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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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Jan Edward Williams analyzes Section 201(n) of the Federal Food, Drug and Cosmetic Act and the Food and Drug Administration's interpretation of it in its proposed regulations concerning misbranded foods and drugs. Mr. Williams, a member of the law firm of Harter, Calhoun & Williams, traces the actions of both the Food and Drug Administration and the Federal Trade Commission in this area. The article, titled "Failure to Disclose Material Facts," begins on page 256.

"Product Liability—1974" contains a discussion of recent court decisions concerning manufacturers' legal responsibility for the products they produce. Written by *William J. Condon*, the article begins on page 267. Mr. Condon, an attorney-at-law, teaches at New York University Law School.

E. Carrington Boggan is the author of "The FDA's Combination Drug Policy." Beginning on page 276, the paper is an examination of the Food and Drug Administration's treatment of combination drugs in both regulation and reaction to case history. Mr. Boggan is Division Counsel of Ayerst Laboratories and Ives Laboratories, Inc., divisions of American Home Products Corporation.

In his article "Food Safety Review —New Concepts for GRAS," *Roger D. Middlekauff* discusses the confusion over the determination of generally recognized as safe substances. Going back to the legislative hearings on the 1958 Food Additives Amendment, he shows the beginnings of the ambiguity of the language in this amendment and also details industry's efforts to deal with the issued regulations. Mr. Middlekauff, whose article begins on page 288, is a member of the law firm of Carr, Bonner, O'Connell, Kaplan & Thompson.

Eighteenth Annual Educational Conference of the FDLI and the FDA. The following paper was presented at the 18th Annual Conference of the Food and Drug Law Institute and the Food and Drug Administration, which was held in Washington, D. C. on December 3rd and 4th, 1974.

David E. Collins, Secretary and Associate General Counsel for Johnson & Johnson, discusses regulatory and scientific matters facing the medical device and diagnostic products industry. Mr. Collins emphasizes the commitment of the Food and Drug Administration to regulation of this industry and urges better methods of communication to and from the Agency. Beginning on page 299 the article is titled "Recognition and Response Critical Industry Needs."

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Failure to Disclose Material Facts

By JAN EDWARD WILLIAMS

Mr. Williams Is a Member of the Law Firm of Harter, Calhoun & Williams.

THE TITLE OF THIS PRESENTATION is "Failure to Disclose Material Facts." This declaration could itself, I suppose, be attacked on the ground of a failure to disclose such facts. I will, therefore, give you an affirmative disclosure of the parameters of this speech. I will discuss primarily Section 201(n) of the Federal Food, Drug and Cosmetic Act (21 U. S. C. A. 301 *et seq.*) and its interpretation by the Food and Drug Administration (FDA) in recent months. Included will be discussion of the Agency's recent regulation setting forth its proposed interpretation of Section 201(n) as applied to foods, drugs, devices and cosmetics, published in the *Federal Register* of September 16, 1974 (39 *F. R.* 33229). I will also touch lightly on the corresponding provision of the Federal Trade Commission (FTC) Act (Section 15(a)(1), 18 U. S. C. A. Section 55(a)(1)).

Section 201(n) (21 U. S. C. A. 321(n)) provides that, in determining whether the labeling of an article such as a food or a drug is misleading, "there shall be taken into account . . . not only representations made or suggested . . . but also the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the article. . ."[1]

Until relatively recently, everyone, including both the FDA and industry, thought that Section 201(n) could be utilized only as an

[1] Section 15(a)(1) of the FTC Act (15 U. S. C. A. Sec. 55(a)(1)), contains almost identical language in connection with the definition of false advertisements of foods, drugs, devices and cosmetics.

aid in determining, administratively or in enforcement action, in particular cases, whether the labeling was false and misleading in any particular under Section 403(a) (21 U. S. C. A. Section 343(a)).

Treatment of Enuresis

For example, a drug whose label bears a flat indication that the medication is for use in the treatment of enuresis or bed-wetting could reasonably be found to be misbranded under Sections 403(a) and 201(n), because of a failure to disclose that the drug is not effective in the treatment of this condition when caused by organic disease.

The FDA, however, has working for it a very imaginative group and has recently issued a slew of labeling regulations based, at least in part, upon Section 201(n). These regulations purport to impose mandatory labeling requirements on certain classes of foods, without regard to whether, in fact, the labeling of a particular food product marketed by a particular company is misbranded under Sections 201 (n) and 403(a). The regulations I am referring to include the following: establishment of common or usual names for seafood cocktails (38 *F. R.* 6964); common or usual names for diluted orange juice beverages (38 *F. R.* 6968); common or usual names for frozen heat-and-serve dinners (38 *F. R.* 20742); common or usual names for plant protein products (39 *F. R.* 20892); common or usual names for formulated meal replacements (39 *F. R.* 20905) and common or usual names for main dish products (39 *F. R.* 20906). In addition, as I mentioned, the FDA has issued a proposed regulation setting forth its interpretation of the principles contained in Section 201(n).

I will now discuss some basic legal aspects common to these various regulations.

Common-or-Usual-Name Regulations

As some of you may know, the regulations of the FDA establishing common or usual names for frozen heat-and-serve dinners and seafood cocktails are currently under challenge in the United States District Court for the District of Columbia.[2] The regulations involved require a declaration of the percentage of characterizing ingredients on seafood cocktail labels and, in the case of frozen dinners, specify that such dinners must contain three basic ingredients. They also provide that the common name of the dinner must include a description

[2] *American Frozen Food Institute v. Weinberger,* Civil Action No. 74-354, filed February 27, 1974.

of each of the three or more prescribed basic components as well as any of the optional ingredients used. The Complaint in this matter alleged, among other things, that the regulations are invalid on the following grounds:

(1) The regulations establishing the composition and common or usual name for frozen heat-and-serve dinners are, in legal effect, standards of identity under Section 401 but were adopted without complying with the procedures prescribed by Section 701(e) of the Act which specifically require the Agency to grant an administrative hearing prior to the promulgation of a final order;

(2) The statute does not authorize mandatory percentage labeling of characterizing ingredients; and

(3) The regulations unlawfully create conclusive presumptions that labeling or composition that fails to conform to the regulations causes the food to be misbranded under the Act without regard to whether, in a particular case, the food is actually misbranded.

One interesting aspect of this case arose in the government's answer to the Complaint, wherein the government alleged that the matter is not justiciable because it was not brought as a class action on behalf of all frozen food manufacturers in the United States, or, alternatively, that it is not justiciable because it was not brought as a class action on behalf of all food manufacturers in the United States. The government followed up its Answer with a series of interrogatories, apparently designed to provide a basis for the class action concept, and when the plaintiff refused to answer the interrogatories, the government filed a motion to compel. The plaintiff opposed the motion successfully. I mention this part of the case because it is, to my knowledge, the first instance in which a defendant has attempted to compel a plaintiff to bring a class action.

Now, returning to Section 201(n), it is my opinion, for reasons I am about to state, that the use of Section 201(n) as the basis for the regulations establishing common or usual names is unauthorized by the statute and its legislative history.

Legislative History

The Commissioner of Food and Drugs has concluded in one of the now famous, some might say infamous, preambles to his orders that a requirement for percentage labeling "... is well within the

Congressional intent" (preamble to order establishing common or usual names for nonstandardized foods (38 *F. R.* 6964)). Following its usual practice, the Agency cited no references in support of this conclusion. The omission of citations is perhaps explained by the fact that there is no support in the legislative history for such a labeling requirement. Indeed, the legislative history shows that Congress chose not to include a provision in the Federal Food, Drug and Cosmetic Act of 1938 which would have permitted the Commissioner to promulgate general rules requiring label declaration of the amount of ingredients in food products. The original bill (S. 1944, 73d Congress (1933)), leading to the enactment of the 1938 law, contained the following language in the section which would later become Section 403(i) of the Act:[3] "(f) . . . The Secretary is hereby authorized to prescribe by regulations requirements for such further information on the label thereof as he may deem necessary to protect the public from deception."[4]

In hearings on S. 1944, the significance of the above provision was discussed by Walter G. Campbell, then Chief of the FDA:

". . . we have a number of exhibits here . . . these are samples of a mixture of chicken and noodles. Notice the variation in the amount of the meat, the expensive part of it. You see it ranges from 9 percent to 15⅔ percent. . . . you can see what this means to the consumer from an economic standpoint . . . Notice the continuing portion of paragraph (f) which says that the Secretary is authorized to prescribe by regulations, requirements for such further information on the label thereof, as he may deem necessary to protect the public from deception. *The Secretary would be authorized to disclose the percentage of meat or to give to the buyer that information in some other form.*" (Emphasis supplied.)[5]

This language was *not* included in the bill which was eventually passed by the Senate. Senator Copeland, one of the chief architects of the statute, and a number of consumer organizations, objected to the bill passed by the Senate (S. 5, 75th Congress (No. 361)), in part because it did not require label declaration of the amount of each ingredient in the food.[6]

Moreover, the Senate Report on S. 5 in the 74th Congress with reference to the section which would become Section 403(i) and which contained the same pertinent language as the section is currently phrased, contains the following statement: "It should be noted

[3] Section 403(i) provides in effect that a nonstandardized food shall be misbranded if it does not bear on the label its common or usual name and a list of the ingredients in the product.

[4] Dunn, Federal Food, Drug and Cosmetic Act: A Statement of Its Legislative Record, p. 40.

[5] Dunn, at 1075-1076.

[6] Dunn, at 749 and 751.

that this provision does not compel disclosure of the formulas of such foods since no information as to proportions is required. . ."[7]

There is further legislative history, not only in connection with passage of the Federal Food, Drug and Cosmetic Act in 1938 but also in connection with passage of the Wheeler-Lea Act, which negates the Commissioner's conclusion in the preamble to the common-name regulation that percentage labeling is authorized by the legislative history of the statute. (The Wheeler-Lea Act resulted in legislation incorporating a provision almost identical to the language of Section 201(n) into the FTC Act (Section 15(a)(1), 18 U. S. C. A. Section 55(a)). In the interest of brevity, I will not go into any further detail.

Authority Under the Statute

Section 201(n) reads:

"If an *article* is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account . . . not only representations made or suggested . . . [in the labeling], but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof or under such conditions of use as are customary or usual." (Emphasis supplied.)

Section 201(n) clearly deals with a particular article which is alleged to be misbranded, as does Section 403(a), the misbranding provision. Therefore, these sections of the statute do not provide support for a regulation which applies to a product (or a class of products) which is not, in fact, misbranded. Moreover, it seems to me to be basic that Section 201(n) comes into play only where there is an allegation of misbranding based upon examination of the labeling of a particular article. It cannot, I believe, be applied to a class of articles of food with diverse labeling. Thus, the fact that the food of one processor may be misbranded, when read in light of Section 201(n), in no way goes to support the determination that the food of another processor is misbranded. Each food product must necessarily be judged on a case-by-case basis in light of the facts involved with respect to each product. Obviously, if Sections 201(n) and 403(a) do not authorize the regulations, Section 701(a), which merely authorizes the promulgation of regulations to aid in the enforcement of the statute, cannot provide that authority.

[7] Dunn, at 247.

The failure to reveal material facts requirement in Section 201(n) is operable only when a representation on the label of a food includes a factual statement inducing its purchase by consumers which can be reasonably construed to require a revelation of material facts in the light of such statement. This clearly indicates the requirement in question involves examination of the representations made in the labeling of particular products, as opposed to a class of products.

Circumvent Safeguards

In my opinion, one of the strongest arguments against the legality of the regulations establishing common or usual names is that the procedures used circumvent the specific requirements and safeguards prescribed by Congress in connection with the promulgation of definitions and standards of identity under Sections 401 and 701(e); namely, a hearing and judicial review. To pick one example, the order establishing a common or usual name for frozen dinners clearly establishes a standard of identity. Thus, it is stated in the preamble to Section 102.1 that: "the name itself will accurately identify or describe the basic nature or characterizing properties of the food in a way that will distinguish it from other foods."[8] Further, the regulation for frozen dinners (Section 102.11) provides that such a dinner:

"(1) shall contain at least three components one of which shall be a significant source of protein and each of which shall consist of one or more of the following... [naming the permissible ingredients].

"(2) may also contain other servings of food (*e.g.*, soup, bread or rolls, beverage, dessert)."

