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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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FOOD DRUG COSMETIC LAW JOURNAL

Table of Contents . . . . July, 1975

Volume 30 Number 7

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

REPORTS

TO THE READER

Annual Meeting of the American Bar Association. The following papers were presented at the Joint Program of the Administrative Law Section and the Food, Drug and Cosmetic Law Committee of the Corporation, Banking and Business Law Section of the American Bar Association Meeting, which was held in Honolulu, Hawaii on August 15, 1974.

Howard S. Epstein's article, "New Directions for Administrative Regulations," is a retrospective look at the Food and Drug Administration's regulation implementing the 1962 amendments to the Federal Food, Drug and Cosmetic Act. Mr. Epstein, whose article begins on page 384, is Assistant Chief, Consumer Affairs Section of the Antitrust Division in the U. S. Department of Justice.

"Recent Procedural Developments in FDA Regulations and Legislative Proposals" is the subject and the title of an article by *David A. Seligman*. Mr. Seligman, a member of the New York and New Jersey bars, analyzes the FDA's hearing regulations proposed in 1973 and discusses the Agency's practice of treating drug products by class. His article begins on page 396.

Food Update XIV. The following papers were presented at the Food and Drug Law Institute's Food Update XIV, which was held in Key Biscayne, Florida on April 20—24, 1975.

Eugene I. Lambert points out the need for the food industry to focus its attention on the nature of criminal liability in his article "Dancing with the Gorilla." Mr. Lambert is a partner in the law firm of Covington & Burling and his article begins on page 410.

"A Rose by Any Other Name" is *Murray D. Sayer's* analysis of the common or usual name regulations issued by the FDA. Mr. Sayer, Assistant General Counsel of General Foods begins his article on page 415.

Norman Bristol, Senior Vice-President and General Counsel of the Kellogg Company discusses the fortification of food in an article beginning on page 421. The article is "How Does One Get Rid of a Dead Horse?"

Pharmaceutical Update V. The following papers were presented at the Food and Drug Law Institute's Pharmaceutical Update V, which was held in New York City on May 22 and 23, 1975.

Robert L. Spencer, Acting Chief of the Precedent Regulations and Legislative Activities Branch of the Bureau of Drugs in the Food and Drug Administration, talks about the Agency's plans to revise its abbreviated new drug application policy. Titled "New Concepts in Abbreviated NDAs," the article begins on page 426.

"The FDA's Acceptance of Foreign Clinical Data," beginning on page 433, discusses the FDA's regulation on international research. It is written by *William E. Ragolia*, an attorney with the legal department of CIBA-GEIGY Corporation.

Eighteenth Annual Educational Conference of the FDLI and the FDA.

"Devices to Control Devices" by *Joseph R. Radzins*, Food and Drug Counsel of the Dow Corning Corporation, was presented at the 18th Annual Educational Conference of the Food and Drug Law Institute and the Food and Drug Administration, which was held in Washington, D. C. on December 3 and 4, 1974. Beginning on page 440, it highlights topics pertinent to regulations concerning the medical devices industry.

Vol. 30, No. 7 July, 1975

Food·Drug·Cosmetic Law Journal

New Directions for Administrative Regulations

By HOWARD S. EPSTEIN

Mr. Epstein Is Assistant Chief of the Consumer Affairs Section of the Antitrust Division in the United States Department of Justice.

I AM PLEASED to discuss a topic that I have wanted to explore for some time. The inducement of this setting to present my views has finally "forced" me to organize my thoughts about the development of the Food and Drug Administration's (FDA's) regulations to implement the 1962 amendments[1] to the Food, Drug and Cosmetic Act which required the removal from the marketplace of ineffective drugs. In this era of heavy emphasis on "consumerism," it is interesting to remember the Federal Food, Drug and Cosmetic Act was the first consumer legislation.

The DESI[2] review program led to one of the most innovative regulatory procedures ever developed by an agency. When I came to the Department of Justice in November of 1969, drug withdrawal orders were first being challenged in the courts. I have been part of the historic development of most of the case law on the Agency's hearing regulations. While I am really a prosecutor, not an administrative law attorney, my experiences have led me to the conclusion that, over the years, the FDA's rule-making has been substantially the result of court litigation. It is not, as one would assume, rule-

[1] 76 Stat. 780 (1962).

[2] Drug Efficacy Study Implementation is the term used by the FDA for the program of reviewing and acting on all drugs required to meet the efficacy requirements of the 1962 amendments, which added "and effective" to the definition for "new drugs" which included only safety.

making followed by court challenges. The DESI cases seem to prove this theory.

After reviewing the number of drug products subject to the efficacy review, the Agency concluded there was no way humanly possible to carry out its statutory mandate without some innovative and creative administrative procedures.

First, and I think most significant, the Agency correctly took the position that the sponsor or holder of an approved NDA[3] had the burden of showing the efficacy of the drug in question in order to continue its marketing. Such proof initially took the form of submission by manufacturers of the best evidence in the form of published literature to the appropriate NAS-NRC[4] review panels. These panels reviewed the data submitted by the manufacturers and forwarded their evaluations to the FDA. The Agency believed, and relied on the assumption, that the drug manufacturers had submitted their best, and complete, evidence to support the efficacy of their drugs to the panels.

Streamlined Administrative Procedure

Accordingly, the Agency's next step was to devise a streamlined administrative procedure to expedite the removal of drugs found to be ineffective from the marketplace. At this point, the Administrative Conference of the United States provided a solution. The Administrative Conference had strongly recommended that administrative agencies seek ways of streamlining their proceedings to reduce the amount of delay in reaching final determinations in agency proceedings.[5]

As a sidelight, it is interesting to note that administrative agencies originally established to have special expertise to deal expeditiously with problems to avoid the unreasonable delay of court proceedings have now come 180 degrees. It is the courts who can give judicial answers years faster than it now takes most administrative agency proceedings to grind to a final determination.

It was the FDA's view that the best way to implement the 1962 amendments was to adopt the suggestion of the Administrative Conference, and adopt an analogy to the "summary judgment" proceeding of Rule 56, F. R. Civ. Proc. This procedure would expedite the pro-

[3] New Drug Application: the mechanism by which the manufacturer obtains marketing approval from the Agency for a drug.

[4] To review all marketed drugs, the Agency contracted with the National Academy of Sciences-National Research Council which in turn assigned review to 27 different panels according to the therapy classification of the drugs.

[5] 38 U. S. L. W. 2658.

cessing of several hundred actions for those drugs found to be ineffective and for which previously approved marketing approval would have to be withdrawn. Indeed, the DESI review program extended to more than 4,000 drug formulations marketed by 237 firms.

Withdrawal of Products

This concept of withdrawal of products without protracted hearings was one of the most creative and effective innovations in the annuals of administrative law procedures. It logically was bottomed on the premise that if the manufacturer had given his best evidence to the NAS-NRC review panels, there woud be no further or different evidence the manufacturer could produce. The Sixth Circuit concurred in that view, succinctly stating: "We agree with the Commissioner that: 'No amount of examination and cross-examination can change the scientific studies and the data reported into something they are not.'"

That language is from the *Upjohn* case,[6] the first court test of an NDA withdrawal of antibiotic certification[7] under the DESI review.

It is amazing that the Agency started with one of the hardest cases and prevailed. The fixed-combination antibiotics were some of the most widely prescribed drugs in the world, yet the Court of Appeals had little difficulty in sustaining the Agency's position. In addition to their wide acceptance in the medical community, the drugs were found by the NAS-NRC panels to be "ineffective as a fixed combination," a category not originally included in those announced by the Agency.[8] I think that the inclusion of novobiocin in the Panalba products made the *Upjohn* case easier for the Agency because of novobiocin's well-known side effect of causing liver disorders. Thus, it was easier to argue for withdrawal of a drug with evidence of a significant medical hazard in using the product.

Clinical Usage

Further, the record in *Upjohn* reveals another strong basis of support for the FDA's position; the drug manufacturer relied on the extensive

[6] *Upjohn Co. v. Finch,* CCH Food Drug Cosmetic Law Reporter ¶ 80,301, 422 F. 2d 944 (CA-6 1970).

[7] Approval of antibiotic drugs took a different form than the straight NDA; antibiotic drugs received Agency certification (approval) of each batch prior to shipping. This is based on underlying Agency regulations which detail the criteria for various types of antibiotic drugs acceptable for certification.

[8] The original categories were "ineffective," "possibly effective," "probably effective" and "effective."

clinical usage of the product to support its efficacy in lieu of any adequate and well-controlled studies.

The result in *Upjohn* not only upheld the Agency's withdrawal without a hearing, but it was also a strong precedent for the Agency's regulations that set out the criteria for adequate and well-controlled studies, the basis for granting an evidentiary hearing to a manufacturer before withdrawing approval for marketing its drug.

On the same day the Commissioner issued his final order on the Upjohn products, he also issued regulations establishing the criteria for adequate and well-controlled clinical investigations necessary to demonstrate the efficacy of drugs subject to the requirements of the 1962 amendments.[9]

Opportunity for Comment

These regulations were immediately challenged by the Pharmaceutical Manufacturers Association (PMA) in a District Court action in Delaware.[10] While the *Upjohn* case was pending in the Sixth Circuit, Judge Latcham, in the Delaware suit, had to decide the challenge to the Agency's regulatory concept that, in effect, would allow the withdrawal of drugs from the marketplace without the administrative evidentiary hearing. The District Court in Delaware essentially rejected all of the plaintiff's substantive arguments but relied on the procedural issue that the regulations were issued without notice and opportunity for comment in violation of Section 4 of the Administrative Procedure Act (APA), 5 U. S. C. 553. It ruled that the Agency would have to follow the mandate of the APA. After the decision in January 1970, the Agency republished the proposed regulations in the *Federal Register* during February 1970 and allowed the appropriate time for comment by interested parties. The final regulations were published on May 8, 1970.[11] Again, the PMA challenged the regulations.[12] This time Judge Latcham had no difficulty in upholding the regulations; the Agency had satisfied the APA requirements and the Court determined that the regulations "reasonably carry out the Congressional mandate that all claims of efficacy for marketed drugs must be supported by substantial evidence." The Delaware court had the benefit of the *Upjohn* decision, but it is clear that Judge Latcham followed his own earlier in-

[9] 34 *F. R.* 14596 (Sept. 19, 1974).

[10] *Pharmaceutical Manufacturers Association v. Finch*, CCH Food Drug Cosmetic Law Reporter ¶ 80,292, 307 F. Supp. 858 (DC Del. 1970).

[11] 35 *F. R.* 7250, subsequently codified 21 CFR 130.12, 130.14.

[12] *Pharmaceutical Manufacturers Association v. Richardson*, CCH Food Drug Cosmetic Law Reporter ¶ 40,429, 318 F. Supp. 301 (DC Del. 1970).

clinations that the regulations were a reasonable interpretation of the Congressional mandate imposed on the Agency.

The watershed had been passed and it was downstream with the current for the DESI regulations. The FDA's regulatory efforts to close the time gap since enactment of the 1962 amendments and remove ineffective drugs from the market had received important judicial endorsement.

