some doubt that this goal could be achieved "because it has become apparent . . . that criteria used in member-states of the EEC for admission to the market of new drugs were and are extremely divergent. . . ." His recommendation: establishment of "a joint competent agency in which all six members of the EEC are represented. Manufacturers should be allowed to submit drug applications directly to this agency, which should be equipped and staffed adequately to fully examine the applications and be given responsibility to deliver or refuse permits for putting the drug concerned on the Common Market.

"On the national level, existing official organizations and facilities for drug control should be kept intact in order to evaluate the safety and efficacy of drugs that are of national significance. This will permit member-states to continue their own policy of screening the drugs on their national market."

World Health Organization Backs International Pharmacopeia

A report on the International Pharmacopeia, which contains "recommended" rather than mandatory standards, was given to the Symposium by Teodor Canbäck, of the World Health Organization. The first edition of the International Pharmacopeia, consisting of two volumes and an addendum, was completed in 1959. Some newer nations preferred it to adopting the standards of any single country, and many have recognized it in their legislation.

Although Dr. Canbäck described the second edition, soon to be published, as still a "traditional book," he felt the need for upgrading information contained in official compendiums. The four problems, more or less interconnected, are (1) to raise the technical standard of the tests chosen; (2) to select parameters of real importance in describing the drug and its purity and efficacy; (3) to include evaluated data on blood levels, etc., required to get a desired clinical response with the drug; and (4) to speed up the publication of the data.

The trend of the work within WHO is developing along three lines: (1) producing a recommendation for an inspection system

similar to that used in the United States ("good manufacturing practices"); (2) establishing reference chemicals to be used in pharmacopeial tests; and (3) issuing data sheets on old and new drugs.

British and Japanese speakers also urged greater international cooperation.

Dr. H. Davis, pharmaceutical consultant in the United Kingdom, listed among several recommendations the establishment of coordinated standards and methods for pharmacopeial drugs. He advocated cooperation between expert committees of national or regional pharmacopeial authorities of the major drug-producing countries at the draft stages of monograph production. "For pharmaceutical specialities which now constitute a high proportion of dispensed medicines, international data sheets are suggested. The setting up of an international clearinghouse under the auspices of WHO or another appropriate international body is recommended," he said.

Kakuma Nagasawa of the National Institute of Hygienic Sciences, Tokyo, asked for international cooperation in adopting reference standards for drug assay. He said in Japan 72 reference standards have been prepared and distributed by his Institute. Many reference standards or working standards for antibiotics and biological products also are distributed by Japan's National Institute of Health.

"It is not easy to establish these standard preparations," he said, and in an era of increasing international interchange of drugs, "it is very inconvenient for clinical purposes if standards with the same name but different natures are established in different countries.

"I hope common reference standards will be used by many countries in the near future. The matter might be settled by relying chiefly on the work of the Committee on Authentic Chemical Substances of the International Pharmacopeia. However, it is an urgent problem to establish such standards promptly on an international basis. I think that sooner or later the international exchange of information relative to specifications and test methods of the reference standard preparations will be essential."

Except in the United States and Great Britain, all major national pharmacopeias have been produced by Government-supported groups. The advantages of those written by non-Government bodies were enumerated by the respective representatives of the U. S. Pharmacopeia and the National Formulary, Drs. Lloyd C. Miller and Edward G. Feldmann. Despite their independent origins, both U. S. P. and N. F. are official Federal compendiums.

From the National Experience to the International Level

U. S. P. has had the "official" designation since 1906 and has worked, in Dr. Miller's words, "with an awareness that, for all practical purposes, the Federal Government has been watching over its shoulder." Yet U. S. P. and N. F. are not solely responsible for setting U. S. drug standards. In 1940, Federal law was passed requiring FDA to set standards of purity and potency for insulin if U. S. P. or N. F. did not. A further step in Federal sharing in standards setting came in 1946 when Congress designated FDA to establish antibiotics standards. Whether there will be a further trend in this direction—and, indeed, whether "internationalization" of pharmacopeias may encourage or impede such a trend—remains to be seen. Dr. Miller, discussing what may be transferred from the national experience to the international level, stressed the value of continuity of effort, a quality he thought likely to be greater in an independent organization. Such independence, however, rests on the organization's ability to gain and retain volunteers for editorial work and on its ability to meet financing problems. Smallness may be another advantage, along with the ability to maintain direct lines of communication with experts, Dr. Miller said.

Dr. Feldmann also spoke for advantages of independence and close cooperation of individuals in Government agencies, the pharmaceutical industry, and academic institutions.

> The compendia have maintained a unique independence of viewpoint and freedom of movement which by nature cannot be duplicated either in Government agencies or in private industry. While the N.F. and U.S.P. are recognized by law as "official" compendia, the completely independent and unfettered position which they enjoy has permitted an unusual degree of voluntary cooperation in working toward the common goals.

As Dr. Miller noted, "It has been said that drafting drug standards is often an exercise in the fine art of plagiary." In this light, perhaps I will be forgiven for borrowing some remarks from Dr. Canbäck for a closing paragraph. In his talk, the WHO representative said:

> In all these fields we need close international cooperation. It is necessary to convince people that the time is gone when it was possible for a group of pharmacists to sit down and produce a handbook of drug standards. Too much copying from sources lacking in basic materials has gone on for too long. Many of the criteria which we are asking for today can only be collected by people specializing in narrow fields. We have to find them, get their cooperation, and start working. It is a big task, but as practically every country is interested, it would be rational to do this on an international level.

[The End]

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