Contrary to a suggestion in the preamble to the regulation, the fact that the ingredients of each component are not listed and that each component is not itself defined does not affect my conclusion that these are, legally speaking, standards of identity. There are numerous standards on the books, which were properly adopted in compliance with Section 701(e) procedures but which contain a list of undefined ingredients whose components are identified only to the extent that they are reflected in the main ingredients.[9] Consider the standards for pasteurized blended cheese with fruits and vegetables or meat, which permit the use of such foods, as is reasonable, without specification of the kind which may be used. Consider also the standard for enriched rice, which assumes a knowledge of what rice is on the part of the consumers, since the term is not defined.

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[8] 38 *F. R.* 6965.

[9] See, for example, the standard for vegetable macaroni products (21 CFR 1625), the standard for bread (21 CFR 17.1), and the standards for various cheeses in part 19 of 21 CFR.

There has been some suggestion that the FDA has not utilized the procedural safeguards of hearing and cross-examination mandated by Sections 401 and 701(e) in order to avoid delay and expense. This reasoning is entitled to no weight in light of the following statement by the Supreme Court:

"Nor can we accord any weight to the argument that to apply the Act to such hearings will cause inconvenience and added expense to the Immigration Service. Of course it will, as it will to nearly every agency to which it is applied. But the power of the purse belongs to Congress, and Congress has determined that the price for greater fairness is not too high. The agencies... have ready and persuasive access to the legislative ear and if error is made by including them, relief from Congress is a simple matter."[10]

The Case Law

Decisions interpreting both the language of Section 201(n) and the comparable language of Section 15(a)(1) (18 U. S. C. A. Section 55(a)(1)) of the FTC Act fully support the proposition that the requirements for disclosure of material facts have been considered by the FDA and the FTC to apply only to allegations that the labeling of particular foods, as opposed to broad categories or classes of foods, is false and misleading. One example, and there are others, will illustrate this point concerning the FTC requirements—the decision of the court in *J. B. Williams Co. v. FTC*, 381 F. 2d 884 (CA-6 1967). The case involved one of the many attacks by the FTC on advertising claims for the product Geritol. It reflects a clear emphasis on the necessity to examine the facts so as to permit a conclusion to be made as to whether disclosure of a "material fact" was necessary within the meaning of that term as used in 18 U. S. C. A. Section 55(a)(1).

I think it pertinent to note that in the case of the FTC, the cases are reviewed by the court upon the basis of evidence adduced at a trial-type hearing, unlike the orders of the FDA prescribing common or usual names.

Decisions of the courts interpreting Section 201(n) of the Federal Food, Drug and Cosmetic Act similarly place emphasis upon the facts involved in each case and further elaboration is not necessary.[11]

[10] *Wong Yang Sung v. McGrath*, 339 U. S. 33, 46—47 (1950).

[11] See, for example, *United States v. 62 Packages * * * Marmola Prescription Tablets*, 48 F. Supp. 878 (W. D. Wis., 1943); *Research Laboratories, Inc. v. United States*, 167 F. 2d 410 (CA-9 1948), cert. denied, 335 U. S. 843 (1948); *Pasadena Research Laboratories, Inc. v. United States*, 169 F. 2d 375 (CA-9 1948), cert. denied, 335 U. S. 853 (1948).

New Drug Provisions

The recent decisions by the Supreme Court of the United States[12] do not, in my opinion, support the FDA's allegation of authority in the matters I have been discussing. Those cases, for the most part, dealt with the new drug provisions of the statute, and involved cases, again for the most part, in which the Commissioner of Food and Drugs at least superficially followed the procedures prescribed by Congress in connection with the withdrawal of approval of the new drug applications for new drugs. It is true that the court extensively amended the new drug provisions of the statute, but the fact that the court held that the FDA had the authority to determine in the first instance its own jurisdiction (which is cited by the government as support for its action in promulgating the regulations under discussion) is not relevant to the question of whether the Agency has improperly circumvented the standard rule-making provisions of the Act.

Parenthetically, I consider it alarming under our form of government and system of jurisprudence for a governmental agency to promulgate a regulation, of the nature of those to which I have referred, which dictates to the industry a mandatory format for the labeling of products without regard to whether there may exist other labeling formats which may not only be reasonable but do not violate any provision of the statute. Such an approach, I submit, violates fundamental principles of fairness.[13]

FDA's Regulation Interpreting Section 201(n)

I would like to turn now to the last topic I intend to deal with, and that is the proposed revision of Section 1.3 of Title 21 of the Code of Federal Regulations dealing with the Agency's interpretation of the requirements of Section 201(n). Although the emphasis in the preamble to the proposal is placed primarily on the labeling of drugs, the proposal, because of its terms, is applicable to foods, drugs, devices and cosmetics.[14] I have one generic difficulty with the proposal. Section 1.3(a) is basically a recital of the language set forth in Section 201(n):

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[12] For example: *Weinberger v. Hynson, Westcott & Dunning, Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,930, 412 U. S. 609 (1973).

[13] The Agency could, of course, have enacted regulations under Sections 401 and 701(e) following the prescribed procedural safeguards and could have established common names having the effect of prohibiting truthful labeling. This is the course that should have been followed.

[14] The preamble discusses in detail, and relies on the decision in *Bradley v. Weinberger*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,978, 483 F. 2d 410 (CA-1 1973).

"(a) Labeling of a food, drug, device or cosmetic shall be deemed to be misbranded if it fails to reveal facts that are material (1) in light of other representations made or suggested by statement, word, design, device or any combination thereof or (2) with respect to consequences which may result from use of the article under (i) the conditions prescribed in such labeling or (ii) such conditions of use as are customary and usual."

Section 1.3(b) of the proposal provides that affirmative disclosure of material facts pursuant to above provision may be required either by specific regulations promulgated pursuant to Section 701(a) of the Act or by direct court enforcement action. The basic or generic difficulty involves the fact that this enforcement approach requires businessmen to guess, with risk of criminal prosecution if their guess is wrong, whether the Agency will choose to enforce the requirements under subparagraph (a) by way of specific regulation or by direct enforcement action. This approach seems to me to be not only arbitrary but constitutionally defective due to its vagueness.

In addition, the requirement in proposed Section 1.3(a) mandating that labeling of a food, drug, device or cosmetic "shall be deemed to be misbranded if it fails to reveal facts that are material" is in conflict with the language of Section 201(n) of the statute, which the proposal purports to interpret. Section 201(n) clearly contemplates that the extent to which labeling fails to reveal material facts is only one factor to be taken into account to determine whether the labeling is misleading.

Substantial Evidence

I have one last comment on this proposed regulation. The regulation would in Section 1.3(c)(2) prohibit a statement of differences of opinion with respect to the effectiveness of a drug unless each of the opinions expressed is supported by substantial evidence of effectiveness as defined in Section 505(d) of the Act. The term "substantial evidence" is, of course, a term defined by the statute and by legislative amendments by the Supreme Court of the United States. Substantial evidence is defined in pertinent part by Section 505(d) of the statute:

"...evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified . . . to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have..."

The regulations of the FDA (21 CFR 314.11 (a)(5)(ii)) define in detail the basic scientific principles which must be complied with in order to meet the statutory test of substantial evidence. The Supreme Court

of the United States, in the *Hynson, Westcott & Dunning* case, has upheld the validity of these regulations, to the extent that the language therein is not of a subjective nature.

As an aside, the Supreme Court in that case drastically amended the definition of a new drug in Section 201(p) to include the requirement that, in order for qualified experts to make a determination as to whether a drug is generally recognized as safe and effective, and therefore a new drug, there must exist substantial evidence of effectiveness for the drug, not merely a consensus of expert opinion. This amounts to a judicial grafting of the substantial evidence test in Section 505(d) onto the definition of new drugs, which, of course, sets forth the conditions for applying the new drug provisions of the statute in Section 505 to a drug in the first place.

Clinical Experience

Naturally, the government, in the preamble to the regulation under discussion, relies on this decision by the court. I do not think this approach is reasonable. It is reasonable to interpret the intention of Section 201(n) to require accurate, informative and nonmisleading labeling information with respect to the effectiveness of drug products. However, the term "substantial evidence" was included by Congress in the 1962 drug amendments and appears only in Sections 505(d) and (e) and 507(h) of the statute. The term does not even appear in Section 201(n). Certainly if Congress had intended to extend the substantial evidence standard to Sections 201(n) and 403(a), it would have specifically done so at the time of enactment of the 1962 amendments. Clinical experience of a "substantial" nature, if you will pardon the expression, concerning differences of medical opinion are, I submit, material facts which should be permitted in drug labeling under appropriate situations.

Moreover, the legislative history of the Federal Food, Drug and Cosmetic Act of 1938 is replete with assurances that Congress did not intend to interfere with the physician's right to practice medicine. Particularly in the case of drugs promoted to physicians, the physician should be permitted the value of clinically substantiated differences of medical opinion so as to permit him to make valid, considered decisions.

It should also be noted that (as indicated in *Bradley v. Weinberger,* 483 F. 2d 410 (CA-1 1973), a case cited favorably in the preamble to the proposal), the physicians who sued the FDA were, as stated

by the court, "eminent" doctors in the field involved. These physicians sued to require a statement of a difference of medical opinion contrary to an Agency-required warning, which was proposed by the Agency with respect to reported incidences of cardiovascular mortality in patients treated with a particular drug. Since the FDA has relied heavily upon physicians selected by the National Academy of Sciences and the National Research Council in implementing its Drug Efficacy Study Implementation (DESI) review, and requires "black boxes" or declarations in labeling of drugs that such drugs have been found to be other than effective by such experts, I can see no basis for the FDA's dismissal of the medical opinions of comparably qualified experts as a basis for a statement that there exists a difference of medical opinion concerning the effectiveness of a drug.

Conclusion

I have touched upon a number of areas and I hope that my discussion has been both informative, and of a sufficiently provocative nature as to give pause to some of you who may be inclined to acquiesce in what can only be termed, at least by me, extra-legal actions in the form of regulations by the FDA. **[The End]**

NATIONAL NUTRITIONAL FOODS ASSOCIATION AND SOLGAR CO., INC. APPEAL TO HIGH COURT

The Supreme Court of the United States has been petitioned to review the decision of the U. S. Court of Appeals for the Second Circuit in *National Nutritional Foods Association and Solgar Co., Inc. v. Weinberger et al.* (509 F. 2d 1236), which upheld Food and Drug Administration authority to promulgate binding regulations on the status of food products by use of the informal rule-making procedures of section 701(a) of the Federal Food, Drug and Cosmetic (FDC) Act. The petitioners claim that such authority, unbounded by requirements for hearings, judicial evidentiary inquiries, or showings of "substantial evidence" to support the agency determination, deprives litigants of statutory rights to either an administrative or judicial factual hearing on the merits with respect to criminal and civil enforcement sanctions under the FDC Act. The petitioners also question whether the FDC Act prescription drug requirements can be applied to otherwise safe products merely because such products can be deliberately and irrationally misused even in the face of cautionary labeling. (*National Nutritional Foods Association and Solgar Co., Inc. v. Weinberger et al.*, U. S. Supreme Court, Docket No. 74-1383.)

Product Liability—1974

By WILLIAM J. CONDON

Mr. Condon, an Attorney-at-Law, Teaches at New York University Law School.

THE PROLIFERATION of product liability cases continues to indicate that this is a fruitful area for trial lawyers. However, the number of cases appended to this report[1] is surprisingly small in light of the overall statistics. This is not to say that the cases concerned with our limited area of interest are not important. They are.

For example, it is certainly important to know that the presence of a banana spider, six inches in diameter, does not render the bananas defective or unfit for their intended purpose (*Anderson v. Associated Grocers, Inc.*). It is likewise important to know that opening a ketchup bottle by thumping on the bottom of it is not such an unintended misuse as to insulate the ketchup manufacturer from liability. Thus, the plaintiff was allowed recovery in such a case for several lacerations to his hand when the bottle broke under these circumstances (*Early-Gary, Inc. and H. J. Heinz Company v. Walters*).

On the other hand, plaintiff, a teen-aged girl, was not allowed to recover against the manufacturer of cologne for severe burns which she received when she poured the cologne on a burning candle. Her theory was that a manufacturer had a duty to warn her of the untoward consequences of such an act. The Court held that there was no evidence that the manufacturer foresaw or should have foreseen such a misuse of its product. Therefore, it had no duty to warn (*Moran v. Williams*).