Demonstrate Efficacy

However, there were still more court tests of the regulations. After the PMA's challenge had failed, individual drug companies challenged the hearing regulations as their own products were ordered withdrawn for failure to demonstrate efficacy. Pfizer challenged its denial of a hearing in the withdrawal of Signemycin.[13] The Second Circuit affirmed the withdrawal of the products without an administrative hearing before the Agency. CIBA-Geigy, which had refused to come forward with any evidence to support a hearing request on the withdrawal order for Ritonic capsules, challenged the regulations on the issue of its absolute right to a hearing.[14] The Second Circuit totally rejected this argument, finding the regulations "to be reasonable and salutary." It again affirmed the FDA's position that if the manufacturer failed to meet the burden of producing adequate and well-controlled studies to show the efficacy of the drug(s) in question, no hearing had to be held in advance of withdrawal.

In retrospect, I think the early court endorsements of the regulations were made easier by the fact that the drugs in issue were combination products. The Agency was able to show that one or more of the components caused harmful side effects and that the dosage levels contained in the combination were not sufficient to treat the condition for which the component was included. For example, if two antibiotics were in the combination and one of them was in a dosage level too low for effective treatment, if the amount of the combination drug administered was increased to an effective level for that component, then an overdose of the other component resulted.

Distinct Advantage

In other words, the Agency had a distinct advantage against the fixed-combination drugs because the manufacturers relied on the ef-

[13] *Pfizer, Inc. v. Richardson,* CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,425, 434 F. 2d 536 (CA-2 1970).

[14] *CIBA-Geigy Corp. v. Richardson,* CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,515, 446 F. 2d 466 (CA-2 1971).

ficacy of the individual components and decided that if the components were good alone, a combination of antibiotics would treat patients' diseases even better. The manufacturers, however, produced no studies to support this proposition.

In all of these cases I have discussed, the courts of appeals had granted stays of the withdrawal orders pending full court review of the manufacturers' challenges to the final orders as provided by Section 505 of the Act.[15] Then, at the end of 1971, American Cyanamid moved for a stay of the withdrawal order against its Achrocidin products.[16] Judge Coffin, sitting alone as the motions judge for the First Circuit Court of Appeals, denied the motion for a stay on the grounds that the petitioner was unlikely to prevail on the merits. His opinion fully reviewed Cyanamid's arguments as to the merits of its position and rejected them. Thus, the *Cyanamid* decision further closed the time gap by denying manufacturers the ability to continue to market their product during the pendancy of the appeal from the Agency's withdrawal order.

In October 1971, based on the *Upjohn* and *Pfizer* decisions, the Agency published its general policy statement on fixed-combination prescription products.[17] Here, the Agency made its job easier by using judicial decisions to establish an Agency policy that aided in removing ineffective combination drugs from the market.

Hardest Job

With the hardest job behind it, the Agency really stubbed its toe when it got to the "easy" cases—withdrawal of nonantibiotic drugs found to be ineffective by the NAS-NRC review panels.

In August 1968, USV Pharmaceutical Corporation filed a suit for declaratory relief in the Eastern District of Virginia seeking to invalidate the FDA's intended withdrawal of USV's bioflavinoid products.[18]

USV's suit raised an entirely new challenge to the Agency's withdrawal procedures on grounds different from those posited in the antibiotic cases. It claimed that its products were not "new drugs" within the meaning of the Food, Drug and Cosmetic Act. It said that its products were "grandfathered" under the transition provisions of the

[15] 21 U. S. C. 355(h).

[16] *American Cyanamid Co. v. Richardson*, CCH Food Drug Cosmetic Law Reporter ¶ 40,616, 456 F. 2d 509 (CA-1 1971).

[17] 36 *F. R.* 20038; 21 C. F. R. 3.86.

[18] *USV Pharmaceutical Corp. v. Secretary*, Civil No. 4915-A (DC Va. E. D. 1968).

1962 amendments[19] and therefore not subject to the efficacy requirements of the statute or to the attendant requirements of producing adequate and well-controlled investigations of efficacy to support continued marketing. USV sought a declaration that its products were exempt from the regulatory withdrawal procedures. After the District Court's ruling that the drugs were exempt from efficacy review under the 1962 amendments, the Fourth Circuit reversed, holding that the products could not qualify for exemption.[20]

"Me Too" Drugs

In South Carolina, more trouble was brewing. A group of drug manufacturers and distributors of drugs containing pentylenetetrazol and/or nicotinic acid brought suit challenging the applicability to their products of withdrawal proceedings by the Agency against NDA holders of drugs with these ingredients. They based their claim on the fact that their products were not NDA drugs, although they contained the same active substances.[21] The District Court entered an order remanding the case to the Agency to determine whether the drugs were "new drugs." Thus, the question of the status of "me too" drugs under the DESI review program was brought into focus. The Agency adopted the position that "me too" drugs were subject to the effects of any withdrawal order against NDAs for drugs of the same composition. The District Court held that the declaratory action was properly before it and that it could determine whether plaintiff's drugs required NDAs in order to be lawfully marketed. But the court found concurrent jurisdiction with the FDA and held that the Agency "as the more able arbiter" should hold administrative hearings to resolve the issue. The Fourth Circuit Court of Appeals reversed, holding that the Act conferred no jurisdiction on the FDA and that the District Court had to resolve the issues.[22]

Hynson, Westcott and Dunning brought suit in the District Court in Maryland for declaratory relief from the proposed withdrawal of NDAs for Lutrexin and Trexinest on the grounds that the products were not new drugs, or, alternatively, that there was *not* a lack of sub-

[19] Sec. 107(c)(4), P. L. 87-781; 21 U. S. C. A. Sec. 321 note (1970 Ed.).

[20] *USV Pharmaceutical Corp. v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,717, 466 F. 2d 455 (CA-2 1972).

[21] *O'Neal, Jones and Feldman, Inc. et al. v. Richardson*, No. 70-1001 (DC S. C.).

[22] *Bentex Pharmaceuticals Inc. v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,665, 463 F. 2d 363 (CA-4 1972).

stantial evidence for the efficacy of the drugs.[23] The District Court dismissed, holding that the issues presented were within the primary jurisdiction of the Agency. The Fourth Circuit reversed on the grounds that, among other things, the submissions proffered by Hynson were of sufficient character to raise questions of fact warranting a hearing.[24] So, after all the victories in the tough cases, the Agency was faced with its first situation in which a hearing would have to be held before the final order of withdrawal. Judge Latcham's caveat in the *PMA* case concerning the specific case where a hearing would be required, had finally come true.

The stage was now set for the Supreme Court to resolve the Agency's regulatory mechanism established to implement the 1962 amendments to the Act.

Supreme Court Bag

One more case was added to the Supreme Court bag. While the Second Circuit had upheld the withdrawal of Ciba's Ritonic products, Ciba had also filed a declaratory action in New Jersey seeking to have the drugs declared exempt from the new drug provisions by virtue of the "grandfather clause" of the 1962 amendments.[25] Judge Augelli dismissed the suit on the defendants' motion that the Court lacked jurisdiction over the subject matter because the issues were primarily vested in the Agency. The Third Circuit affirmed.[26]

On June 18th, 1973, the Supreme Court rather tightly tied all of the loose ends together and gave the FDA an extensive victory. The Agency's rules were more thoroughly vindicated than even we who had defended its actions all along dared hope for. All of the legal issues the Agency had argued to the courts for almost four years were upheld.

However, the Supreme Court affirmed the Fourth Circuit's view that Hynson, Westcott and Dunning was entitled to an administrative hearing on whether Hynson's submissions were adequate and well-controlled under the regulations. The reason given was that there was a "contrariety of opinion within the Court concerning the adequacy of Hynson's submission." In addition, the Supreme Court indirectly upheld the Agency's pending over-the-counter (OTC) drug review in the *Bentex* decision.

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[23] *Hynson, Westcott and Dunning, Inc. v. Finch*, No. 2112 (DC Md.).

[24] *Hynson, Westcott and Dunning, Inc. v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,666, 461 F. 2d 215 (CA-4 1972).

[25] *Ciba Corporation v. Richardson*, No. 1210-70 (DC N. J. 1970).

[26] *Ciba Corporation v. Richardson*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,676, 463 F. 2d 225 (CA-3 1972).

Summary Judgment Procedures

But, the Agency's summary judgment procedures almost foundered in another appellate proceeding before the Supreme Court decisions. Again it was USV's bioflavinoids. During the pendency of USV's declaratory judgment suit, the FDA withdrew the NDAs for USV's bioflavinoid drugs since there was no stay in effect. USV immediately petitioned for review of that order in the D. C. Circuit. That court found that the procedures followed by the Commissioner in withdrawing the NDAs "were fundamentally defective." The court went a big step further and held that the summary judgment rule required the Commissioner to come forward with at least a "prima facie case" for denial of a hearing.[27] This decision appeared on its face to force a radical alteration in the Agency's procedure for withdrawals. One of the problems was that the USV situation was highly complicated by procedural difficulties as well as by inarticulately drafted *Federal Register* notices. In October 1970, when the Commissioner issued his final order for the bioflavinoid products, the language was far from the increasingly more sophisticated *Federal Register* notices published by the Agency after a few of the decisions had been announced by the circuit courts. Because the facts in *USV* did not enhance the government's position, no petition for certiorari was sought. But the Supreme Court subsequently saved the day anyway.

When the opinions of the Supreme Court spelled out the Agency's authority, the decision not to go for certiorari in the second *USV* case was justified. In the *Hynson* decision, the Supreme Court said, "The drug manufacturers have full and precise notice of the evidence they must present to sustain their NDAs, and under these circumstances we find the FDA hearing regulations unexceptional on any statutory or constitutional ground." The D. C. Court of Appeals holding in *USV* seemed to be significantly undercut, if not entirely vitiated.

Resounding Victory

Less than three years after the Delaware District Court's decision, and only four years after the DESI program of removal of ineffective drugs had gone into high gear, the FDA had gained one of the most resounding victories ever achieved for an agency's administrative procedures.

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[27] *USV Pharmaceutical Corp v. Richardson*, CCH Food Drug Cosmetic Law Reporter ¶ 40,717, 466 F. 2d 455 (CA DofC 1972).

However, the D. C. Circuit had not had its final say on the subject. Acting under its summary procedures, the Agency withdrew, in 1973, New Animal Drug Applications for diethylstilbestrol, commonly known as DES. The D. C. Circuit, while retreating somewhat from its "prima facie case" requirement, held that the manufacturers of DES had not been provided adequate notice for the grounds stated by the Agency for the withdrawal orders.[28]

Then, the same court spoke again on the same subject in the spring of 1974 in its *Cooper Laboratories* decision.[29] A majority of the panel supported the Agency's procedure in the *Cooper* case and apparently laid the "prima facie case" problem to its proper rest. But Judge Leventhal wrote a vigorous dissent. While acceding to the Supreme Court's ruling in *Hynson*, Judge Leventhal was still of the view that the FDA's procedures for summary withdrawal were not fair to the drug manufacturers.