Section 402A of Restatement of Torts, Second, has been the subject of unending comment by courts and commentators over a period of a decade or so. This, of course, is the basic statement of

[1] See page 274.

the concept of strict tort liability in connection with products. Little, if any, attention has been paid to its companion section, 402B, promulgated and adopted at the same time. This is another and more specific strict liability section. It provides that:

"One engaged in the business of selling chattels who, by advertising, labels, or otherwise, makes to the public a misrepresentation of a material fact concerning the character or quality of a chattel sold by him is subject to a liability for physical harm to a consumer of the chattel caused by justifiable reliance upon the misrepresentation, even though

(a) it is not made fraudulently or negligently, and

(b) the consumer has not bought the chattel from or entered into any contractual relation with the seller."

The application of this language was severely limited by the Texas Court of Civil Appeals in the case of *Winthrop Laboratories v. Crocker*. Plaintiff's intestate had suffered an industrial accident which resulted in long-term treatment and numerous hospitalizations. During the course of his treatment he became addicted to a pain killing drug sold by defendant which, as the jury found, ultimately caused his death. Among other things, the jury found that the addiction to the drug, in this case, was an abreaction; and that at the time in question, the state of medical knowledge was such that the drug company could not reasonably have foreseen that this drug could cause addiction in an appreciable number of people. The drug company sold this product as a non-narcotic drug. Although its literature did not indicate that the use of the drug would not cause addiction, it did indicate that patients who used this drug for prolonged periods (over 300 days) experienced no withdrawal symptoms even when administration was stopped abruptly. The prescribing physician testified that defendant's detail man assured him that the drug was harmless and that it would not cause addiction.

Failure-to-Warn Case

The Court of Civil Appeals treated this as a failure-to-warn case. It held that, in light of the miniscule history of abreaction to this drug, the injury to the plaintiff was not foreseeable and the defendant therefore had no duty to warn the prescribing physician of the possibility of harm. It is obvious that, although the plaintiff sought relief under Section 402B, the Court decided the case as though it had been brought under Section 402A.

On appeal, the Supreme Court of Texas reversed. The Court said:

"Whatever the danger and state of medical knowledge, and however rare the susceptibility of the user, when the drug company positively and specifically represents its

product to be free and safe from all danger of addiction, and when the treating physician relies upon that representation, the drug company is liable when the representation proves to be false and harm results."

As a general proposition, the manufacturer of a prescription drug discharges his duty to warn when he communicates appropriate warnings concerning the dangerous propensities of his product to the prescribing physician. In 1968 the United States Court of Appeals for the Ninth Circuit found an exception to this rule in the case of a manufacturer of oral polio vaccine, where the vaccine was administered in the course of a mass immunization program (*Davis v. Wyeth Laboratories,* CCH PRODUCTS LIABILITY REPORTER ¶ 5908, 399 F. 2nd 121). While the holding was of great concern to drug companies, it was widely felt that it might be restricted to its peculiar facts. The case involved a mass immunization by a county medical society, in which a representative of the defendant was very active. As a result of two cases decided in 1974, it is now reasonably clear that this restricted application of the *Davis* doctrine is not to be.

The first of these cases is *Reyes v. Wyeth Laboratories,* decided by the Court of Appeals for the Fifth Circuit. Unlike *Davis,* this case did not involve a mass immunization program but, rather, routine immunization of the infant plaintiff at a County Health Department facility at the request of her parents. The activity of the defendant manufacturer was confined to the sale of the vaccine to the State Health Department, which in turn distributed it to the counties. Nevertheless, liability was assessed against the defendant.

Dramatic Decline

Obviously, the public policy considerations in this decision are tremendous. There is substantial evidence to suggest that the Court agonized over its decision. First of all, this decision was not issued until 18 months after argument. Second, it begins with a recitation of statistics to indicate that the incidence of reported cases of polio in the United States had decreased from nearly 58,000 cases in 1952 to just 33 cases in 1970 when the plaintiff was afflicted. The Court noted, quite properly, that the credit for this dramatic decline belonged to the researchers who had isolated the viruses and reproduced them in an inactive or attenuated form, as well as to manufacturers such as the defendant and massive public health programs for the ad-

ministration of the vaccine. And it ended with a restatement of the proposition that the rare loss in this circumstance should not lie on the victim where it falls, but rather should be borne by the manufacturer and passed on to his customers as part of the cost of doing business. In between, there is a very closely reasoned and interesting decision. Much of this concerns evidentiary matters which we will not pause to consider here. However, there are some matters of substance with which we are properly concerned.

At the outset, the Court makes the point that the requirements of "defective" and "unreasonably dangerous," to support an action for strict liability, are essentially synonymous. As we read the case, we suspect that what the Court means is that if a product is unreasonably dangerous, it is, *ipso facto,* defective. The converse would not necessarily be true. Recognizing that many products, particularly drug products, are unavoidably unsafe, the Court proceeds to divide the concept of unreasonably dangerous into products which are "unreasonably dangerous per se" and those which are "unreasonably dangerous as marketed." In this latter category go those products which have an essential utility but which should be accompanied by appropriate directions and warnings so as to minimize their inherent dangers. This latter category includes the unavoidably unsafe drug.

Mass Immunizations

The evidence was plain that Wyeth had included all appropriate warnings and information on the package insert included with its product, and that this information had been read and understood by the public health nurse who administered the vaccine to the plaintiff. It was equally plain that the warnings contained therein were not communicated by the nurse to the plaintiff's parents. Under these circumstances, it was held that the defendant had not discharged its duty to warn. The Court pointed out that the exception in favor of prescription drugs is based upon the concept that there will be a one-to-one relationship between physician and patient, and that the physician will be in a position to exercise an informed medical judgment, taking into consideration the risks involved and the condition of the patient. In the case of mass immunizations, or immunization programs conducted by public health clinics, it is well known, and certainly should be known to the defendant, that this personal relationship between physician and patient does not exist. Indeed, in

most cases, as in this case, the vaccines are not administered by a physician at all. Therefore, under the circumstances, the defendant drug manufacturer has a duty comparable to that which it has with respect to over-the-counter medications, to wit, a duty to communicate appropriate warnings to the ultimate consumer of the drug.

Polio Vaccine

Having decided that the defendant had a duty to warn the plaintiff, the Court turned to the issue of causation. In most product liability cases, causation is a two-headed question: (1) Was the defendant's product the producing cause of the plaintiff's injury? (2) Was the defect in the defendant's product the proximate cause of the plaintiff's injury? In *Reyes,* the jury found that the defendant's vaccine was the producing cause of the plaintiff's injury. However, the District Court judge refused to charge the jury or to submit an interrogatory on the question of proximate cause. The issue, of course, is whether the absence of a warning communicated to the plaintiff's parents was the cause of the plaintiff's illness. One would expect that the jury would always have to find proximate cause, particularly in a failure-to-warn situation. However, the Court held to the contrary. It said that in this type of situation there is a rebuttable presumption that the consumer would have read any warning provided by the manufacturer, and acted so as to minimize the risk. In the absence of evidence rebutting this presumption, a finding that the defendant's product was the producing cause of the injury is enough to hold him liable. The effect of a rebuttable presumption is to shift the burden of proof to the defendant. In this type of case, it is a heavy burden indeed. Of more than passing interest in this connection is the fact that the Court did recognize that there was some evidence tending to rebut the presumption. It nowhere, however, alludes to the fact that the jury was not instructed to consider whether this evidence was adequate for that purpose. One can only conclude that, under the test laid down in this case, proximate cause should not be a major factor in a failure-to-warn situation.

A somewhat different result was reached in *Cunningham v. Charles Pfizer & Co., Inc.* This was also a polio vaccine case and involved the same issues of failure to warn and proximate cause. The Oklahoma Supreme Court accepted the doctrine of *Davis* and *Reyes* to the effect that the drug manufacturer in this type of situation has an obligation

to make sure that appropriate warnings are communicated to the ultimate user. The Court also agreed with the Fifth Circuit that the plaintiff was entitled to a rebuttable presumption that he would have heeded any warning which might have been given. However, in this case, the Court noted that there was evidence which tended to overcome this presumption. This evidence indicated that there was considerable risk of contracting polio from natural sources at the time the plaintiff took the vaccine. There had been 12 cases of polio in Tulsa that year and Oklahoma was an epidemic state. In these circumstances, the Court concluded that the question of whether the plaintiff would have refused to take the vaccine if adequate warning had been given should have gone to the jury. The Court went further to say that the test to be applied is an objective test, that is, "in light of all circumstances existing on the date plaintiff took the vaccine, would a reasonably prudent person in plaintiff's position have refused the vaccine if adequate warning of risk had been given." Thus, the rebuttable presumption can be overcome by evidence which the Court feels might motivate a reasonable person to proceed with the immunization in spite of the warning.

It is interesting that the Fifth Circuit Court in *Reyes* noted some evidence which tended to rebut the presumption, but, apparently, did not feel that it was worthy of jury consideration. It is not clear whether the Court felt that reasonable men could not differ concerning the impact of the conflicting evidence, or whether it was considered to be a matter of law for the Court. The approach taken by the Oklahoma Court, in referring the matter for jury consideration, appears to be much more desirable.

There was a development enunciated by a trial level judge in New York which is of more than passing significance. The case is *Vincent, et al. v. Thompson, et al.*, decided by the Supreme Court, Nassau County, and reported in the New York Law Journal of December 3, 1974. The case involved a product called Quadrigen, manufactured by defendant Parke-Davis & Company. The same product had been involved in a previous case, *Tinnerholm v. Parke-Davis & Company*, CCH PRODUCTS LIABILITY REPORTER ¶ 6178, 411 F. 2d 48, in which the Federal Court had found that the defendant manufactured a dangerously defective drug and tested it improperly before releasing it to the public. In light of this case, the Court in *Vincent* held that defendant was collaterally estopped from denying that it defectively manufactured and marketed Quadrigen. As a result, this issue was taken

away from the jury and the trial of the case was limited to the issues of causation and damages. The Court was applying a very liberal doctrine of collateral estoppel which it claims prevails in New York. This doctrine eliminates the concept of "mutuality" from its application. Suffice it to say, that if this doctrine should receive widespread application, it will have a tremendous effect upon products liability, particularly in the areas of failure to warn and defective design.

Battle of Experts

We have frequently referred to the fact that the trial of a products liability case involves "a battle of the experts." It has always been realized that there exists a danger that the expert who testifies frequently for one side or the other of the litigation process may tend to become more an advocate than a witness. Nowhere have I seen this more dramatically exemplified than in the case of *Smith v. Michigan Beverage Company, Inc.* The case involved a bursting soda bottle. Plaintiff's expert, so long as he testified with respect to matters within his scientific training, remained the soul of probity. He had examined the bottle and agreed that it had been broken by the application of external force. He further agreed that there was nothing unusual about the bottle and that at the time it left the defendant's plant it had no mechanical or material defects. However, he went on to say that while the bottle had no physical defect, it did contain what he called a "philosophical defect," because it broke. The United States Court of Appeals for the Seventh Circuit found this evidence inadequate to sustain a verdict for the plaintiff.

Many other very interesting questions were considered by the courts during 1974. Time does not permit discussing, or even mentioning, them here. It is enough to note that the area remains dynamic, that the exposure of the manufacturer to liability is great, and that standards of proof are eroding. What the future holds is anyone's guess. The attitude of many of our courts is clearly reflected by the concluding lines of Mr. Justice Harnett's opinion in the *Vincent* case, following his conclusion that collateral estoppel applied to Parke-Davis: "Now, on the manufacture and testing issues, it is seeking to re-litigate, twisting and squirming, hoping to snatch somewhere a favorable result from the hands of a relatively disadvantaged consumer. Justice is not about that!"

PRODUCT LIABILITY CASES FOR 1974

The list of cases for 1974, grouped according to classification, is as follows: (All paragraph numbers refer to CCH PRODUCTS LIABILITY REPORTER)

Foreign Substance and Contaminated Food Cases

Rotolo v. Continental Insurance Co., ¶ 7110 (La. Ct. App.)

Wisniewski v. The Great Atlantic and Pacific Tea Co., ¶ 7159 (Pa. Super. Ct.)

Renna v. Bishop's Cafeteria Co. of Omaha, ¶ 7215 (Neb. S. Ct.)

Anderson v. Associated Grocers, Inc., ¶ 7279 (Wash. Ct. App.)

Foreign Substance Beverage Cases

Lynchburg Coca-Cola Bottling Co., Inc. v. Reynolds, ¶ 7212 (Va. S. Ct.)