Meanwhile the Agency, heeding the sharp questioning of the Supreme Court at oral argument on the drug cases in April 1973, and the setbacks of the *Hess and Clark* and *Chemetron* decisions, revised its regulations somewhat as to the mechanics of its hearing regulations.[30]

Rebuttal

The PMA, joining as *amicus* for the first time in Cooper's petition to the D. C. Circuit for a rehearing, brought the new regulations into question. The petition was denied[31] and Judge Leventhal wrote that the modified summary judgment procedures of the Agency would operate to correct the problems the D. C. Circuit found in *Hess and Clark*. Essentially, the modified regulations require the Commissioner to set forth his findings and conclusions in detail when denying a hearing. More importantly, where no detailed regulations exist, the Commissioner's findings must be given to the person requesting a hearing for rebuttal. The rebuttal must then be analyzed by the Agency and answered before a withdrawal order can be issued

[28] *Hess and Clark et al. v. FDA*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,073, 495 F. 2d 975 (CA DofC 1974)and *Chemetron Corp. et al. v. HEW et al.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,074, 495 F. 2d 995 (CA DofC 1974).

[29] *Cooper Laboratories, Inc. v. Commissioner*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,128, 501 F. 2d 772 (CA DofC 1974).

[30] 39 *F. R.* 9750 (March 13, 1974).

[31] Slip Opinion, June 26, 1974.

While the Supreme Court decisions seemed to lay all the issues to rest, the question of the adequacy of submissions to support efficacy and thus warrant the FDA's granting a hearing is somewhat cloudy at this point. Since the Supreme Court required a hearing for Hynson's submissions, the Third Circuit in the *Squibb* case[32] could not decide whether Squibb's submissions were sufficient to warrant a hearing. The court remanded the withdrawal of NDAs for Squibb's diuretic-potassium drugs to the Agency for further proceedings.

Innovative Approach

In the midst of the cases involving DESI withdrawals, the FDA had a changing of the guard. William Goodrich, the first and only Assistant General Counsel for food and drugs (essentially the FDA's general counsel) retired. Mr. Goodrich cannot be given enough credit for his vigorous and innovative approach to the enforcement of the Food, Drug and Cosmetic Act. Under his regime, the courts hammered out the precedents for the Agency's actions. But most important, his summary judgment regulations are a landmark, now fully vindicated by the highest court in the land.

His successor, Peter Hutt, who arrived in September of 1971, has developed a different approach. The *Federal Register* has now become the most important tool of the FDA. In announcing Agency regulatory action, the *Federal Register* notices now contain lengthy and extensive commentary and justification by way of preamble to the proposed regulations. Those of us who deal with them know these notices as "Peter Preambles." I cannot improve on the comments, already rendered on these notices, by the distinguished elder statesman of our Food and Drug Bar, Thomas Austern.[33] I commend his comments to you.

Peanut Butter Hearings

After this lengthy discourse, I suppose some summing up is appropriate. The developments of the FDA's regulatory procedures over the last few years give rise to several conclusions. First, I think that

[32] *E. R. Squibb & Sons, Inc. v. Weinberger*, CCH Food Drug Cosmetic Law Reporter ¶ 40,993, 483 F. 2d 1382 (CA-3 1973).

[33] H. Thomas Austern, "The Regulatory Gospel According to St. Peter," 29 Food Drug Cosmetic Law Journal 316 (June 1974).

the era of protracted regulatory proceedings at the FDA—such as the peanut butter and vitamin hearings—are over. It appears that the Agency is moving to procedures that call for comments on proposed regulations by way of extensive written submissions. The food and drug industry will have to marshal its evidence and arguments and present them in writing rather than via cross-examinations in a trial setting. Secondly, I think that we will see less court development of Agency authority and more reliance on the regulatory mechanism of *Federal Register* notice, comment and promulgation. Subsequent court challenges to the Agency's regulations will be more difficult because there will be a better administrative record most effectively summarized and set forth in the *Federal Register*. Courts will be more loath to disturb the Agency's well-documented conclusions.

I suspect that the real answer is that we will all have to wait and see what develops. That is what makes practicing law in this area so fascinating.

I should note that the case law and the procedures to date have been concerned with those drugs found to be ineffective. How the Agency will deal with the "possibly effective" and "probably effective" drugs is not clear at this time. I would assume that manufacturers whose drugs are in those categories are presently conducting adequate and well-controlled investigations to support their drugs. **[The End]**

Recent Procedural Developments in FDA Regulations and Legislative Proposals

By DAVID A. SELIGMAN

Mr. Seligman Is a Member of the New York and New Jersey Bars.

THE ASSIGNMENT FOR THIS PRESENTATION was to review and comment upon recent procedural developments, both in new Food and Drug Administration (FDA) regulations and in important pending legislative proposals, which reflect new or innovative approaches to regulation of the drug industry.

Rather than attempting a "survey" presentation, I thought it might be better to concentrate basically upon certain questions which I believe are presented in the regulations concerning the "requirements of notice of opportunity for hearings" and the "class" approach to drug regulation as exemplified by the over-the-counter (OTC) review. I will finish with a few comments on expected future developments.

The "Drug Amendments of 1962,"[1] amended the Federal Food, Drug and Cosmetic Act to require the refusal of approval of a new drug application (NDA) if there was "...a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof."[2]

"Substantial evidence" was defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. . . ."[3]

[1] P. L. 87-781, 76 Stat. 780 (Oct. 10, 1962).

[2] P. L. 87-781, Sec. 102(c) amending 21 U. S. C. Sec. 355(d).

[3] See footnote 2.

Drugs whose NDAs had been allowed to become "effective"[4] prior to the 1962 amendments had a period of two years before they could be questioned as to lack of "substantial evidence" of effectiveness.[5]

Although the FDA first attempted to review such pre-1962 drugs utilizing its own resources, only small progress was made. On June 17, 1966, a contract was signed by the FDA with the National Academy of Sciences-National Research Council (NAS-NRC) for a drug efficacy study.[6]

As a result of the efficacy review of drugs approved prior to 1962, a number of suits between the Agency and industry arose. These resulted in decisions changing many concepts and procedural aspects of drug law. Included among these cases were four decisions of the Supreme Court issued on June 18, 1973 (the *Hynson*,[7] *Bentex*,[8] *Ciba*[9] and *USV*[10] cases), a decision of the Court of Appeals for the District of Columbia involving USV Pharmaceutical Corporation,[11] as well as the *Hess and Clark*,[12] *Chemetron*,[13] and *Cooper*[14] cases, among others. These suits have been well commented upon in the past by a number of individuals[15] and I will only briefly mention a few of the cases in direct relation to specific points.

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[4] 21 U. S. C. 505, prior to Drug Amendments of 1962, allowed an NDA to become "effective" sixty days after its filing date, rather than requiring specific approval.

[5] *Supra* note 1, Sec. 107(c)(3)(B).

[6] "Drug Efficacy Study," Final Report to the Commissioner of Food and Drugs of the FDA from the Division of Medical Sciences, National Research Council (1969).

[7] *Weinberger v. Hynson, Westcott and Dunning, Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,930, 93 S. Ct. 2469, 412 U. S. 609 (1973).

[8] *Weinberger v. Bentex Pharmaceuticals, Inc.*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,932, 93 S. Ct. 2488, 412 U. S. 645 (1973).

[9] *Ciba Corp. v. Weinberger*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,933, 83 S. Ct. 2495, 412 U. S. 640 (1973).

[10] *USV Pharmaceutical Corp. v. Weinberger*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,931, 93 S. Ct. 2498, 412 U. S. 655 (1973).

[11] *USV Pharmaceutical Corp. v. Secretary of HEW*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 40,717, 466 F. 2d 455 (CA DofC 1972).

[12] *Hess and Clark, Division of Rhodia, Inc. v. FDA*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,073, 495 F. 2d 975 (1974).

[13] *Chemetron Corp. et al. v. HEW*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,074, 495 F. 2d 995 (1974).

[14] *Cooper Laboratories, Inc. v. The Commissioner of the FDA*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,128, CA DofC, No. 72-1866 (April 19, 1974).

[15] Levine, "Recent 'New Drug' Litigation Involving the 'Grandfather Clause' and Hearing Rights," 28 *The Business Lawyer* 769 (1973); McMurray, "Legal Update Overview of Recent Judicial and Regulatory Developments in Rx and OTC Law," presented at Pharmaceutical Update IV, May 22, 1974. See also "1973 Court Cases Involving Rule-making: Implications for Federal Regulations," 28 FOOD DRUG COSMETIC LAW JOURNAL 661, *et seq.* (Nov. 1973).

FDA Hearing Regulations

On December 21, 1973, the FDA published proposed regulations in the *Federal Register*[16] entitled "Proposed Requirements for Notice of Opportunity for Hearing and Appearance."

As stated in the preamble to these proposed regulations,[17] the purpose of the revision was ". . . in order clearly to set forth . . . (the) principles established by the Supreme Court Decisions."

The proposed regulation provided that: "The notice . . . of an opportunity for a hearing . . . will state the reasons for . . . (the Commissioner's) action and the grounds upon which he proposes to issue his order."[18]

The regulations then provided that if the request for hearing in response to this notice did not present a substantial issue of fact, a hearing would be denied.[19]

Comments[20] filed concerning the lack of specificity required in a notice of opportunity for hearing under this provision, and the failure of the provision to follow the holdings of the courts in *USV, Hess and Clark,* and *Chemetron* concerning the degree of specificity required in such notices, in order for the Commissioner to exercise summary judgment in denying a hearing (*Cooper* had not yet been decided), resulted in an unusual approach by the FDA to this notice provision.

The final regulations now provide for two types of notice of opportunity for hearing:

(1) a general notice, stated to be ". . . sufficient to initiate a hearing, but . . . not sufficient immediately to initiate summary disposition;" and

(2) a specific notice.[21]

Specific Notice

The specific notice could either refer ". . . to specific requirements in the statute and regulations with which there is a lack of compliance, or . . . (provide) a detailed description and analysis of the specific facts resulting in the notice."[22]

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[16] 38 *F. R.* 35024.

[17] 38 *F. R.* 35024, preamble paragraph number 6.

[18] *Supra* note 16, proposed regulations 21 CFR 130.14(a), 146.1(d)(1).

[19] *Supra* note 16, 21 CFR 130.14(f) as proposed.

[20] Comments dated March 26, 1974, filed by the Pharmaceutical Manufacturers Association (PMA), pp. 3, 4 and 5.

[21] 39 *F. R.* 9750 (March 13, 1974), preamble to regulations, 21 CFR 130, 146.

[22] 21 CFR 130.14(a)(1), now 314.200(a)(1). See also 21 CFR 146.1, now 430.30(d)(1).

Certain questionable points yet remain, however, on the notice provisions in these regulations. First, although the preamble states that a specific notice referring to specific regulations (rather than one analyzing all the facts in detail) is sufficient for summary judgment under *Hynson,*[23] I question whether this point was sufficiently focused on and would be upheld as such "sufficient notice" except in perhaps an unusual case.