Bursting Bottle Cases

Smith v. Michigan Beverage Co., Inc., ¶ 7155 (CA-7)

Mattes v. Coca-Cola Bottling Co. of Miami, ¶ 7194 (Fla. DC App.); Rehearing Denied ¶ 7321

Lindenauer v. State of New York, ¶ 7217 (N. Y. S. Ct., App. Div. 3rd Dept.)

Coca-Cola Bottling Co. v. Clark, ¶ 7250 (Fla. DC App.)

Drug Cases

Gravis v. Parke-Davis & Co., ¶ 7082 (Tex. Ct. Civ. App.)

Winthrop Laboratories Division v. Crocker, ¶ 7089 (Tex. Ct. Civ. App.); ¶ 7296 (Tex. S. Ct.)

Redfield v. Mead, Johnson & Co., ¶ 7091 (Ore. S. Ct.)

Berry v. G. D. Searle & Co., ¶ 7151 (Ill. S. Ct.)

Reyes v. Wyeth Laboratories, ¶ 7255 (CA-5); Cert. Denied — U. S. —, 12/23/74

Moore v. Lederle Laboratories, ¶ 7275 (Mich. S. Ct.)

Hoffman v. Sterling Drug, Inc., ¶ 7289 (DC Pa., M. D.)

Granoff v. Ayerst Laboratories Division, ¶ 7315 (N. Y. S. Ct.)

Cunningham v. Chas. Pfizer & Co., Inc., ¶ 7318 (Okla. S. Ct.)

Vincent v. Thompson, ¶ 7362 (N. Y. S. Ct.) N. Y. L. J. 12/3/74

Cosmetic Cases

Moran v. Williams, ¶ 7136 (Md. Ct. Spec. App.)

Jerry v. The Borden Co., ¶ 7243 (N. Y. S. Ct., App. Div. 2nd Dept.)

Device Cases

Fogal v. The Genesee Hospital et al., ¶ 7150 (N. Y. S. Ct., App. Div. 4th Dept.)

Haftel v. Kestler, ¶ 7311 (N. Y. S. Ct.)

Economic Poisons Cases

Buffington v. Amchem Products, Inc., ¶ 7094 (CA-8)

Shields v. Morton Chemical Co., ¶ 7107 (Idaho S. Ct.)

Chemco Industrial Applicators Co. v. E. I. duPont de Nemours & Co., ¶ 7122 (DC Mo., E. D.)

Yellow Bayou Plantation, Inc. v. Shell Chemical, Inc., ¶ 7154 (CA-5)

Veretto v. Eli Lilly and Co., ¶ 7211 (DC Tex., N. D.)

Portnoy v. Capobianco, ¶ 7271 (N. Y. S. Ct.)

Lewis and Deane v. Amchem Products, Inc., ¶ 7314 (Mo. Ct. App.)

Blood Transfusion Cases

Schmaltz v. St. Luke's Hospital, ¶ 7149 (Col. Ct. App.)

Florulli v. Schrag, ¶ 7167 (N. Y. S. Ct., Spec. Term)

Brody v. Overlook Hospital, ¶ 7251 (N. J. Super. Ct., App. Div.)

Bartholomew v. Quakertown Hospital Association, ¶ 7270 (Pa. Ct. Of Com. Pleas)

Hines v. St. Joseph's Hospital, ¶ 7294 (N. M. Ct. App.)

McKinstrie v. Henry Ford Hospital, ¶ 7317 (Mich. Ct. App.)

Animal Feed Cases

Brown v. Western Farmers Association, ¶ 7225 (Ore. S. Ct.)

Heil v. Standard Chemical Manufacturing Co., ¶ 7297 (Minn. S. Ct.)

Defective Container Cases

Peterson v. Crown Zellerbach Corporation, ¶ 7081 (Minn. S. Ct.)

Early-Gary, Inc. and H. J. Heinz Co. v. Walters, ¶ 7187 (Miss. S. Ct.)

Powers v. Hunt-Wesson Foods, Inc., ¶ 7245 (Wis. S. Ct.)

[The End]

The FDA's Combination Drug Policy

By E. CARRINGTON BOGGAN

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THE STATEMENT OF EDITORIAL POLICY of the FOOD DRUG COSMETIC LAW JOURNAL, which is printed on the inside cover of every issue, contains several observations with respect to the policy of the JOURNAL which are of particular application to the topic I am examining—the Food and Drug Administration's (FDA's) combination drug policy. The JOURNAL statement says that: "While . . . [the food, drug and cosmetic 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 combination drug policy has had and will continue to have as profound an effect on the type of drugs that will be manufactured and administered in the United States as any other action taken by the FDA in recent years. Despite the lack of use of the term "combination drug" anywhere in the Federal Food, Drug and Cosmetic Act, the FDA policy with respect to those drugs is on the way to becoming one of the "fundamental laws of the land" to which we would be well advised in the words of the FDC LAW JOURNAL, to give "appropriate study."

In the earliest and most dramatic applications of the combination drug policy,[1] it was used successfully to remove from the market combinations of antibiotic and other drugs which had sales of many millions of dollars a year. In its developing application and interpreta-

[1] *Upjohn Co. v. Finch*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 80,301, 422 F. 2d 944 (CA-6 1970); *Pfizer Inc. v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,425, 434 F. 2d 536 (CA-2 1970); *American Cyanamid Co. v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,616, 456 F. 2d 509 (CA-1 1971).

tion by the FDA, the combination policy will have perhaps a more subtle yet equally pronounced effect on many more drugs currently marketed and on the possibilities of drug marketing in the future.

It is appropriate to examine the combination policy at this time because we are beginning to have just enough experience with the developing application of it to take a look at the direction in which that application may be going. We should also examine what the consequences, and the direction, of that application might be.

Initial Proposal

A bit of history is necessary to a consideration of more recent developments. On Thursday, February 18, 1971, more than four years ago, the FDA published in the *Federal Register* its "Proposed Statement Amplifying Policy on Drugs in Fixed Combinations."[2] That initial proposal, which applied to both prescription and over-the-counter (OTC) drugs, gave rise to a veritable flood of criticism. Twenty-nine drug manufacturers and over 1000 physicians, among others, filed comments with the Agency on the proposal, an unusual response to a proposed rule-making. The uproar was so great that Congressman Rogers held hearings on the proposal, announcing that:

"The Congress has received hundreds of complaints from practicing physicians about the effect on their practice of medicine of certain proposed regulations of the Food and Drug Administration, and it is our purpose in these hearings to find out to what extent these complaints are justified, and whether legislative action by the Congress is necessary."

Commissioner Edwards felt compelled to begin his testimony at those hearings with the following assurance: "I want to open by very emphatically stating that the FDA is not against fixed combination dosage forms. To the contrary we are developing a policy that will assure the safe and effective use of combination drugs. . . ."

The Commissioner went on to state that the Agency fully expected to modify its proposal to reflect the valid objections to the proposal.

The practical effects of the proposal were potentially very great from the outset. The proposal itself referred to figures indicating that of the 200 most widely used prescription drugs, approximately 40 percent were combinations, and that almost all OTC drugs were combinations.

Many private physicians were concerned that the combination policy was, as Chief Judge Coffin of the First Circuit so aptly para-

[2] 36 *F. R.* 3126 (Feb. 18, 1971).

phrased and summarized the physicians' reactions, "bureaucratic ivory tower meddling in medicine."[3] Dr. Gilbert McMahon of Tulane University Medical School stated that "regulations involving clinicians ought to be made with the advice of clinicians and not simply armchair M.D.'s on blue ribbon committees."[4]

Blue Ribbon Committees

To a great extent, of course, the proposed regulations *were* generated by ivory tower blue ribbon committees, for they had their genesis in the National Academy of Sciences-National Research Counsel (NAS-NRC) Drug Efficacy Review Panels, particularly with the "White Paper on Fixed Combinations of Antimicrobial Agents" of the Panels on Anti-Infective Drugs.[5] The *Final Report* of the Drug Efficacy Study stated the rationale for the policy as follows:

"The rating 'Ineffective as a fixed combination' was brought into use to deal rationally with certain combinations of drugs, notably combinations of two or more antibiotics, one or more of which when administered alone is acknowledged to be effective for the cited indication. It is a basic principle of medical practice that more than one drug should be administered for the treatment of a given condition only if the physician is persuaded that there is substantial reason to believe that each drug will make a positive contribution to the effect he seeks. Risks of adverse drug reactions should not be multiplied unless there be overriding benefit. * * *"

Now I think that, if we hadn't realized it at the beginning of the combination policy saga, we all probably have now come to understand that, no matter what the emotions involved in this issue may be, decisions on the validity, interpretation and application of this fundamental policy adopted by the FDA are not ultimately going to be made as a result simply of attacks on ivory tower meddling in the practice of medicine.

There are nonetheless serious issues with respect to the meaning, application and validity of the policy as applied, the full ramifications of which we are just recently beginning to see.

Irrationality in Medicine

The basic question from the outset of the development of the combination policy has been, and remains, whether a policy which was clearly developed as a response to possibilities of serious con-

[3] *American Cyanamid, supra,* 456 F. 2d at 512, n. 4.

[4] McMahon, "Drug Combinations: A Critique of Proposed New Federal Regulations," *JAMA* 216:1008 (1971).

[5] NAS, *Drug Efficacy Study: A Report to the Commissioner of Food & Drugs* (1960), pp. 7—8, 123—125.

sequences from concurrent administration of two or more potent anti-infective agents can have valid general application, and if so, how. While I believe, contrary perhaps to some of my colleagues, that there is both a place for and a need for a combination drug policy, some of the recent developments and applications of the present prescription drug combination policy partake of a degree of the "irrationality" in medicine which the combination policy was initially formulated to combat.

The FDA almost immediately came to realize, back in 1971, that there were important differences among drugs which its initial combination policy proposal overlooked. It soon became evident, for example, that one of "The principal effect[s] of the proposed new regulations [would be] to threaten removal from the market of hundreds of proprietary drug combinations and most of the so-called 'over-the-counter' (OTC), i.e., nonprescription drugs."[6]

The preamble to the revised policy statement, published in the *Federal Register*,[7] recognized that further consideration had to be given to OTC drugs, and the final policy statement then published was therefore limited to combination *prescription* drugs. A separate statement on *OTC* combination drugs was promised at a later time.

Significant Revisions

The prescription drug policy as finally published did contain some significant revisions of the policy statement as initially proposed. The principal ones were the deletion of the statements that "A combination of drugs in one product suggests and implies an added usefulness over one component alone," and that "The advantage of the combination must obtain for *all* conditions for which it is labeled, for the various dose schedules recommended, for the duration of dosage suggested, and for *most patients* for which the product is recommended." (Emphasis added.) The final prescription drug policy statement, in fact, was quite streamlined. The substance of the policy reads as follows:

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a *significant patient* population requiring such *concurrent therapy* as *defined in the labeling for the drug*. Special cases of this general rule are where a component is added:

(1) To enhance the safety or effectiveness of the principal active component.

[6] McMahon, *supra*.

[7] 36 *F. R.* 20038 (Oct. 15, 1971).

(2) To minimize the potential for abuse of the principal active component." (Emphasis added.)

The revisions in the prescription drug combination policy, as finally published, eliminated, at least facially, some of the more obvious grounds of attack. If they had not been eliminated, they might well have led to prompt legal challenges to the regulation, even though the regulation purported to be merely interpretive rather than substantive. Whether, with respect to the policy *as applied,* those grounds of attack have been eliminated is another question, one which I will cover later.

A principal objection to the proposal had been that, in its premise that "A combination of drugs in one product suggests and implies an added usefulness over one component alone," the Agency was getting into the forbidden territory of relative or comparative efficacy. This had been a key concern of the medical profession and the pharmaceutical industry when the 1962 effectiveness amendments were under consideration. To allay such fears, then-Secretary of Health, Education and Welfare Ribicoff had testified that he wanted to:

"[M]ake it absolutely clear that we are not dealing here with what some have called 'relative efficacy'....

"The proposed amendments would merely require a showing that the new drug described in the application is safe for use and is effective in use, under conditions prescribed, recommended or suggested in the labeling thereof. This would not require a showing of relatively greater efficacy than that of other drugs."[8]

Interesting Colloquy

An interesting colloquy on the meaning of this language developed at Congressman Rogers' hearings on the combination proposal in 1971. Congressman Pryor said:

"One thing I would like to get clear is that I think the legislative history of the 1962 amendments is very clear, in fact it is very explicit, that it was not the intention of those amendments for the Food and Drug Administration to get into the business of saying this drug is more effective than some other product. But your mission was to say this drug is safe and effective. Is that your understanding of the intention of the 1962 amendments?"

After Commissioner Edwards responded "Yes" to that question, Mr. Goodrich, then the FDA's Counsel, said:

"I was there when then Secretary Ribicoff made that statement. What he said was that we would have no business evaluating relative efficacy and precluding

[8] Hearings Before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary, U. S. Senate, 87th Congress, 1st Session, p. 2585 (Sept. 13, 1961).

a drug from the market, that if the drug worked for a limited population where another one worked for a wider population, there was room for both of them on the market, but that the claims would have to be fully supported by adequate proof of effectiveness.

Now, there are two different things. One is precluding the product from the market and the other one is to hold it to its claim. *Relative efficacy is a factor in the latter but not the former.*" (Emphasis added.)

What Mr. Goodrich meant by that statement is made clear in an exchange between him and Congressman Satterfield. Mr. Satterfield asked: "Is there any place in the law where a distinction is made between single entity drugs or combination, where two or more active ingredients are combined?"

To which Mr. Goodrich replied:

"Only in the terms of the language . . . that a drug must have the effectiveness which it is represented or purports to possess. As I said, every combination I have ever seen is represented to be better than either component alone . . . [o]therwise [you] wouldn't put them together. This is the part of the law we rely on."

Again, Mr. Goodrich said:

"Many people have said that we are going into an unlawful area of judging relative efficacy. No such thing, except where the claim is made. If a relative efficacy claim is made, then we go back to the provision I was quoting."

Of course, the problem some have with Mr. Goodrich's rationale is that it would find a relative efficacy claim, that is, a claim of superior efficacy, implicit for every drug which combined two or more active ingredients. Otherwise, he reasoned, why would you put them together? If that is the case, however, then Mr. Goodrich's further statement as to how to deal with relative efficacy is most interesting and, some might feel, somewhat inconsistent. Congressman Satterfield asked whether: "All that would be necessary is to change the label on the claim."

Mr. Goodrich replied: "Yes, that is certainly a possibility."

More recently, Commissioner Edwards has also reiterated the possibility of labeling changes for combination drugs. Because of that possibility, and other factors, the immediate sting was taken out of the policy. The other factors include the removal of OTC drugs from the statement, the elimination of the requirement that the "advantages of the combination must obtain . . . for *most* patients for whom it is recommended," and the revision of the final prescription drug policy statement. That revision apparently removed the direct link between a mere combination of ingredients per se and an implicit relative efficacy claim. Despite some lingering doubts, the industry now appears at the least to be able to live with the *language*

of the final combination policy for prescription drugs. In a nutshell, that policy now permits combination when:

(1) each drug makes a contribution to the claimed effects; and

(2) the dosage is such that the combination is safe and effective for a *significant* patient population requiring such *concurrent therapy*.

Concurrent Therapy

"Concurrent therapy" may have two meanings. It may mean, in the case of some drugs, therapy for a single condition but with *two or more active ingredients* in combination. This combination is used because using two drugs which are active therapeutically for that condition has advantages over the use of a single drug for a significant patient population, or because it enhances safety or effectiveness, or because it minimizes the potential for abuse.

It may also mean, for other drugs, therapy by the use of two or more drugs, each aimed at one of the conditions involved, for two or more *conditions* which concur frequently in a significant patient population.

There would seem to remain few, if any, problems with these concepts in basic theory. I think it is now generally acknowledged that each ingredient claimed to be active in a combination must make a contribution to the combination, and that the combination must be of use to a significant patient population.

We may, however, have some continuing problems over precisely how the contribution of each ingredient is to be shown. There is also some evidence that another type of problem may arise in the application of the combination prescription drug policy.

In a Final Order published in 1973, the FDA withdrew approval of the new drug application (NDA) of a drug used in inhalation therapy on the ground, never previously raised in five years of prior Agency proceedings with respect to the drug, that it was a fixed-combination drug. Therefore, studies submitted by the NDA holder which simply compared the drug to two other solutions commonly used in inhalation therapy were irrelevant. The Court of Appeals for the Second Circuit subsequently set aside that order[9] because the FDA had never given notice that it considered the drug a fixed combination.

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[9] *Sterling Drug Inc. v. Weinberger*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,143, 503 F. 2d 675 (CA-2 1974).

Lines of Reasoning

This case is quite instructive of the difficulty of following some of the lines of reasoning that can emerge from our brethren at the FDA. The drug involved was reviewed by the NAS-NRC drug efficacy study and was found, along with another agent reviewed at the same time, to be no more effective for its indication in respiratory diseases than simple humidification of the lungs. The drug was ***not,*** however, classified by the NAS-NRC as a fixed-combination drug, nor did the FDA ever raise such a contention until after the NDA holders had undertaken studies in response to the NAS-NRC report which compared the product with both simple humidification and with another commonly used solution. Then, according to the Court of Appeals, after the Supreme Court decision in *Hynson, Westcott & Dunning v. Weinberger*[10] in which the Court held that the data submitted by *Hynson* was sufficient to warrant a hearing, the FDA switched its theory. The Agency announced that the studies submitted by the NDA holders were not "relevant" because the product was a combination drug and the studies did not establish the contribution to the claimed effect of what the FDA then asserted were *three* active ingredients. Approval of the NDA was withdrawn.

Although the Court of Appeals reinstated approval of the NDAs for lack of notice of the fixed combination theory, the FDA issued a new notice in August 1974.[11] This time, however, the Agency felt that there were probably only *two* active ingredients in the drug, rather than the three its previous final order had said. Alternatively, however—to add to the confusion—the notice offered the NDA holders the opportunity to establish that the drug was in fact a single active ingredient drug after all.

Therapeutic Activity

There are two reasons this case is disturbing in terms of the development and application of the combination drug policy. The first is that the case does not fit within the criteria set forth in the combination prescription drug policy with respect to *concurrent therapy,* of *either* of the two types discussed earlier. As we have seen, the combination policy allows for two or more drugs to be combined when useful in a significant target population for concurrent therapy of two possible types: (1) two or more agents both of which are in-

[10] CCH Food Drug Cosmetic Law Reporter ¶ 40,930, 412 U. S. 609 (1973).

[11] 39 *F. R.* 20913.

cluded for their *therapeutic activity* against the same condition, and which are combined for one of the several reasons permitted by the policy, such as increased safety or effectiveness; or (2) two or more agents therapeutically active against different conditions, each included because of its *different* therapeutic activity for *different conditions* which occur concurrently in a significant target population. In the case being discussed, the NDA holders have claimed therapeutic activity of the drug as a whole against only one basic condition, and for only one of the ingredients. Because of the other ingredient, which the NDA holders assert is added as a pharmaceutical necessity, the FDA says it is a combination drug.

If agents which have long been added to drugs of all types as binders, or to adjust pH levels, or for other such *pharmaceutic*, as opposed to *therapeutic*, purposes, are from now on able to cause a prescription drug to become a fixed-combination drug within the meaning of the FDA policy, then almost every drug on the market, no matter what its claims, is a candidate for such treatment.

The second reason the case is disturbing is that it is the most blatant relative efficacy proposal to come out of the FDA. The product involved is a single indication product, and it is claimed simply to be effective for the indicated condition. The FDA, however, in its pending Notice, would require a series of tests to demonstrate that the product is *more effective* for the single recommended indication than various hypothetical formulations of the product minus, respectively, each of the other ingredients added only for pharmaceutic effect, and for which no therapeutic claims are made.

NDA Holders

Further, even if the NDA holders were able to convince the FDA that the product is a single entity drug, they would still be required, under the FDA's outstanding Notice of Opportunity for Hearing, to prove that it is *more effective* than its vehicle.

In short, even though the FDA deleted from its proposal in 1971 the contention that the mere inclusion of an ingredient was an implicit claim of greater effectiveness, it has now reverted to that theory in its application of the policy. It has even extended it to mere pharmaceutic agents and to *single active ingredient* drugs, so that, even though the only claim made is for simple effectiveness, a manufacturer must prove *superior* effectiveness over any other possible for-

mulation. If the FDA persists in this type of interpretation, significant legal tests of the combination policy as so applied may be in the offing.

So much for the current application of the combination *prescription* drug policy. What about the combination OTC drug policy? After OTC combination drugs were excluded from the initial combination drug proposal, a separate OTC combination drug proposal was not issued until the issuance of the general regulations for the OTC Drug Review. In the criteria or standards of effectiveness for drugs subject to review, the following standard for combinations appears:

"An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."[12]

The key tests under this standard are: (1) that each ingredient makes a contribution to the claimed effects; and (2) that the combination provides rational concurrent therapy for a *significant portion* of the target population.

OTC Review Panels

There has been great concern over how this policy would be interpreted and administered by the OTC review panels, considering the profound effect it can have on the future of OTC medicines, most of which are combinations. Hopefully, relative efficacy will not be a problem in the OTC area. In responding to the comments received on the initial proposal, the Commissioner said:

"One comment stated that the combination policy is deficient in that it fails to require that the combination enhance the safety and efficacy of the drug or that the combination represent an advantage for all the conditions listed in the labeling. As long as there is no decrease in safety, however, there is no sound basis for requiring increased effectiveness or any other advantage for the combination."[13]

There has been much concern over how the OTC review panels would respond to the general philosophy of OTC combination drugs, and what requirements for demonstrating effectiveness of the combinations would be established. The preamble to the general OTC review regulation stated that, generally, the proof necessary to show effectiveness for a particular drug will be determined by the panel

[12] 39 *F. R.* 11743 (Mar. 29, 1974).

[13] 39 *F. R.* 9664 (May 11, 1974).

using the expertise of its members and based on the data submitted. Commissioner Edwards, in commenting on the standards, said that:

"Evidence of effectiveness for the OTC's may be somewhat less sophisticated [than for prescription drugs]; it may be less extensive...

"It must in the final analysis allow the consumer a reasonable expectation that the product he buys will be safe and will give him the relief he seeks..."

Progressive Stages

In applying the criteria for OTC combinations, the panels to date have seemed to go through progressive stages. Commissioner Schmidt recently stated:

"We have had enough experience with [the Review panels] to know that they do go through an evolutionary cycle at first, trying to come to grips with what it is they have to do. Then, very frequently they will go through a period of taking an extremely hard line and saying, 'Nothing will be said that is not supported by substantial evidence, by well-controlled clinical studies, and so on.'

"Even some of the preliminary reports are very hard-lined in this respect. But then there is a reaction to that, as the impact sinks into the Panel of what it has said and what it has done. We very clearly could tie up all the research facilities in this country for a long period of time generating data about every ingredient in every OTC product."

The experience with some of the panels to date seems to support the Commissioner's analysis. The Laxative Panel at first insisted that drugs in combination had to offer reduced toxicity and increased efficacy over the active ingredients taken separately. After further discussion with Peter Hutt, however, the panel adopted guidelines which stated that:

"there are no restrictions as to the number of active ingredients or classes of active ingredients that may be combined in a laxative product so long as there is a logical rationale, and the ingredients can meet the criterion of "contributing significantly to the product's effectiveness."

The Antacid Panel final monograph has been published, and it provides for combination products where considered "rational." In responding to a comment received on the tentative final antacid monograph, the Commissioner said:

"One comment stated that the Food and Drug Administration has misinterpreted the OTC combination drug policy as to an antacid/analgesic combination, because the policy requires that *each* ingredient contribute to *each* effect. The comment contended that each ingredient in the antacid/analgesic combination would need to be shown to contribute to both effects, e.g., the antacid ingredient would also need to be effective for a headache.

"The Commissioner advises that the comment misinterprets the plain meaning of the OTC combination policy contained in § 330.10(a)(4)(iv) (formerly § 130.301 (a)(4)(iv)) and explained in paragraphs 63-66 of the preamble to the final regulations establishing the procedures for the OTC drug review published in the Federal Register of May 11, 1972 (37 F. R. 9664). The policy states that each

active ingredient must make a contribution to the effect claimed for it, and *not* that each active ingredient must contribute to *all* effects claimed for the product. To adopt the approach suggested by the comment would require removal of all dual purpose combination drugs from the market because rational concurrent therapy could only be found where all the ingredients had the same effects. The Commissioner states that this was not the intent of the regulation and that such a policy would be unreasonable from a medical standpoint." (Emphasis added.)