With respect to this point, the preamble itself quotes from *Hess and Clark:*[24]

"Hynson in effect reaffirms the propriety of administrative summary judgment, if taken in a context where the pleadings on their face 'conclusively' show that the hearing can serve no useful purpose. It did not overturn USV's requirement that the agency make some showing as a predicate for summary adjudication. It rather found that such a showing and predicate was supplied by particularized regulations setting forth precisely what the manufacturer was required to supply *and by findings that the study adduced was conclusively deficient.*" (Emphasis supplied.)[25]

A second point in question is the section of the regulation which provides that:

"Where a general or specific notice of opportunity for hearing is used and the person(s) requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Bureau of Drugs concludes that summary judgment against such person(s) should be considered, he shall serve upon such person(s) by registered mail a proposed order denying a hearing."[26]

However, there is no requirement in the regulations that this order responding to a request for hearing, after a general notice, be specific either as to the factual basis or even the regulatory basis for the proposed summary judgment proceeding.

We do note that the preamble to the regulation states: ". . . in order to deny a hearing the Commissioner must review the analysis submitted by the person requesting the hearing and must reply to each specific contention made."[27]

This brings up the legal significance of a preamble to a regulation which, as is noted later, will be covered by the FDA in procedural regulations scheduled for future publication.

Identical, Related and Similar Drugs

Another question concerns the provisions of the regulation on "identical, related and similar" drugs.

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[23] *Supra* note 21, p. 9751.
[24] *Supra* note 12.
[25] *Supra* note 21, p. 9751.
[26] 21 CFR 130.14(g)(3), now 314.200(g)(3). See also 21 CFR 130.14(g)(2), now 314.200(g)(2).
[27] *Supra* note 21, comment 2, p. 9754.

These regulations provide that: "A notice of opportunity for hearing encompasses all issues relating to the legal status of the drug product(s) subject to it, including identical, related, and similar drug products as defined in Sec. 130.40."[28]

Section 130.40[29] defines identical, related, or similar drugs as including:

". . . other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties. Where experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs would conclude that the findings in a drug efficacy notice or notice of opportunity for hearing concerning effectiveness are applicable to an identical, related, or similar drug product, such product is affected by the notice."

The preamble to the regulations cites *Hynson* and *North American Pharmacal*[30] as the authorities endorsing the "identical, related or similar" drug provision in these regulations.

On this point, the Court in *Hynson* spoke of: "A *generic* drug . . . which is found to be unsafe and/or lacking in efficacy . . . may be manufactured by several persons or manufacturers." (Emphasis supplied.)

The Court then went on to say that the FDA: ". . . may issue a declaratory order governing all drugs covered by a *particular* N. D. A." (Emphasis supplied.)

"Me Too" Drugs

In *North American Pharmacal*, the Court continually referred to "me too" drugs. In discussing the sufficiency of the notice involved in the litigation, the Court stated:

"Since the 'me-toos' are riding on the backs of the NDA's and thus vicariously receive the benefits of the NDA's approval, it is incumbent upon the 'me-too' drug manufacturers to keep advised of the status and the validity of the NDA's that form the basis for the manufacture and distribution of their 'me-too' product.

. . .

"Notice in the *Federal Register* is calculated to reach all such 'me-too' manufacturers who, because of their dependence for validity upon the NDA's, should be required . . . to keep abreast of the FDA regulations affecting their products."

The courts in these instances were speaking clearly of "me too" or generic drugs. They referred to drugs containing the *same* "drug moiety," not drugs containing a "drug moiety related in chemical structure or known pharmacological properties."

I believe the courts might very well reach a different conclusion concerning the sufficiency of the identical, related or similar provi-

[28] 21 CFR 130.14(e), now 314.200(e).
[29] 21 CFR 310.6.
[30] *North American Pharmacal, Inc. v. HEW*, 491 F. 2d 546 (CA-8 1973).

sion if a notice of opportunity for hearing were attempted to be applied to a related drug, rather than a "me too" drug.

Note that the preamble to the regulation recognized a potential problem with respect to the lack of specificity of the present definition of identical, related or similar drugs, contained in Section 310.6 which comments:

"Possible amendment of that regulation to achieve greater clarity deserves separate proposal, and should not be undertaken without time for comment. Any person interested in revision of Section 130.40 may submit an appropriate petition specifying revised language that would better describe the drug products covered by a notice of opportunity for hearing."[31]

The comments submitted by the Pharmaceutical Manufacturers Association (PMA) at the time Section 310.6 (then Section 130.40) was proposed contain a much more reasonable definition of the term "identical, related or similar."[32]

Note also that the FDA in the development of language relating to "me too" drug notices used more specific, and reasonable wording in a notice published in 1970. This notice stated:

"Promulgation of the proposed order will cause *any drug for human use containing the same active ingredients and offered for the same conditions of use to be* a new drug for which an approved new drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings." (Emphasis supplied.)[33]

I believe that this wording is within the comments of the courts referred to above and suggest that notices of opportunity for hearing should contain a provision to this effect rather than the "identical, related or similar" wording now used.

IND Rejection Situation

An interesting situation also exists with these regulations[34] and the FDA's practices as the result of a case decided in 1964, *Turkel and Ubiotica Corp. v. FDA*.[35]

Upon an appeal to review the termination of Ubiotica's investigational new drug (IND) application for an experimental drug, the Sixth Circuit Court stated:

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[31] 39 *F. R.* 9758, comment 26.

[32] PMA comments on proposal entitled "Drug Efficacy Study Implementation Notices, Applicability of DESI Notices to Identical, Related and Similar Drug Products," dated April 10, 1972.

[33] 35 *F. R.* 8405 (May 28, 1970), "Notice on Certain Sulfonamide Decongestant Nasal Preparations."

[34] The present situation discussed with respect to *Turkel* was created some four years ago with the promulgation of the May 8, 1970 hearing regulations, published at 35 *F. R.* 7250.

[35] *Dr. Henry Turkel and Ubiotica Corp. v. FDA, HEW*, 334 F. 2d 844 (CA-6 1964).

"It is our interpretation of the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C. Section 355(h) applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug. The denial of investigational exemption does not prohibit the processing of an application for distribution and sale of a new drug through the statutorily provided hearing and final administrative order called for in 21 U. S. C. Section 355(b), (c), (d), (e) and (f).

"Essentially, petitioners contend before us that requiring them to proceed with the New Drug Application and hearing prior to judicial review is a futile exercise, since they contend denial is a foregone conclusion. The answer to this is that by proceeding through the New Drug Application procedure and hearing, an adequate record for review will be developed in accordance with the congressional intent. The statute appears to us to contemplate appeal to the courts only after exhaustion of the administrative remedies and entry of a final administrative order."

The Court quotes the applicable section of the regulations then in effect[36] and goes on to state:

"In the event a petitioner's New Drug Application is rejected on grounds of inadequacy of human investigational data, where an investigational exemption had previously been refused, it appears that the merits of such refusal could be a proper issue at the New Drug Application hearing and thus be preserved for appellate review.

"Such an interpretation of the statute and regulations appears to us also to be strongly suggested by the due process requirements of the Fifth Amendment."

(It seems that not only industry interpreted Section 355 in a particular manner.)

With respect to such court appeal on rejection of an IND, the general rule is: "No one is entitled to judicial relief for a supposed or threatened injury until the prescribed administrative remedy has been exhausted."[37]

However, it has been held that where an administrative appeal would be futile, an attempt to exhaust administrative remedies may be excused.[38] Filing of an NDA after the rejection of an IND would, I believe, be clearly a futile act, as the NDA would unquestionably be deficient on its face and, thus, the request for hearing would, under the present regulations,[39] be rejected by the FDA. Therefore, hope-

[36] Sec. 130.5 reasons for refusing to file applications: "(d) if an applicant disputes the finding that his application is incomplete or inadequate, he may make written request to file the application over protest. In such case, the application shall be reevaluated, and within 30 days of the date of receipt of such written request, the application shall be approved, or the applicant shall be given written notice of an opportunity for a hearing on the question whether the application is approvable." 21 CFR, Sec. 130.5(d), as revised June 20, 1963, 28 *F. R.* 6380.

[37] *Myers v. Bethlehem Ship-Building Corp.*, 303 U. S. 41 (1938).

[38] *Wolf v. Selective Service Board No. 16*, 373 F. 2d 817.

[39] See 21 CFR 314.200(g).

fully, in view of the present hearing regulations, the rejection or revocation of an IND by the Agency could be appealed directly to the courts.

By the preceding comments I do not mean to imply only criticism of this set of regulations. The regulations do contain certain positive changes, such as the separation of the functions of the Commissioner from the Bureau of Drugs,[40] in determining whether a request for hearing sets forth grounds sufficient to justify a hearing. The separation of such functions had previously been recommended by both the American Bar Association (ABA)[41] and the Administrative Conference,[42] as well as being the subject of a previously proposed regulation from the FDA.[43]

It is, however, noted that this separation of functions, as worded, applies only to the initial consideration of whether a hearing should be granted and not to any determinations during, or as a result of, the hearing.

Regulation by Drug Class

Possibly the most important general regulatory development in drug law over the past few years is the actions by the FDA treating drug products by class rather than by individual product. This activity commenced basically with the NAS-NRC review.[44] Although the reports of the panels were issued on an individual NDA basis, the panels themselves reviewed drugs by class category. The FDA, on issuance of the Drug Efficacy Study Implementation (DESI) notices, included within their scope at first "any such drug"[45] and later any "identical, related and similar"[46] drugs.

The treatment of drugs by class was a change from the FDA's previous position of treating drugs as individual to the party holding the NDA.[47]

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[40] 21 CFR 130.14(f), now 314.200(f). See also 39 *F. R.* 9745, point 3 preamble to regulation re notice of opportunity for hearing.

[41] Pendergast, "The Nature of Section 701 Hearings and Suggestions for Improving the Procedures for the Conduct of Such Hearings," 24 FOOD DRUG COSMETIC LAW JOURNAL 527 (1969), reporting on recommendations of Joint ABA Committee representing the Section of Administrative Law and the Food, Drug and Cosmetic Law Committee of the Section of Corporation, Banking and Business Law.

[42] Recommendation No. 29, Administrative Conference of the U. S. 1971-72 Rep. 66 (1972). See also Hamilton, "Rule-Making on a Record by the Food and Drug Administration," 50 *Tex. L. Rev.* 1132 (1972).

[43] 37 *F. R.* 6107 (March 24, 1972).

[44] *Supra* note 6.

[45] 34 *F. R.* 5960 (March 24, 1969), "Notice on Combination Drugs Containing Oxalic Acid and Malonic Acid or their Ethyl Esters."

[46] 37 *F. R.* 24205 (Nov. 15, 1972). See also 21 CFR 310.6.

[47] CCH FOOD DRUG COSMETIC LAW REPORTER, ¶ 71,051.09.

Following the NAS-NRC drug efficacy study, the FDA commenced a separate "Procedure for Classification" of OTC drugs.[48]

This procedure included a number of innovative aspects. The regulation provided first for the appointment of advisory review panels by the Commissioner "to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded."[49]

These panels, in an unusual step, included both industry and consumer nonvoting, liaison members.