Require Comprehensive Testing

The Cough-Cold Preparations review panel initially issued a statement of tentative principles which took the position that "As a general principle, restriction of OTC products to single ingredients is recommended." The panel's tentative principles also contained other restrictive provisions on the types of ingredients which could be combined in products. It also seemed to require comprehensive testing of all combinations, even those consisting only of active ingredients which were recognized as both safe and effective. After consideration of further data, however, the panel now seems willing to consider modification of some of these restrictions.

Hopefully, therefore, with attention and with submission of appropriate data and information by concerned parties, the conclusions of the OTC review with respect to combination OTC medicines will ultimately be rational ones which, while they will undoubtedly require reformulation and relabeling in some instances, will not jeopardize the availability of convenient OTC combinations for rational concurrent therapy for a significant portion of the various target populations.

As indicated earlier, I have more doubts about the rationality of the developing application of the *prescription* combination drug policy, but perhaps some of the more rational criteria developed with respect to OTC combinations can ultimately be carried over as well to the prescription drug area. **[The End]**

Food Safety Review— New Concepts for GRAS

By ROGER D. MIDDLEKAUFF

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ONCE IN EVERY GENERATION there appears a wise man, one with a vision far advanced over that of his contemporaries. Unfortunately, such men are often not appreciated or recognized until long after they have expressed their thoughts. "A prophet is not without honor, save in his own country, and in his own house."[1] Today, I propose to recognize one of such men, one who predicted with uncanny clarity the problems which are impacting the food industry because of the final and proposed regulations of the Food and Drug Administration (FDA) as published in the *Federal Register* on September 23, 1974.

Congressman Dies, Jr., was elected by the State of Texas as a Congressman-at-large to the 72nd Congress and to six succeeding Congresses. After a brief respite, he was elected to the 83rd, 84th, and 85th Sessions. He did not seek re-election in 1958. By then he had stated his mind and the country had not listened to him. I cannot explain the source of his wisdom, but I do know that he was a lawyer.

He happened to serve on the Subcommittee on Health and Science of the House Committee on Interstate and Foreign Commerce. His service included the hearings on the legislative proposals which eventually became the Food Additives Amendment of 1958.

During the initial hearings in 1956, one of the key problems with the proposed legislation was highlighted by the testimony of the Adhesives Manufacturers' Association of America. Please bear with

[1] Matthew 14:57.

my several quotations. I feel that the witnesses' actual words are preferable to my paraphrasing. The testimony stated: "Our problem lies in the words 'generally recognized'. These gems of ambiguity were included in the definition of new drugs in the . . . Act of 1938."[2]

"In contesting the application of the law, only evidence bearing upon general recognition by experts would be admissible although other relevant facts might be in existence. The real issue should be whether or not the use of a substance presents a reasonable probability of injury to health, and all relevant evidence, including expert testimony, should be admissible."[3]

Mr. Dies agreed, "It is very, very vague and indefinite. I do not see how anyone could tell whether you came within the law or not."[4]

Functional Value

Another controversial aspect of the proposed legislation was commented upon by George P. Larrick, then the Commissioner of Food and Drugs, who stated as a witness: "If an additive is wholly innocuous under any circumstances of use, the question of its functional value is not of any concern in this amendment."[5] Even when pressed further on this point by the Chairman of the Subcommittee, Mr. Larrick restated that view. And, in response to a comment by Congressman O'Hara, "Should not Food and Drug have to use a little common sense?" Mr. Larrick firmly replied, "They should."

Not satisfied, Mr. Dies pressed on: "Mr. Larrick, the thing that troubles me about this bill is the standard here . . . I think that is so vague and indefinite and general that it puts the manufacturer, the processor, in a very bad situation."[6] Still, he pressed on:

"There is another thing that troubles me. This question of function and use . . . (T)he best criteria is whether the public is willing to buy the product. They are the final arbiters of this thing. Now you step in and you have a third party take over that function and say, 'We are going to determine whether it is functional.' "[7]

Then Mr. Dies made his main point:

"As long as you have a good department, men that have respect for our system and who want to uphold it, you are all right; but suppose you get some fellow in there who is obsessed with the idea of wanting to change it, and I have seen a few drift in here in my twenty-odd years, and I have seen some queer ideas."[8]

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[2] Hearings before a Subcommittee of the Committee on Interstate and Foreign Commerce, House of Representatives, 84th Congress, 2nd Session, on H. R. 4475 et al., 1956, at p. 150.

[3] Ibid., at p. 151.

[4] Ibid., at p. 152.

[5] Ibid., at p. 195.

[6] Ibid., at p. 203.

[7] Ibid., at p. 205.

[8] Ibid., at p. 206.

Best Drafting

As might be expected, Mr. Larrick, not being a lawyer, did not fare well against Mr. Dies. Mr. William Goodrich, then the Assistant General Counsel for Food and Drug, appeared as a witness. Mr. Dies stated: "(T)he test whether he has violated a criminal statute . . . is whether it is generally recognized by the experts to be safe."[9] Mr. Goodrich replied, "Yes, sir." He added, "We have the burden, no matter how this bill goes, of proving that a product is not generally recognized as safe among experts in the courts."[10] After further discussion, Mr. Goodrich stated: "We believe that the generally recognized is the best drafting that we can do."[11] This left Mr. Dies with the final word, "I think that is all, Mr. Chairman."[12] As you know, that was not all; the hearings continued during 1957 and 1958.[13]

The Food Additives Amendment of 1958 was enacted, and Mr. Dies did not seek re-election. Despite Mr. Dies' prophesies, the Amendment contained the definition in Section 201(s) that a substance is not a food additive:

"if such substance is . . . generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. . . ."

For the following several years, while the FDA concentrated on regulating food additives, labeling and other matters, the situation was relatively quiet for the users of generally recognized as safe (GRAS) substances. In 1959 and 1960, the FDA undertook a limited effort to develop a list of less than 200 GRAS substances.[14] For the next ten years, the FDA made no public effort to deal with the GRAS problem.

Grandfather Clause

In June, 1971, the FDA established Section 121.3 "Eligibility for Classification as GRAS."[15] With this regulation, it became evident that: (1) the FDA wanted to take control of GRAS determinations;

[9] Ibid., at p. 226.
[10] Ibid., at p. 226.
[11] Ibid., at p. 228.
[12] Ibid., at p. 228.
[13] Hearings before a Subcommittee of the Committee on Interstate and Foreign Commerce, House of Representatives, 85th Congress, on H. R. 366 et al., 1957-58, at p. 453.
[14] Richard L. Hall, "GRAS—Concept and Application," 49 *Food Technology*, Vol. 1, p. 48 (Jan. 1975).
[15] 21 CFR Sec. 121.3.

and (2) the FDA believed that some GRAS substances are more GRAS than others. In the regulation, the grandfather clause was to be considered as obviously applicable to a select group of substances which would be considered GRAS without the need for soliciting advice from any other experts. This group was identified as being those substances of natural biological origin consumed for nutrient properties in the United States prior to January 1, 1958, without detrimental effect when used under reasonably anticipated patterns of consumption, including such of those substances modified by conventional processing as practiced prior to January 1, 1958. As for the group of lesser GRAS substances, the FDA announced that experts should be solicited through the use of the *Federal Register* for comments with regard to GRAS substances. The FDA wanted advice concerning:

(1) GRAS substances which have been modified by processes proposed for introduction into commercial use after January 1, 1958, where such processes may reasonably be expected to significantly alter the composition of the substance;

(2) GRAS substances which have been subjected to breeding or selection which may reasonably be expected to alter to a significant degree the nutritive value of the concentration of toxic constituents;

(3) the safety of distillates, isolates, extracts, concentrates of extract or reaction products.

The FDA had two final categories of so-called lesser GRAS substances:

(1) those not of natural biological origin, even if nature-identical;

(2) substances of natural biological origin intended for consumption for other than their nutrient properties.

In all lesser GRAS situations, the FDA's regulation required publication in the *Federal Register* and a finding of convincing evidence of their general recognition of safety.

Prescribed Limitations

Finally, the FDA stated in Section 121.3 that, except as set forth in those categories, no other substance would be eligible for GRAS status if it had no history of food use or if it required prescribed limitations for safe use.

Let us consider this action, particularly the extent to which Section 121.3 may be considered to deviate from the statutory language. The differences are as follows:

(1) The FDA arbitrarily drew a distinction between substances consumed for nutrient purposes and those consumed for other reasons, implying that a substance consumed for nutrient purposes is intrinsically safer than a substance consumed for other reasons.

(2) The FDA established a distinction between treatment processes based on the extent of their *commercial* use prior to 1958, without justification.

(3) The FDA established the principle that derivatives of a substance are to be considered as potentially less GRAS than the substance itself, again without justification.

(4) The FDA announced that a substance would not be eligible for GRAS unless it had a history of food use. This position is not supported by the Act's provisions.

Effort to Act

The significance of these distinctions was further felt in December of 1972, upon the publication of a new procedure for "Affirmation of Generally Recognized As Safe (GRAS) Status," as Section 121.40.[16] The petition process is similar to that process established for food additive petitions, without, however, certain vital procedural protections. For example, rather than include in Section 121.40 a time limitation for review of petitions, the preamble stated that the Commissioner would "make every effort to act on such petitions within 90 days after the comments are received."[17]

The significance of the lack of procedural protections and the GRAS and lesser GRAS distinctions is realized upon recognizing that the FDA required until September of 1974 to issue the first of the final GRAS affirmation petitions, more than one and one-half years after the method was proposed and at least one year after the first of the petitions were filed.[18]

Except for those few companies that filed GRAS affirmation petitions, I do not imagine that the impact of Sections 121.3 and 121.40 interfered with the food industry. It could probably be said that, for the most part, attorneys and their clients were able to con-

[16] 21 CFR Sec. 121.40.
[17] 37 *F. R.* 25706 (1972).
[18] 39 *F. R.* 34184 et al. (1974).

tinue as before. We were all concentrating our efforts on trying to anticipate the impact and meaning of the Comprehensive GRAS Review that was in progress. If successfully accomplished, we assumed that the Comprehensive GRAS Review would serve the bulk of the needs of the industry.

The Comprehensive GRAS Review has developed an enormous amount of information regarding "GRAS substances." All the significant companies in the food industry were solicited for survey data regarding the use of GRAS substances. The Survey brought in 16,000 reports of information on flavors alone. From this data, the National Academy of Sciences (NAS) made a valiant effort to do what had never been done before on this scale; that is, develop an estimate of an individual's daily intake of all GRAS substances. The Academy admits that the results have some failings, but they are considering means to improve the data.

Scholarly Presentation

In addition to the Survey, the FDA contracted for the preparation of Scientific Literature Reviews on GRAS substances. Each review was to be a scholarly presentation of all facts on the safety of the substances. Here again, there were failings. Mainly, these problems stemmed from the fact that the reviews were prepared without industry input.

The Select Committee on GRAS Substances of the Federated American Societies for Experimental Biology analyzed the information and submitted very exceptional evaluations of the safety of these substances to the FDA, albeit somewhat conservative.

Maybe all this was simply too much for one agency to digest. The FDA's personnel were trying to digest in months what industry had hundreds of years to work with and what mankind had millions of years to eat. One could say that the FDA had indigestion. If that is so, why did they permit it to happen?

Scientific Inquiry

Perhaps it was their success before the Supreme Court. That Court held that the scientific inquiry regarding the effectiveness of GRAS drugs under Section 201(p) had to conform to the require-

ments of new drugs under Section 505(b).[19] By analogy, the FDA concluded that the phrase "scientific procedures" under Section 201(s) required the same investigations to prove safety as were established in Section 409 for food additives.[20] The FDA's Section 121.3 of the current regulations does not contain any reference as to the criteria for safety on which the experts could act. Therefore, the FDA used the Supreme Court ruling to require that any expert, who considers whether or not a substance is safe, had to consider the same quantity and quality of scientific evidence as is required for proof of safety under Section 409. Thus, dramatically, the FDA completely changed the ground rules for determination of safety of GRAS substances. No longer is the issue simply whether or not experts consider the substance safe. The issue now is also whether the substance meets the criteria for a food additive.

The FDA used the Supreme Court decision in the *Bentex* case as support for the proposition that GRAS status must be based on information disclosed in published literature.[21] Experts are no longer permitted to make their decisions on unpublished material or research; they must rely on published literature. Whether a substance is GRAS or a food additive may depend on whether or not the available toxicological studies are published or unpublished. But, going one step further, the FDA takes the position that publication alone may not assure the GRAS status of a borderline substance; the scientific community must be given an indefinite period of time to absorb the meaning of the publication. Thus, whether the substance is GRAS or a food additive may depend on whether the article was published 11 months ago or 12 months ago.

Extreme Steps

A completely revised Section 121.3 was proposed in the *Federal Register* on September 23, 1974. The FDA took even more extreme steps to deviate from the simple statutory premise of GRAS status in Section 201(s) of the Act.[22]

(1) Let us start with the uncomplicated phrase "common use in food." The proposed regulation requires a substantial history of

[19] *Weinberger v. Hynson, Westcott & Dunning, Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,930, 412 U. S. 609 (1973); *Weinberger v. Bentex Pharmaceuticals, Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,932, 412 U. S. 645 (1973).

[20] 39 *F. R.* 34194 (1974).

[21] *Weinberger v. Bentex Pharmaceuticals, Inc., supra.*

[22] 39 *F. R.* 34195-6 (1974).

consumption of a substance by a significant number of consumers in the United States.[23] What impact will this have on the ethnic diet?

(2) Instead of using the statutory requirement of "general recognition of safety by experts qualified by training and experience," the proposed regulation would have the decision based on "common knowledge about the substance throughout the scientific community knowledgeable about the safety of food ingredients."[24]

(3) Under the proposed regulation GRAS substances must be shown to be performing an appropriate function in food in which they are used. The safety is dependent not only on the Section 409(c)(5) factors applicable to food additives; the substance must also provide a benefit.

Limitations on GRAS Substances

(4) As another item, in 1971 Section 121.3 excluded from GRAS status any substance for which prescribed limitations for safe use were required. In contrast, proposed Section 121.3 contemplates three types of GRAS substances which anticipate the placing of limitations on GRAS substances:

(a) Subject to no limitation other than good manufacturing practice (GMP).

(b) Subject to specific limitations as to category of food use, functional use and level of use. Any deviation from those specific limitations requires a food additive petition.

(c) Permissible for only a specified use, subject to reconsideration when the substance undergoes the general evaluation pursuant to the Comprehensive GRAS Review.[25]

(5) Application of the criteria required by the September 23rd proposal results in GRAS regulations that describe uses with an extensive amount of detail. The first group of proposed regulations published September 23rd include garlic and dill. Even though the regulations are detailed, no effort was made to relate the data to other known derivatives of those substances. For example, since only dill and oil of dill are proposed to be regulated, what does this mean regarding the status of oleoresin of dill? Ginger is used as the fresh rhizome, the dried rhizome, the essential oil, the oleoresin, the extract and the solid extract. Will there be a regulation for each derivative, and for each form?

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[23] Proposed 21 CFR Sec. 121.1, 39 *F. R.* 34195 (1974).

[24] 39 *F. R.* 34195-6 (1974).

[25] 39 *F. R.* 34196 (1974).

Purpose of Use

(6) As we look to the meaning of the phrase "good manufacturing practice," we should realize that this phrase must incorporate flexibility so that one manufacturer can deviate manyfold from another manufacturer in the use of the ingredient, depending upon the purpose of its use. Somehow, it should be made clear in this regulation that GMPs are not intended to restrict the effective use of the substances.

(7) The NAS-NRC survey data were extremely detailed. For some reason, the FDA concluded that this requires the regulations to be equally detailed. With each use level, the functions and food categories are spelled out explicitly. If a substance need not be restricted in use for reasons of safety, why should a regulation try to spell out in manifold detail levels of uses and function, with respect to particular food categories? Only where specific limitations restrict use of a substance, does the specificity of use, function and food categories seem appropriate.

Let us view these complications in the background of Section 121.104, the regulation which will eventually contain all "Substances Added Directly to Human Food Affirmed as Generally Recognized as Safe (GRAS)." The general provisions of Section 121.104 will apply to all ingredients which are affirmed as GRAS, whether limited by specific limitations or only by GMP.

Rigid Tolerances

To make certain that the GMPs and specific limitations are complied with, Section 121.104(f) provides that in any intermediate mix (whatever that is), the label must bear a statement of concentration of any GRAS ingredient in such a mix. Thus, any ingredient affirmed as GRAS must be specifically identified by name and concentration, even though subject only to GMP. In contrast, food additives need not be so identified. Food additives are subject to rigid tolerances and are not GRAS, yet their concentrations need not be specifically identified. The full impact of the literal application of the requirement for disclosure of concentration is evident when one sees that it could require a disclosure of flavors, spices and colors, even though the statute permits only a generic description, let alone a statement of concentration. And it may have an impact on standardized foods. This makes it more desirable to have a substance be a food additive than to have it affirmed as GRAS. We have the

anomalous situation of a substance subject to a tolerance being considered less a threat than a substance subject to GMP. This appears to be a misguided state of priorities.

As another point, I bring to your attention the requirement of the FDA that regulations must incorporate sufficient information regarding methods of manufacture in order to differentiate one variation of an ingredient from other variations of the ingredient that have not yet been determined to be GRAS. The FDA notes: "The law does not contemplate uncontrolled use of new methods of manufacture which could result in increased levels of impurities or contaminants."[26] Despite historical precedence to the contrary, the FDA states that there are no better means of describing significant alterations in chemical composition of food ingredients than by describing a manufacturing method of acceptable reference. Consequently, we find that methods of manufacture become food additives and are granted food additive status because they were not commercially used until after 1958 or because their safety is not established in published literature. Wouldn't it be much simpler to define a substance by its physical properties?

New Methodology

Let us try to apply the new methodology as established by proposed Section 121.3. Suppose your client tells you he is using gum arabic, also known as gum acacia, for the purpose of encapsulating a flavor. He tells you that gum acacia represents 1.6 percent of the flavoring compound, which is eventually incorporated into oleomargarine at a level of 0.02 percent of flavor to olemargarine. He wants to know if he may continue the practice under the proposed regulations.

To help him in resolving this question, let us look at proposed Section 121.105(f)(4).[27] According to that regulation, gum acacia may be used in fats and oils as a stabilizer and thickener at 1.5 percent. This raises the following questions:

(1) Is the 1.5 percent a limitation as to use in an intermediate mix or as used in finished food?

(2) If the 1.5 percent level is a limit as to the intermediate mix, is a 1.6 percent use simply a violation of GMP or is it adulteration?

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[26] 39 *F. R.* 34177 (1974)

[27] 39 *F. R.* 34205 (1974).

(3) If this is only a question of violating a GMP, what can and what will the FDA do as enforcement measures?

(4) Does the use of gum acacia as an encapsulating agent fit within the definition of stabilizer and thickener?

(5) If not, is it simply not GMP or is it a misdemeanor and grounds for seizure to use gum acacia as an encapsulating agent, when the level of use will be well within the guidelines set for use as a stabilizer and thickener?

(6) Is the answer any different if the oleomargine does not otherwise contain any gum acacia?

Basic Questions

Let us consider other, perhaps even more basic, questions:

(1) How does one challenge or correct a final regulation under Section 121.104? Is there anything to challenge if the regulation simply defines GMPs, which we all know are unenforceable? But, if specific limitations exist, what judicial review is available? Are proposed changes possible by GRAS affirmation petition or must food additive petitions be used?

(2) Is an affirmation of GRAS status by the FDA the final word on the matter? If your independent determination is contrary to that of the FDA's, must you wait until a seizure takes place to justify your position? Is it possible for a nonregulated use of a regulated food additive or even a regulated food additive itself to become GRAS in time, after publication of safety data has been absorbed by the requisite number of experts?

These and other questions have yet to be resolved. I hope that it may be accomplished without a plethora of regulations which would only serve to confuse the food industry, reduce incentives, discourage creativity and increase food prices. We should all work towards a meaningful solution.

If Congressman Dies is watching this scene, I am certain that he finds it amusing. **[The End]**

Recognition and Response—Critical Industry Needs

By DAVID E. COLLINS

Mr. Collins Is Secretary and Associate General Counsel for Johnson & Johnson.

IN DISCUSSING REGULATORY AND SCIENTIFIC MATTERS facing the device and diagnostic industry, I will focus not only on the current programs and projects, but also on certain implications to be drawn from these current matters. These implications, which have long-range significance for the industry, perhaps have only begun to be recognized by industry. Industry must begin to respond, both individually by company and in an organized fashion through trade and professional associations.

The members of another panel gave you a fairly detailed picture of current Food and Drug Administration (FDA), industry and professional projects now active in the device and diagnostic fields. Let me briefly summarize these.

In the legislative area, the staff markup of the proposed device legislation is underway with a hope for committee and possibly House action in 1974. However, because of the shortness of time, it now appears that legislation will not be achieved in 1974. What 1975 will bring is anyone's guess. Certainly, however, we can expect reintroduction in the 94th Congress but from there we have only questions. Will Congressman Rogers' Subcommittee have jurisdiction? Will FDA personnel so familiar with this bill still be at the Agency? What effect will the new complexion of Congress have? Will the appointment of a permanent director of the Bureau of Medical Devices and Diagnostic Products (BUDD) help or hurt? Hasten or hinder? One thing is sure, we can expect a continuation of activity on this front at an accelerated pace.

In the meantime, as you have heard, the FDA is not waiting for passage of implementing legislation. It is engaged in a multifaceted program of regulation destined to impact on the entire industry with or without legislation. The best example of this is the extensive program to classify existing products into regulatory categories. Carl Bruch referred to this project in his presentation and you know the massive character of this effort.

GMP Guidelines

The FDA is also engaged in a project to develop good manufacturing practice (GMP) guidelines for the device and diagnostic industry. In conjunction with committees representing various manufacturer trade associations, work has progressed to the point of discussion of several draft documents covering specific types of medical devices and diagnostic products. Indeed, the draft GMP for dental products was discussed at the open session of the Dental Products Classification Panel meeting.

In another area of standards, the FDA has a number of projects designed to produce product standards. These include work on a defillabrator standard through an outside contractor, a series of pacemaker standards through the Association for Advancement of Medical Instrumentation (AAMI), another outside contractor, and a standard for insulin syringes being developed by the Agency itself. And in the *in vitro* diagnostic (IVD) area, there is the ongoing work on the glucose standard under the IVD regulations. Additionally, the Agency is engaged in a program to develop information and recommendations on minimum safety requirements for residues resulting from ethylene oxide sterilization of medical device products.

Let us not forget the efforts of the Compliance Division of the Bureau of Medical Devices and Diagnostic Products, which was the subject of Larry Pilot's presentation.[1] These efforts include a significant increase in factory inspections, a greatly accelerated recall program as evidenced by the weekly publication of recall lists, as well as the facing of special problems as they arise. Here I have in mind their work in gathering and evaluating data on the interuterine device (IUD), as well as a fairly recent development—the inquiry to catheter manufacturers with regard to particulate matter associated with intravenous catheters.

[1] Larry R. Pilot, "Regulatory Options and Ramifications of Recall," 30 FOOD DRUG COSMETIC LAW JOURNAL 239 (April 1975).

This quick and very summary list of current FDA activities pictures rather well the regulatory and scientific matters confronting industry. Add to this the statistics on manpower and planned manpower of the Device Bureau as provided by David Link. Mr. Link has indicated a headquarters population of 90 personnel in July of 1974 with a target of 135 by July of 1975. Should legislation pass, the target would be raised to 200 to 250 headquarter personnel. As far as the field force goes, the Bureau of Medical Devices and Diagnostic Products has been assigned 60 man-years of field force time for fiscal 1974 with a target of 80 man-years for fiscal 1975—without legislation. These figures will be considerably higher if legislation passes.

Let me now try to focus your consideration of these projects, programs and personnel so as to highlight four conclusions of long-range significance which, although they are obvious to the informed observer, have not, I believe, been sufficiently recognized by industry. These represent, I suggest, important areas both for industry recognition and for its response.

Commitment to Regulation

First, industry must recognize and accept the extent of the FDA commitment to the regulation of the device and diagnostic industry. This may sound obvious, but, believe me, it is not. Many people, including some within my own company, have suggested that since there is no express statutory authority, the FDA cannot possibly move against the industry. Some feel that industry need not be concerned with additional regulation until a statute is passed. Others continue to hold that industry should oppose any legislation as long as possible in order to avoid regulation as long as possible. While these sentiments may have had some validity several years ago, in my judgment, they have none now. BUDD is not going to disappear. Its multimillion dollar budget is not going to be withdrawn. The regulations which they have published and which they are working on will be implemented with or without legislation. Further, let me suggest that the device industry with its many low-volume products may be an ideal target for the current expanding theories of misbranding and adulteration that are currently in vogue with the FDA's General Counsel's Office. Small volume products do not support high cost lawsuits. Only after recognizing the permanence and depth of the FDA's involvement in this regulatory area will industry begin to respond adequately to the Agency's initiatives by devoting personnel and resources to the task.