OTC Drug Review

The advisory panel for a designated category of OTC drugs reviews data submitted from interested persons in response to a request published in the *Federal Register*.[50] The panel can "consult any individual group," and any interested person may present written data and views or "request an opportunity to present oral views to the panel."[51] The report of the advisory panel to the Commissioner, along with its conclusions and recommendations, sets forth:

> (1) a proposed monograph establishing conditions relating to ingredients, labeling and other points under which the drugs involved are generally recognized as safe and effective (GRASE) and not misbranded (Category I);
>
> (2) a statement of what is excluded from the monograph on the basis that the inclusion thereof would result in the drugs not being GRASE or would result in misbranding (Category II); and
>
> (3) a statement of what is excluded from the monograph due to insufficient data (Category III).[52]

The Commissioner, after review of the panel's report, publishes a proposed monograph, covering the same points as the panel's report and including the full panel report.

Sixty days are provided for comment on the proposed monograph. Thirty additional days are provided for another unique feature—reply comments—which reply to comments made by other persons.[53]

The Commissioner, after evaluation of all comments, publishes in the *Federal Register* a "tentative final monograph"—another unusual step.

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[48] 37 *F. R.* 9464.
[49] 37 *F. R.* 9473, 21 CFR 130.301(a)(1), now 330.10(a)(1).
[50] 21 CFR 130.301(a)(2), now 330.10(a)(2).
[51] 21 CFR 130.301(a)(3).
[52] 21 CFR 130.301(a)(5).
[53] 21 CFR 130.301(a)(6).

Written objections may then be filed within 30 days and an oral hearing may be requested.[54] An oral hearing, presided over by the Commissioner, would then be held, if necessary. Judging from the proceedings on the Antacid Products,[55] such a hearing would be quite brief.[56]

Final Monograph

The Commissioner then issues a final monograph[57] from which an appeal, as a final Agency action, may be taken to the courts.[58]

The Commissioner, on his own initiative, or any interested person by petition, may propose a change in a monograph.[59] Deviations from the monograph are permitted upon submission of an NDA.[60]

As can be seen, this procedure falls somewhere between a bare 701(a)[61] notice and comment regulatory approach and a full trial type 701(e)[62] hearing.

The FDA position favoring the "class" approach to regulation is shown by a statement made by Commissioner Schmidt:

"The OTC review is testing—with every promise of success—the monograph approach to regulation. It is demonstrating the feasibility, the efficiency, and the sheer necessity of regulation by product classes instead of by isolated product actions.

"This procedural concept is being applied—or soon will be—in five other ongoing programs:

The GRAS review

Medical devices

Old drug regulation

Safety and efficacy review of biologics, and

... the vitamin-mineral definitions."[63]

Thus, the legal significance of the OTC review and the monograph or class approach have broad effects, beyond the OTC review itself, into many product areas subject to FDA regulation.

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[54] 21 CFR 130.301(a)(7).

[55] 39 *F. R.* 1359 (1973).

[56] O'Keefe, "A Fine New Twist—A Brief Commentary on the Commissioner of Food and Drugs' First Oral Hearing," 29 Food Drug Cosmetic Law Journal 116 (March 1974).

[57] 21 CFR 130.301(a)(9), now 330.10(a)(4).

[58] 21 CFR 130.301(a)(10).

[59] 21 CFR 130.301(a)(11).

[60] 21 CFR 130.301(a)(13), now 21 CFR 330.11.

[61] 21 U. S. C. 371(a).

[62] 21 U. S. C. 371(e).

[63] Schmidt, "Communication as the Basis of Regulation," 29 Food Drug Cosmetic Law Journal 9 (Jan. 1974).

From the initial publication of the proposal for the OTC review, industry[64] and counsel[65] have questioned the classification of the monographs as "substantive" regulation. This concern still exists.[66]

The problem to industry is that, if the monographs are substantive rather than procedural, the basis for attack on a monograph is severely restricted.

Binding Substantive Rule

Although the legal effect of the monograph is not set out in the final regulation or in the preamble, the notice of the proposed regulation stated that a monograph would "constitute a binding substantive rule."[67]

Further, the government's brief in *Bentex* referred to the OTC drug review regulations as "... substantive rule-making, by therapeutic class. . . ."[68]

The strict legal argument with respect to "substantive" versus "interpretive" as it stands today is significantly weaker than when it was argued in some earlier papers on the subject.[69]

The Supreme Court in both *Hynson*[70] and *Bentex*[71] endorsed the FDA's taking action by rule-making procedures rather than on a case-by-case basis.

The decision of the Court of Appeals for the District of Columbia in *National Petroleum Refiners Association*[72] holding that the Federal Trade Commission (FTC) has substantive rule-making authority appears to cover most of the points which could be made in the OTC monograph argument. There is also the recently decided *National*

[64] PMA comments on proposal entitled "Over-The-Counter Drugs, Proposal Establishing Rule-Making Procedures for Classification," appearing in the *Federal Register* of Jan. 5, 1972 (37 *F. R.* 85), dated March 2, 1972. See also comments of the Proprietary Association (filed March 2, 1972).

[65] DiPrima, "The OTC Review—Viewpoint of the Industry House Counsel," 27 FOOD DRUG COSMETIC LAW JOURNAL 532 (Sept. 1972); Levine, "Legal Ramifications of the OTC Review," 27 FOOD DRUG COSMETIC LAW JOURNAL 571 (Sept. 1972).

[66] See *FDC Reports*, p. B-22 (May 20, 1974); O'Keefe "The Over-the-Counter Drug Review—Helping the Client Make Decisions," 29 FOOD DRUG COSMETIC LAW JOURNAL 262 (May 1974).

[67] 37 *F. R.* 85, proposed 21 CFR 130.-301(b)(1).

[68] *Weinberger v. Bentex Pharmaceutical, Inc.*, brief for petitioner, p. 24.

[69] *Supra* note 65. See also Uram, "The OTC Drug Review and Section 701(a)," 28 FOOD DRUG COSMETIC LAW JOURNAL 447 (July 1973).

[70] *Supra* note 7, 93 S. Ct. 2469, 2480-81.

[71] *Supra* note 8, 93 S. Ct. 2488, 2492, 2494.

[72] *National Petroleum Refiners Association et al. v. FTC et al.*, 482 F. 2d 672 (1973).

Nutritional Foods Association case[73] which directly discussed the FDA's rule-making authority, and referred, in footnote 7, to the OTC regulations as "of clearly substantive proportion."

However, even if the monograph is held to be interpretive, how much value will that be? When you consider the amount of time and effort spent by the panels and the FDA; the opportunity for initial input, review and subsequent comment, including an oral presentation, although limited, available to interested persons; along with the concept expressed by the Supreme Court in *Hynson*, referring to the FDA as the "expert agency" in drug matters; the distinction between "legislative" and "interpretive" with respect to these regulations shrinks considerably.

The possibility of getting a court, even if the monographs are interpretive, to reject a monograph is, I believe, clearly remote.

What Lies Ahead?

What developments can we expect in the future with respect to FDA regulations or legislative developments?

First, and I believe possibly most important, we have the drive by the FDA as exemplified by comments made by Commissioner Schmidt[74] to obtain subpoena power comparable to that possessed by the FTC. S. 2373, which passed the Senate on a unanimous vote on July 11, 1974, although basically concerned with foods, contains many provisions which also apply to drugs. Included are subpoena authority and authorization for the FDA to argue its own cases in court and to initiate civil but not criminal proceedings without Justice Department participation.[75]

As previously noted, in the quotation of the comment made by Commissioner Schmidt, the Administration plans to review a previously attempted monograph approach to the regulation of prescription drugs.[76] A commentary by the FDA on the prescription drug monographs states:

"The regulation will provide a mechanism for all interested persons, including manufacturers and drug trade or manufacturers associations, to petition the Agency for the establishment of drug monographs. This procedure will afford these interested persons the opportunity to define the conditions for marketing

[73] *The National Nutritional Foods Association and Solgar Co. Inc. v. Caspar W. Weinberger, Secretary of HEW, and Alexander M. Schmidt, Commissioner of Food and Drug*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,127, 376 F. Supp. 142 (DC NY 1974).

[74] *Washington Drug and Device Letter*, No. 277 (June 24, 1974); *FDC Reports* (June 17, 1974) T & G 3.

[75] *Food Chemical News*, p. 37 (July 15, 1974).

[76] See 33 *F. R.* 7762 (1968).

the drug and to write the labeling to be included in the monograph for the drug. Each monograph will be tailored for the specific drug which is the subject of the monograph."[77]

Substantial Revisions

It is also reported that the FDA plans substantial revisions and new provisions concerning procedural regulations.

As presented to the annual convention of the Association of Food and Drug Officials of the United States, Food and Drug Administration General Counsel, Peter Hutt, said the procedural regulations will provide:[78]

(1) methods for petitioning the FDA to take action or stop an action already begun, including rules for seeking reconsideration of decisions or to obtain stays of Agency orders, pending Agency or court review of appeals;

(2) procedures for instituting court review of administrative actions including a determination of the record for appeal;

(3) a method for issuing binding formal advisory opinions;

(4) procedures for conducting and making available records of conferences, discussions and meetings with the FDA;

(5) guidelines for the publication of drafts of proposals and final orders;

(6) rules to split decision-making from litigating functions;

(7) procedures covering utilization of advisory committees;

(8) new procedures for Section 701(e) hearings plus the institution of other types of informal hearing procedures;

(9) a document prepared by the staff of the Senate Select Committee on Nutrition which listed four types of hearings which may be covered in these new procedural regulations:[79]

(A) the traditional evidentiary public hearing;

(B) a public hearing before a standing or *ad hoc* advisory committee;

(C) a public hearing before the Commissioner; and

(D) a regulatory hearing before any authorized employee of the FDA;

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[77] McEniry, "Drug Monographs," 29 FOOD DRUG COSMETIC LAW JOURNAL 166 (March 1974).

[78] *Food Chemical News*, p. 48 (June 24, 1974).

[79] *Food Chemical News*, p. 39 (June 24, 1974).

(10) The legal status of preambles to regulations, as previously mentioned.

With respect to these prospective hearing procedures, a note on "The Judicial Role in Defining Procedural Requirements for Agency Rulemaking" in an issue of the *Harvard Law Review* commented:

"While most authorities agree that a trial-type hearing is normally inappropriate for rule making, there is now some recognition that notice-and-comment procedures alone may not be satisfactory in all rule-making situations. Intermediate procedures, such as legislative-type hearings or trial-type hearings, limited to certain factual issues, may sometimes be useful."[80]

Thus, not only do we have an interesting past in the FDA procedural area, but we also have the promise of a very interesting future.

[The End]

NEW LABELING REQUIREMENTS PROPOSED FOR ORAL HYPOGLYCEMIC DRUGS

Information about potential risks of oral hypoglycemic drugs obtained subsequent to their initial approval for marketing has prompted the Food and Drug Administration (FDA) to propose new labeling requirements for the drugs. The information was obtained from a 1961-1970 University Group Diabetes Program study (UGDP) sponsored by the National Institutes of Health, involving 12 university medical centers and more than 1,000 patients. Specifically, the study found increased cardiovascular disease among patients treated with oral hypoglycemics. An independent review of the UGDP study by the Biometric Society concluded that the evidence of harmfulness was "moderately strong," and that, in light of its findings, it remained with the proponents of oral hypoglycemics to conduct scientifically-adequate studies to justify continued use of such agents.

A hearing will be held by the FDA on August 20, 1975 to help resolve the five-year controversy around oral hypoglycemic drugs and to specifically discuss the proposed labeling requirements. The proposed requirements deal with the two categories of oral hypoglycemic drugs, the sulfonylureas and the biguanides, with separate labeling proposed for each category. The labeling would warn physicians that there may be an increased risk of cardiovascular death in diabetic patients treated with the oral drugs, and that the oral drugs are indicated for use only for people whose symptoms or blood sugar cannot be controlled by diet and who cannot use insulin.

The comment closing date on the proposed labeling requirements for oral hypoglycemics is September 5, 1975.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,285

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[80] 87 *Harvard Law Review* 782, p. 796.

Dancing with the Gorilla

By EUGENE I. LAMBERT

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I SUSPECT THAT MOST OF YOU have at least some curiosity as to what a primate minuet has to do with food regulation, either now or in the future. It has been reported that it was Commissioner Schmidt who drew the analogy between doing business with the Food and Drug Administration (FDA) and dancing with a gorilla—one stops dancing when the gorilla gets tired.

The food industry, along with its compatriots in those other segments of industry subject to the Federal Food, Drug and Cosmetic Act, is very much in the gorilla's embrace. What I would like to discuss is the FDA's use of its court enforcement sanctions—particularly criminal liability—not only to call the tune but to drag the unwilling company out on the floor when the FDA says, "Waltz me around again, Willie."

John R. Park is President of Acme Markets. He also stands convicted of violating the Federal Food, Drug and Cosmetic Act in that he "caused" food to be held in a vermin-infested Acme Baltimore warehouse so that the food was held under insanitary conditions.

How did Mr. Park "cause" this to happen? The Government's proof consisted of establishing that Mr. Park was President of Acme and that the corporate bylaws charged him with the "general and active supervision of the affairs, business, officers, and employees of the company." Under instructions growing out of a 1943 Supreme Court case[1] that neither knowledge nor intent was necessary for violation of the Act, the jury returned a verdict of guilty and the District Court entered a judgment of conviction.

The Court of Appeals reversed the conviction[2] and the Government sought and was granted Supreme Court review. The case has

[1] *U. S. v. Dotterweich*, 320 U. S. 277 (1943).

[2] *U. S. v. Park*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 41,167, 499 F. 2d 839 (CA-4 1974).

been briefed and argued and will be decided before the end of the Court's term in June.[3]

Strict Criminal Liability

The case presents the issue of the use of what is called "strict criminal liability"—guilt without either knowledge of the specific wrongdoing or intent to commit it. Both Mr. Park and the *amicus* briefs filed by industry associations dealt with the changes that have occurred since Mr. Dotterweich ran a one-floor enterprise with 26 employees. The briefs focused on the necessity for proof of personal participation and responsibility, in addition to the need for the Court to spell out the scope of liability, which the Court in 1943 specifically declined to do.

There was a specific attack on the wide discretion that the FDA now has, and would have, should Mr. Park's conviction be affirmed. As one brief put it, it is "an arrogant assertion that it is proper to visit the moral condemnation of the community upon one of its members on the basis solely of the private judgment of his prosecutors." Those who are engaged in the production end of the food business might well ask whether or not this case represents a lawyer's theological tempest in a teapot. For certainly most production personnel are fair game—indeed, probably sitting ducks—under any theory of liability. Even today, however, the issue is a real one, and it is likely to become even more significant for the future.

An FDA plant inspection today goes far beyond a simple visual sweep for patent filth and vermin. The inspector may well have had specialized training in microbiology or mechanical engineering. The samples that are taken will be examined by FDA laboratories for minute contamination by common filth and for cross-contamination or the migration of industrial chemicals from processing equipment.

Low-Acid Canned Foods

If the food plant manufactures low-acid canned foods, the inspector has a plumbing bible as a guide. He will march around measuring the diameter of pipes and counting vent openings and other mechanical orifices. He has, for the first time, access to processing records.

Before the inspector shows up, he has often gotten some background information (which may or may not be accurate) concerning

[3] The Supreme Court upheld Mr. Park's conviction. See *U. S. v. Park*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 38,018, No. 74-215 (June 9, 1975).

the nature of the processing in the food plant and the possible areas of contamination or difficulty. He will go far beyond the so-called umbrella good manufacturing practices (GMPs) in providing comments on plant sanitation and manufacturing practices.

Any adverse findings will, of course, be recorded on Form 483 and presented to the plant manager or some other responsible official. That step, however, is today only the beginning of corporate involvement. The FDA has developed two other regulatory tools that it uses to involve higher management in individual plant inspections.

The first of these is an "information letter." If the plant manager is not a corporate officer, the FDA will often send a copy of the Form 483 to a corporate officer having supervision over the plant involved. In the past, this was done in the guise of a "courtesy" so that corporate officials were kept apprised of FDA findings.

Information Letter

The FDA now uses an information letter that requests a written response within 30 days regarding both the reason for the observed problems and a statement of corrective measures taken or planned.

If very serious observations are noted or if original observations are not corrected at a follow-up inspection, the FDA may issue a "regulatory letter." This letter puts a firm on notice that the FDA is prepared to take court action to correct what it believes is a violation of the Act. The firm is given ten days to respond as to how the violation is being corrected. This letter is very commonly sent to the chief executive officer of the firm involved, and certainly not to anyone lower than the corporate officer responsible for the operating division involved.

Both of these regulatory techniques are designed to place high corporate officials on notice of FDA concerns about plant sanitation and operating practices. Regardless of the outcome of the *Park* case, this approach also serves to satisfy the FDA's internal standards as to the liability of a corporate official in a subsequent proposed criminal action. The Agency believes that, if the response includes proposed action that is not fulfilled, the officer is guilty by reason of direct participation in the unlawful act. If the response attempts to delegate the responsibility for compliance, the corporate officer may be guilty by reason of failure to adequately supervise corporate compliance. Catch-22 could have as effectively taken place at 200 C Street in Washington as in the European theater of operations.

Pending Legislation

If the present situation leaves every food processing employee edgy as to whether a U. S. marshal will come knocking on the door, legislation pending in Congress can only exacerbate the situation. This legislation would multiply endlessly statutory responsibilities and the criminal risks of deviation from these demanded norms.

I am referring, of course, to the Food Safety Act, S. 641, which commands each processor to write his own criminal code and never vary from it, unwittingly or otherwise.

The bill would mandate that each manufacturer commit to writing safety-assurance procedures. These procedures would:

(1) identify critical control points;

(2) identify the hazards involved at these points;

(3) require adequate controls to avoid the hazard at each point;

(4) require adequate monitoring of the operation of these controls;

(5) cover all adulteration provisions, including misuse of food additives, unavoidable contaminants, decomposition, and sanitation;

(6) require that the procedures be reviewed and updated at least annually;

(7) make those control records designated by the FDA subject to FDA inspection; and

(8) require that any deviation from the procedures be reported to the Agency, as food manufactured other than in accordance with the procedures is "adulterated."

Those who are manufacturers of low-acid canned foods already know how tight and long-lasting is the FDA's embrace when it conducts an establishment inspection for conformity with the low-acid canned food GMPs and the umbrella GMPs. The Food Safety Bill would extend this bureaucratic bear hug to all segments of the food industry. If the Supreme Court upholds the FDA's concept of strict criminal liability and the FDA's unfettered discretion in its applications, industry will indeed be dancing to the gorilla's tune and in its embrace.[4]

There has been no formal Congressional action yet on the Food Safety Bill. A counterpart measure is yet to be introduced in the

[4] See footnote 2.

House. Thus, there remains time for industry to focus its attention on the nature of criminal liability and on the relationship between the adoption of safety-assurance procedures and criminal liability.

Grammatical Point

Very careful consideration also has to be given to a grammatical point of the kind that was only of interest to high school English teachers when I grew up—the distinction between "shall" and "should." This distinction is not drawn in the umbrella GMPs. In the low-acid canning food GMPs, however, the definitional section states: " 'shall' refers to mandatory requirements and 'should' refers to recommended or advisory procedures or equipment." If safety-assurance procedures become a self-imposed criminal code, this distinction will then become the touchstone of *per se* criminal liability. Each manufacturer will have to determine what safety-assurance procedures are critical and unavoidable in assuring the safety of the food product. Those procedures "shall" be carried out, and the adequacy of the safety-assurance plan will necessarily be measured against whether the right mandatory procedures have been adopted.

A company should not, however, conclude that something "shall" be done under a safety assurance plan simply because it is company policy or desirable or an accepted procedure. Perhaps these "should" be done but it would be a wholly unnecessary expansion of criminal liability to insist that they "shall" be done. Perhaps to this degree English majors will end up playing a key role in determining whether corporate officers are held criminally liable for the operation of their plants in the future. **[The End]**

FOOD SAFETY STIRS CONTROVERSY IN JOINT SENATE HEARINGS

In hearings on two bills, S. 641 and S. 1168, which would amend the Federal Food, Drug and Cosmetic Act to provide for the establishment of food surveillance authority, the registration of food establishments, and the labeling of food to meet certain requirements, especially if a standard of identity has been issued, the Food and Drug Administration and many segments of the food industry differed sharply in their assessment of the need for food legislation and the extent to which such legislation is required. Although some doubted certain provisions in the bills, none questioned their potential impact on food processors since, as the National Canners Association stated, the amendments would constitute the most significant revision of food regulatory provisions of the Act since its 1938 passage.

CCH Food Drug Cosmetic Law Reporter, No. 550

A Rose by Any Other Name

By MURRAY D. SAYER

Mr. Sayer Is Assistant General Counsel of General Foods.

MY TEXT FOR TODAY is taken from Will Shakespeare's classic tragedy, "Romeo and Juliet." The oft-quoted phrase is, of course: "What's in a name? A rose by any other name would smell as sweet." On various occasions in dealing with food labeling matters, it has occurred to me that if Shakespeare were writing today within the context of our regulated society, he would have to change that line to read: "What's in a name? A rose by any other name would be misbranded."

As you all know, the Food and Drug Act requires all foods to bear on their principal display panels a common or usual name, if there is any. While this might have been a relatively simple requirement when the Act was passed in 1938, with today's advances in food technology, finding a name for a new food product often becomes a major hassle. This is particularly so since the name must pass regulatory muster and, as many know from experience, the Food and Drug Administration (FDA) has no poetry in its soul when it comes to the names of food products.

With this in mind, I thought I might address the question, "What's in a name?" as it relates to food products, with particular emphasis on some of our own problems over the years. To start off, I would like to tell you a parable.