Extent of Authority

A second area in need of recognition by industry is the extent of authority granted to the FDA under the proposed new legislation. Here I am assuming that whatever happens during the final days of the 93rd Congress, it is most likely that any device bill will follow the patterns already established. These patterns indicate that the authority given to the Agency over the development, testing, manufacture, advertising, labeling, sale and return of devices and diagnostic products are broader than any we have seen before. The new legislation gives to the Agency substantive rule-making authority, subject only to court review, over:

(1) the regulatory class into which all existing and all future products are to be placed—premarket clearance, performance standards or general controls, or a combination thereof;

(2) the contents of any performance standards including the labeling of the product and any pre-sale testing, such as batch or lot testing;

(3) the type of scientific evidence which is acceptable for submission in connection with an application for premarket clearance;

(4) the proper methods and facilities for the manufacture of a product; in other words, GMPs;

(5) on a selective basis, the content of prescription device advertising;

(6) the final decision on public notice of a product defect and on recall of that product plus the assignment of financial responsibility for that recall.

Let me emphasize that this is a summary list only and it does not begin to touch on all the authority granted to the Agency under this legislation. I am sure you have read the Agency's own estimate that there will be more than 70 different regulations required under this law. This list, however, sufficiently demonstrates, I believe, that the authority given to the Agency is different both quantitatively and qualitatively from that granted to them over drugs under the Food, Drug and Cosmetic Act. Only after recognizing this will industry begin to respond adequately to this new circumstance. And response is necessary if industry is to influence the Agency's regulatory reflexes with which it must live for years to come.

Importance of Standards

A third consideration which needs urgent industry recognition is the impact and importance of standards. The early results of the FDA classification project, particularly the Card Panel's decisions, as well as the public pronouncements of various FDA officials, clearly signal the Agency's intent to rely on product performance standards as an important—perhaps the most important—regulatory tool under this new law.

It is my feeling, and one that I know is shared by a number of other attorneys in this area, that too little recognition has been given to the implications of widespread imposition of performance standards on the device and diagnostic industry. Further, too little attention has been paid to current FDA pronouncements regarding, and approaches to, the development of product standards. It is impossible to estimate the number of product standards which will be generated by the new legislation and/or the FDA activity in the device and diagnostic area. It is obvious to any informed observer, however, that the number will be quite large, easily in the thousands. It is of extraordinary importance, therefore, that the process of developing, debating, formulating and implementing standards be thoroughly understood by all concerned. A product performance standard which is just that—a performance standard —can achieve its objective of performance and safety without unduly limiting the innovative manufacturer in his selection of methods, materials and designs to achieve the minimum performance level. However, a product performance standard which reads like a purchase specification will do just the opposite. A product standard which is developed after due consideration for the economic consequences of this standards requirement can adequately balance the benefit-to-risk priorities inherent in any final standard. A product standard which is developed without adequate input from the manufacturer, however, cannot possibly take this very important element of economics into account.

Learning Mode

The FDA, in its current approaches to the development of standards, is, as it admits itself, in a learning mode. I believe that today, it is willing and open to industry inputs on standard content, as well as on procedures for the development of standards. But it is not waiting for that input and it is not going to slow its learning process to wait for that input. I suggest that its current projects show a clear need for the input. These projects show standards being developed by the Agency,

as in the case of the insulin syringe standard, or being developed by third parties under contract with the Agency, as in the case of the defillabrator and pacemaker standards. In each case, there is no clear and formal procedure or timetable for adequate industry consideration, discussion or debate. No time has been given for the development of a consensus with regard to the standards content. There are no formal procedures for public notification, no officially published writings upon which to comment, no procedure for a public meeting to discuss comments and no clear deadline for finalization of the standard itself. Nor has there been any public indication from the Agency as to what it will do with these standards once they are developed. The point is that there are obvious contributions that industry can make to the Agency's programs. Failure to do so will result, not in delaying the programs but, rather, in insuring that when finalized, they will be finalized without adequate industry evaluation and comment.

Better Methods of Communication

Each of these areas I have mentioned—the extent of the FDA commitment to regulating the device area, the breadth of authority granted to them in the new legislation, and the emphasis they are putting on standards and the importance of standards to industry—point to a fourth consideration which critically needs recognition by industry; that is, the need for better methods of communication to and from the Agency. In this area, the *Federal Register* is virtually useless. The Agency and its expert panels, such as the classification panels, industry panels (such as those working on GMPs) and professional associations (such as AAMI and its committees working on pacemaker standards) are creating a veritable blizzard of paper in this area. This problem can only grow as the Agency's regulatory program, such as class meetings, standard development and regulations proposals. The recent blossoming of independent publications dealing with the device and diagnostic industry are, I believe, a response to this obvious need. So too are the steps taken by the FDA, in connection with its classification panel meetings, to develop a mailing list for communicating agendas and minutes, rather than relying on the *Federal Register*. Here again, I feel the Agency is on a learning curve and needs input from industry. Together we must work out better methods of communication. One of the obvious concerns is the small companies for whom the *Federal Register* is not a practical answer. The mailing list concept is much better, as long as all affected parties know of and take advan-

tage of the availability. Only after recognizing the inadequacy of existing communication media to handle current and future needs will industry begin to respond to this enormous need.

Double-Tier Involvement

The final points which I would like to make today have to do with the industry response which I have mentioned. I know that a number of companies have decided to remain passive in this area until the passage of legislation. I do not consider this to be the correct course. The proper approach, I believe, is one which involves an active posture on the part of industry. And this requires a double-tier involvement.

First of all, within the individual companies, it is important to achieve a structure which supports an active interface with the Agency and its activities during these times. Let me describe what we have done at Johnson & Johnson. We have seven companies in the United States engaged, in whole or in part, in the manufacture and sale of devices and diagnostic products. We have formed a temporary task force made up of representatives from each of these companies, along with members of our Law Department. This task force has assumed responsibility for monitoring and becoming involved in, to the extent deemed necessary, current regulatory problems affecting medical devices and diagnostic products in the United States today. The seven company representatives have alternates who stand in their stead in the event of their absence. By assigning responsibilities within this task force, we have found it possible to share the load of tracking 14 classification panels, between 5 and 10 trade and professional associations, the wide variety of standards developments, the *in vitro* diagnostic developments and all the other areas of current FDA interest in the device and diagnostic field. Obviously, not all companies will be able to achieve a structure like ours but it is important, I believe, for management to recognize the need to assign to an individual or individuals responsibility for this area and to assure them adequate time for their activities.

Trade Associations

The second tier for adequate active industry response is through the interested trade and professional associations. We are members of more than half a dozen associations currently active in this field.

These include the Pharmaceutical Manufacturers Association, the American Dental Trade Association, the Othopedic Surgical Manufacturers Association, the Association for the Advancement of Medical Instrumentation, the Health Industry Manufacturers Association, and the Scientific Apparatus Manufacturers Association. Through these associations, we are able to keep informed of current developments and to impact in a concerted and, hence, more effective manner on the Agency and its deliberations as well as on all other activities going on in this area. As the drug industry has shown us, an effective and well-organized trade association can be of substantial benefit in learning to live with and live well with a regulatory agency such as the FDA.

In closing, let me use a phrase which has become a favorite of mine in characterising the need for industry involvement in this developing area. There is no Rumplestilskin in Washington. There is no one there who will turn your common yarn to threads of gold over night. If industry does not devote the personnel and the talent to spinning the cloth, it cannot expect the end result to be a garment that fits properly.

[The End]

VA AND FDA EXECUTE AGREEMENT TO EXCHANGE MEDICAL DEVICE EXPERIENCE DATA

The Veterans Administration and the Food and Drug Administration have executed a Memorandum of Understanding for exchanging medical device experience data gathered in the VA's hospital system. In addition to providing data, the VA will give the FDA technical assistance in the identification and resolution of medical device and diagnostic product problems.

The FDA and the VA will establish telephone and teletype links between the VA Marketing Center and the FDA Bureau of Medical Devices and Diagnostic Products, and will initiate an education and awareness program to acquaint VA health personnel with the information exchange program.

CCH FOOD DRUG COSMETIC LAW REPORTER, ¶ 41,371

BILL INTRODUCED TO STRENGTHEN COSMETIC SAFETY RULES

Senator Thomas Eagleton has introduced Senate Bill 1681, to amend the Federal Food, Drug and Cosmetic Act with respect to cosmetic safety. The bill would grant clear statutory authority to the Food and Drug Administration (FDA) to promulgate substantive regulations in the areas of ingredient labeling and safety substantiation. Under the bill, the Agency would have the authority to require premarket submission of safety test data. The FDA would also be allowed to require specific safety testing for the setting of screening levels for toxicity, sensitization, and irritancy of cosmetics, and to prohibit certain ingredients, prescribe tolerance limits, require added labeling, or ban a cosmetic. The measure would require manufacturers to register with the FDA, submit formulas for cosmetic products, and periodically forward to the Agency consumer complaints about adverse reactions. It would broaden the Agency's powers of inspection of cosmetic facilities, as well as provide for ingredient, cautionary, and informational labeling.

The bill, which was introduced May 7, has been referred to the Committee on Labor and Public Welfare.

CCH Food Drug Cosmetic Law Reporter

FDA EMPLOYEES HELD IMMUNE FROM SUIT

Food and Drug Administration (FDA) employees who had made official inspections of plaintiff's drug establishment and taken samples of certain drugs were immune from suit for violating plaintiff's right to be free from unlawful searches and seizures since the FDA employees acted clearly within the authority conferred upon them by the Federal Food, Drug and Cosmetic Act. The absence of probable cause or a search warrant did not make the searches and seizures illegal, because the Supreme Court in *United States v. Biswell*, 406 U. S. 311 (1972), held that inspections and collections in business establishments made pursuant to statute did not require probable cause or search warants, and several courts have affirmed application of that doctrine to inspections and collections made under the FDC Act.

Dianovin Pharmaceuticals, Inc., et al. v. Fry, et al.,
CCH Food Drug Cosmetic Law Reporter, ¶ 38,014

GENERAL ACCOUNTING OFFICE REPORT ON IN VITRO MEDICAL DIAGNOSTIC PRODUCTS

Report by the Comptroller General titled "Public Hazards from Unsatisfactory Medical Diagnostic Products." Released April 30, 1975.

A General Accounting Office study conducted to see how effective federal controls are in insuring the reliability of *in vitro* medical diagnostic products has concluded that Food and Drug Administration (FDA) regulation of such diagnostic products has been ineffective. The report noted that the FDA did not have a formal program to control diagnostic products until two years ago and that the present program providing for voluntary registration of *in vitro* diagnostic product manufacturers has not been effectively implemented. The report estimated that only about 13 percent of all medical diagnostic products are made by manufacturers registered with the FDA.

A Center for Disease Control (CDC) official estimated that 25 percent of all diagnostic test products are unreliable. A CDC test of 44 *in vitro* diagnostic test kits found that about 73 percent of the kits were unsatisfactory for diagnostic use. Although the CDC tests were limited in number, both the CDC and other studies indicate that information on the unacceptability of certain *in vitro* diagnostics has been available for many years and that such unsatisfactory products have been a continua problem.

The report stressed the need for clarification of the FDA's authority over biological *in vitro* diagnostics, and recommend that the FDA take immediate steps to strengthen its control program for *in vitro* diagnostics. The GAO specifically suggested that the FDA hasten development of diagnostic product class standards, establish criteria under which *in vitro* diagnostics must be manufacturerd, and implement an adequate surveillance program to assure compliance to labeling and performance standards. It was also recommended that the FDA expand operation of the problem-reporting system for diagnostic products, work more closely with foreign users of *in vitro* diagnostics produced in the United States, and evaluate the need to allocate additional resources to an expanded *in vitro* diagnostic product program.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,376

FDA ANNUAL REPORT NOTICE

The Food and Drug Administration's Annual Report for the year 1974 will be available for distribution later this summer. The Report reviews food, drug and cosmetic regulation for the period, and contains summaries of significant court decisions. For a single copy, the address is:

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