Once upon a time, there was a Land of Orange. The Land of Orange was divided into three parts: Upper U. S.; Lower U. S. and Pacific U. S. The clansmen of the three regions were related since they all had orange juice in their veins. At the center of the country lay the Citadel where the Great Wizard of Orange resided. It was the responsibility of the Wizard of Orange to issue laws to all the

clansmen and to sit in judgment on Tort Feasors. For many years, peace reigned throughout the land.

Instant Breakfast Drink

Then one year, the clansmen of Upper U. S. brought forth a new child, conceived of as a vitamin C-fortified orange beverage powder, and dedicated to those who could not or would not drink orange juice. The child was, after much consideration, christened with the name, "Instant Breakfast Drink." At the Citadel, the Wizard of Orange looked at this child and muttered, "belly wash." However, he could find no legal fault with it and, therefore, it waxed in strength until it eventually justified many facings in the market.

Some years later the clansmen of Upper U. S. begat a new progeny of the same family. But this child was different from the previous one. Born at a time when orange juice was dear, it was designed to satisfy the purse as much as the pallet. Instead of being a powder, it was liquid. Instead of being dry, it was a frozen concentrate. Indeed, it looked very much like another member of the family, frozen concentrated orange juice. A surprisingly large number of clansmen even thought the resemblance went to the very taste of orange juice. Yet there was no orange juice in it.

With some consternation, the clansmen of Upper U. S. faced the problem of what to name this child. At that time, there was a law of the land which decreed that if an illegitimate child resembled his brother, he must bear the name of his brother. But as a mark of shame, that name must be preceded by the word "Imitation," of equal size and prominence with the name. What to do? There were some of the clansmen of Upper U. S. who thought the resemblance was so striking that the child should be called "Imitation." But many others, with a loud voice cried, "Nay! He is as legitimate as his brother, 'Instant Breakfast Drink.' He should not have to carry the mark of shame." And so it was done. The child was named "Frozen Concentrate for Orange-Flavored Breakfast Drink," and was sent forth to slay dragons, a mere child on a knight's errand.

Imitation Orange Juice

Alas, it was not to be. The clansmen of Lower U. S. saw this child from afar. They seized him and examined him. With a great voice they cried, "Upper U. S., t'is a bastard you have begotten and he does not bear the mark of shame." By dog and pony, they con-

veyed their findings to the Wizard at the Citadel. The Wizard viewed this child and muttered, "belly wash." But he agreed that the child did bear a striking resemblance to orange juice. He therefore issued writs demanding that "Frozen Concentrate for Orange-Flavored Breakfast Drink's" name be changed or he would be summarily executed. To save the child, the clansmen of Upper U. S. stripped him of his legitimacy and painted on his breastplate, in bold orange letters, the name "Imitation."

Percentage of Juice

Subsequently, the Wizard came to realize that there were many little bastards populating the countryside bearing such names as "Orange Ade" and "Orange Drink." Since he could not eliminate them all, he decided to legitimize them. He issued a proposed decree which said that if a bastard had any orange juice in its veins, it could adopt the appropriate name prescribed by the Wizard. One name proposed by the Wizard was "Orange Juice Drink" for those having from 35 percent to 70 percent orange juice in their veins.

About this time, the clansmen of Upper U. S. brought forth another child which contained 50 percent orange juice. The clansmen were overjoyed because they believed the child had been legitimized by the Wizard and they gave it the name, "Frozen Concentrate for Orange Juice Drink" and proudly stamped across his breastplate, "Contains 50% Orange Juice." But even before this child reached the market, the clansmen of Lower U. S. cried, "Foul, t'is another bastard."

By the same dog and pony, the clansmen of Lower U. S. trekked to the Citadel to advise the Wizard of their conclusions. The Wizard looked at the child and muttered, "belly wash," but again he agreed that this child should be called "Imitation." But, said the clansmen of Upper U. S., appealing to the Wizard, "What of the decree which would change the name of the child to 'Orange Juice Drink'?" The Wizard responded, "That decree is not yet final and, therefore, you must change the name to "Imitation." And so it was done and the clansmen of Upper U. S. sat back to await the final decree so they could once again change the name of this child to "Orange Juice Drink."

But that was not to be. For now the clansmen of Lower U. S. and Pacific U. S. began to engage in a great internecine struggle. Through lawyers and lobbyists, they jousted with each other to have the decree changed to favor their own children. After much

juice had been shed, the Wizard cried, "Hold! Enough! A plague on both your houses!" He then withdrew the decree and issued a new one in its place which said, "Call your children what you wish, but spread upon their breastplate the percentage of orange juice in their veins." About the same time, the Wizard made a new discovery. He perceived that the clansmen were not getting enough nutrition in their foods. He therefore decided to issue a new decree to the effect that a child should be called "imitation" only if it was nutritionally inferior to its brother.

The clansmen of Upper U. S. could hardly believe this. However, they took their strongest child, pumped him full of vitamins and paraded him before the Wizard. The Wizard nodded solemnly and said, "No longer is he 'Imitation.' Henceforth, his name shall be 'Orange Breakfast Beverage—Contains 50 percent Orange Juice.' "

Here ends the parable, but not the story. As of now General Foods has three breakfast beverage products. One is called "Instant Breakfast Drink," one is called "Imitation Orange Juice," and one is called "Orange Breakfast Beverage—Contains 50 percent orange juice."

However, the FDA's new regulation which states that a product is an imitation only if it is nutritionally inferior to the product it replaces and resembles, is based on, at best, tenuous reasoning. While no one in industry has argued against this new regulation, the American Federation of Homemakers has challenged in court the appropriateness and validity of this regulation. A district court has upheld the regulation, presumably on the grounds that father, or FDA, knows best. That decision has in turn been appealed to the Court of Appeals. In the quite possible event that the Court of Appeals will reverse the decision, we may once more be painting the mark of shame on our 50 percent orange juice product.

Future Problems

The purpose of the parable is to demonstrate some of the problems one can run into when trying to find a name for a new product. It is also intended to show how questions with respect to a product name were formerly considered and resolved by the FDA. Today, however, times are changing and I would like to discuss briefly some of the future problems we may face with respect to common or usual names for food products.

As indicated in the parable, selection of a common or usual name for a food product has been the responsibility of the manufacturer. If the FDA disagreed with the name, the procedure was either to call the manufacturer in for a discussion to resolve the problem or to make a seizure on the grounds that the product was misbranded. Of course, some product names were dictated by reason of the fact that standards of identity were established for some food products. Such standards also included the common or usual name of the product, such as jam, white bread, mayonnaise, macaroni and chocolate. But for the most part, it was the manufacturer's responsibility to name the product in a way that was not false and misleading. Problems had to be resolved, for the most part, on a product-by-product basis.

However, for about three years, the winds of change have been blowing. In 1972, the FDA discovered that they were not operating under an Act, but rather a Constitution. In a change of policy enunciated at the 1972 Food and Drug Law Institute-Food and Drug Administration Conference in Washington, the FDA stated that, hereafter, instead of following the dictates of the Food and Drug Act, it would operate on the basis that it had authority to do anything which was not prohibited to it by the Act. The potential impact of such a philosophy is obviously tremendous since most laws regulating a given industry are aimed at regulating the industry, not regulating the regulators.

IBM Computer Run Amok

The implementation of this new policy was not long in coming. Since January 1973, the FDA has spewed forth new regulations in quantity equalled only by an IBM computer run amok. Among the myriad new regulations is one directed to common or usual names. Now, in theory, regulations governing common or usual names might seem practicable. However, aside from the question of whether the FDA has legal authority to impose such common or usual names by regulation, there are a number of problems.

First, it puts a straitjacket on all new products in terms of their common or usual name if they happen to fall within a given class. Of course, a manufacturer can always petition the FDA for a new common or usual name regulation if its new product does not fit the regulation name. But anyone who has attempted the petition route is aware of the frustrating futility of such a process. And, if an amended regulation is finally issued, it is more often than not the traditional three-humped camel.

Second, the FDA is noted for being very literal in its approach to common or usual names; it uses what I sometimes call the "1, 2, button my shoe, 3, 4, shut the door" approach. For example, under the proposed common or usual name regulation for plant protein products, a formula is set forth for naming such a product. To save you from some of the deadliest prose ever written, I will give the common or usual name of a hypothetical product using this regulation to develop the name. Suppose a manufacturer develops a synthetic ham slice using soy concentrate and fish flour as the major protein sources. Under this regulation, the common or usual name would be "Artificially ham flavored textured soy concentrate and fish flour slices." When I mentioned that name to my wife, she almost gagged. From the FDA's point of view, this mouthful is supposed to be informative and helpful to the consumer.

Common or Usual Names

Finally, this common or usual name regulation does much more than establish a name. It also requires a percentage declaration of any characterizing ingredients if such characterizing ingredients have a material bearing on price or consumer acceptance. In addition, if the label shows characterizing, or other, ingredients not contained in the package, one must also indicate that as a part of the common or usual name. To carry this to the ludicrous extreme, assume that the protein sources in the common or usual name previously mentioned are considered characterizing ingredients. Further, assume that the vignette on the package shows mashed potatoes and peas along with the slice of product. The common or usual name would become "Artificially ham flavored textured soy concentrate and fish flour slices—containing 30% soy concentrate and 15% fish flour—contains no mashed potatoes or peas."

For any marketing people, how does the name "Imitation Ham" sound by comparison?

And so we come full circle. The question which I asked at the beginning of this discussion—"What's in a name?"—may soon be the question many manufacturers will ask if these regulations are sustained by the courts and implemented by the FDA in its very literal approach to naming products. In closing, I would like to quote that famous line of poetry by Gertrude Stein which goes "A rose is a rose is a rose." Would that this were as true for food names as for roses. **[The End]**

How Does One Get Rid of a Dead Horse?

By NORMAN BRISTOL

Mr. Bristol Is Senior Vice-President and General Counsel of the Kellogg Company.

THOSE GRIZZLED VETERANS of the intermediate distance food and drug controversies will remember the frantic days of June of 1966 which followed the publication of a Food and Drug administrator's final order[1] in which appeared for the first time a new regulatory idea. This idea was embodied in proposed Part 80.2 of the Food and Drug Act regulations. The operative provision was Section 80.2(c) which provided, in effect, that a food producer may fortify with vitamins and minerals only a few specified foods and those with only a few nutrients and at relatively low levels.

The final order was said to be based on a proposal published four years earlier[2] but while some of the regulations proposed in 1962 reappeared in 1966, this particular feature was not to be found anywhere.

The next 30 days were taken up by preparation of requests for extensions of time (unsuccessful) and objections. There followed a period of amendments, one reportedly to accommodate the Commissioner's favorite quick lunch product.[3] Then the matter appeared to go into another hiatus. During this period those who thought that the philosophy behind Section 80.2(c) was unwise had their hopes raised too high that the Food and Drug Administration (FDA) might have thought better of the idea.

But this proceeding was too massive, too all-encompassing, to just lie there. Maybe there was too much time invested, but the thing had to move along and the hearing got under way in 1968. In the course of the next two years, counsel supporting the regulation were able to

[1] 31 *F. R.* 8521 (June 18, 1966).
[2] 27 *F. R.* 5815 (June 20, 1962).
[3] 31 *F. R.* 15476 (Dec. 14, 1966).

offer testimony such as that of a practicing physician who, based on the comments of his patients, thought the regulation was reasonable. Also heard was the testimony of a person who sat in a consumer cooperative retail store and heard complaints and extraneous comments of customers, and the testimony of an expert who stalked out of the hearing during cross-examination.

Qualified Support

Those persons who can be considered to be responsible professionals testifying in their fields of expertise were generally opposed to this regulation. Those who offered support offered only qualified support.

The hearing finally ended two years later and the whole matter again returned to the cocoon. Opponents of the idea waited to see what kind of a moth, if any, would come out.

It took a while but in the *Federal Register* of January 19, 1973, the Commissioner dropped an equivocal shoe. He

". . . concluded that it would be in the public interest to develop regulations for such foods utilizing the approach of establishing nutritional quality guidelines for certain classes of foods, including those to which vitamins and/or minerals may be added. These guidelines may replace the approach of developing standards for these foods as originally proposed in the form of 21 CFR 80.2. . . . The Commissioner is deferring final action on 21 CFR 80.2 until experience is gained under [nutritional quality guideline]."[4]

Even for those who were up to their ears in dealing with other matters in that January 19 *Federal Register,* this was a fair warning that, failure of proof aside, the FDA was going to prescribe fortification content one way or another.

Moreover, there was a specific reference at this time to the 1971 publication of proposals for a general regulation on nutritional quality guidelines and a specific regulation on heat-and-serve dinners.[5]

Nonconforming Products

These proposals may have seemed relatively harmless at the time they were published. Comments as reported by the *Food Chemical News* seem to have been almost entirely devoted to problems with respect to the nutrients and levels in the heat-and-serve dinner proposal.[6] However, the regulation adopted provided for a harsh label statement with respect to nonconforming products in the guideline

[4] 38 *F. R.* 2144 (Jan. 19, 1973).
[5] 36 *F. R.* 24822 (Dec. 23, 1971).
[6] *Food Chemical News,* p. 65 (Jan. 1, 1973).

class of foods.[7] But the full impact of the FDA's plans was not revealed to the world until the *Federal Register* of June 14, 1974 in which were published proposals for nutritional quality guidelines for breakfast beverages,[8] hot breakfast cereals,[9] formulated meal replacements,[10] main dish products,[11] ready-to-eat breakfast cereals,[12] and, most important and sweeping, General Principles Governing the Addition of Nutrients to Foods.[13]

This last proposal includes an amendment to the earlier promulgated general regulation on guidelines. The essence of the scheme is that no nonguideline, nonstandardized food may be fortified except to restoration levels unless its label contains the statement that the addition of those nutrients has been determined by the United States Government to be unnecessary and inappropriate (which is not true since the Government has, at this point, made no determination at all) and does not increase the dietary value of the food (which may or may not be true depending on a wide range of variables).[14]

The proposed regulation requires a corresponding crepe label statement if the class of food covered by a nutritional quality guideline is fortified other than in conformity with the guideline.[15] With respect to those foods, the required statement may or may not be true, depending on the way in which the fortification differs from the guideline.

Note here that the proposed regulations permit, without the crepe label statement, a balanced food in which calories, protein and all the other nutrients are in the same proportion of the recommended daily allowance. I venture the view that this class of foods will remain small, at least for the foreseeable future, because of organoleptic, technological, economic and other problems.

Crepe Label Statement

Thus, the scheme is essentially the same and is against the fortification of foods except as prescribed by regulation. It acts against fortification of many foods, including those for which the FDA has not gotten around to working up a nutritional guideline and those foods which are essentially new foods. We are back where we were in 1966, although the current proposal is different in that higher levels are allowed. The sanction—the crepe label statement—is different than

[7] 38 *F. R.* 6972 (March 14, 1973).
[8] 39 *F. R.* 20895.
[9] 39 *F. R.* 20896.
[10] 39 *F. R.* 20905.
[11] 39 *F. R.* 20906.
[12] 39 *F. R.* 20898.
[13] 39 *F. R.* 20900, corrected 39 *F. R.* 26747.
[14] Proposed Sec. 100.1(h).
[15] Proposed 100.1(f).

the sanction under proposed Part 80.2 which I supposed was imitation or substandard labeling.

This is somewhat suprising since the White House Conference recommended abandonment of Part 80.2[16] and made a host of other recommendations looking toward further addition of nutrients to foods.

In the same *Federal Register* issue with this proposal, the Commissioner notes the White House Conference consensus that nutritional quality guidelines should assure a *minimal* nutrient content, and that nutrition information and food consumption patterns are too dynamic to be governed by inflexible rules.[17] He also points to the success of fortification in preventing nutritional diseases when he states that:

". . . addition of nutrients to foods . . . have provided a safeguard in national diets and have been effective in reducing the prevalence of deficiency diseases in many countries. Such programs remain valuable today. . . ."[18]

He quotes the 1968 joint policy statement of the Food and Nutrition Board of the National Academy of Sciences-National Research Council and the Council on Foods and Nutrition of the American Medical Association in which they endorse the enrichment, fortification and restoration of the nutritional value of foods.[19] And he recognizes the need for flexibility when he says:

"With the increased use of convenience foods, fabrication of foods from new ingredients, and substitute foods, there is need to maintain the nutritional quality of diets when there are changes in food patterns."[20]

He determines:

". . . that a single standard of identity listing all foods to which a vitamin, mineral and protein may be properly added is unnecessarily inflexible in the light of developing knowledge about nutrition."[21]

With all this, one could be led to expect a flexible approach, hopefully making some kind of use of the new nutritional labeling regulations which were then becoming widely adopted. Hopefully it would allow some sort of label statement, which might enhance marketing, on a product which met a guideline. But the message was loud and clear in Dr. Wodicka's accompanying press statement that "[nutrient] additions will be allowed in five ways." Although he did not say "in no other ways," he did not mention that two of the ways, balanced foods and analogs, would not be particularly significant in the diet.

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[16] Recommendation No. 13 of Panel VI A-2.
[17] 39 *F. R.* 20901 (June 14, 1974).
[18] 39 *F. R.* 20900 (June 14, 1974).
[19] 39 *F. R.* 20900 (June 14, 1974).
[20] See footnote 17.
[21] See footnote 18.

Irrational Fortification

And deep in the discussion are mentioned briefly those two regulatory hobgoblins, "irrational fortification"[22] and "horsepower race."[23] These problems are not defined nor are examples given of what they consist of. But whatever these two phrases mean, this is all that passes for proof that there is need of some regulation of this sort. This contrasts sharply with the rather convincing showing made as to playing around with serving sizes on the adoption of nutrition labeling.[24]

I see two possible effects if this scheme is finally adopted. One possibility is that food marketers will generally be reluctant to display the crepe label statement. Where additional vitamins not found in a guideline are being included, they will be eliminated. Where a guideline requires a nutrient which cannot be incorporated in a food, all fortification will be eliminated. And, in the largest number of cases, there will be no guideline, and fortification will be eliminated. The net result will be a reduction in the total intake of vitamins and minerals. There is no way of knowing the extent of the reduction in intake or the extent to which it may jeopardize health.

Grocery Store Shelves

The alternative may be more likely. Food marketers may conclude that the crepe label statement is about as effective as the warning on a pack of cigarettes, and the grocery store shelves will abound with packages declaring the presence of nutrients determined by the United States Government to be unnecessary and inappropriate and not increasing the dietary value of the food.

This will also be a surely unfortunate situation, leading to an unnecessary loss of confidence in both the United States Government and the food companies.

I urge the rejection of the approach represented by the once-rejected Part 80.2 and the crepe label statements in proposed Section 100.1 and in the guideline proposals. **[The End]**

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[22] See footnote 17.

[23] 39 *F. R.* 20899, in the discussion relating to a nutritional quality guideline for fortified ready-to-eat cereals, proposed Sec. 100.10.

[24] 39 *F. R.* 20837 (June 14, 1974).

New Concepts in Abbreviated NDAs

By ROBERT L. SPENCER

Mr. Spencer Is Acting Chief of the Precedent Regulations and Legislative Activities Branch of the Bureau of Drugs in the Food and Drug Administration.

I THANK THE FOOD AND DRUG LAW INSTITUTE for this opportunity to speak at this pharmaceutical update meeting. I believe that it is self-evident that programs such as this are held because there are continual changes in drug laws and regulations. As changes occur in technical knowledge and as our experience with drug laws and regulations increases, it becomes obvious that changes are needed to reflect this increased knowledge and experience. The Food and Drug Administration (FDA) now has under consideration a change in policy regarding the abbreviated new drug application (NDA).

The present abbreviated NDA concept grew out of the FDA's efforts to implement the findings of the drug efficacy study carried out by the National Academy of Sciences-National Research Council (NAS-NRC). Of the approximately 4,000 prescription drug products reviewed in the study, about 1,400 were found to be effective as well as safe for at least one indication. These drug products are the subject of the abbreviated NDA program.

The abbreviated NDA program applies to drug products with or without previously approved NDAs. It should be remembered that the NAS-NRC reviewed only those products which went through the NDA preclearance process. At the time of the NAS-NRC review there were a large number of drug products without NDAs on the market. These drug products were identical, similar or related to those with NDAs and frequently have been referred to as "me too" drugs. It has been the consistent intention of the FDA to apply the NAS-NRC efficacy findings to these identical, similar or related drug

products, as well as to the pioneer drug products specifically reviewed in the drug efficacy study.

Regulatory Mechanism

To apply the findings of the drug efficacy study to drugs rated as effective, a new regulatory mechanism had to be devised. Full NDAs contemplated by Section 505(b) of the Federal Food, Drug and Cosmetic Act were determined to be unnecessary. Since the drug entities had been determined to be safe and effective for use, it would have been a futile exercise for new manufacturers to develop such data over again and for the FDA to review them. On the other hand, there was a reluctance to classify these products unreservedly as "old" drugs. Some control over these products was necessary in order to assure drug quality and to require the submission to the Agency of certain records and reports of drug experience. For other drug products it was considered necessary to require filing of evidence of bioavailability. In addition, prior to the Drug Listing Act of 1972, the FDA was not authorized by statute to conduct a census of the marketplace and thereby assure that the efforts to implement the findings of the drug efficacy study were broadly effective. A mechanism between declaring pure "old" drug status and requiring full NDAs for these drugs was adopted. This regulatory mechanism is the abbreviated NDA.

The abbreviated NDA is unique in that the requirements for submission of redundant safety and effectiveness data have been deleted for all drugs rated as effective in the drug efficacy study. The amount and kind of data to be submitted with respect to manufacturer's processes and other categories of information contained in a full NDA have been streamlined, modified or deleted in tailoring the abbreviated NDA to each particular drug to fit the need for information.

Abbreviated NDA

The drug products for which an abbreviated NDA currently may be submitted fall into two broad categories. The first and largest category includes drugs which are generally recognized among experts as safe and effective for use and which present no drug quality problems if manufactured in accordance with current good manufacturing practices (GMPs).

The second category consists of drug products with a known or potential bioequivalence or special manufacturing problems. These

drug products are either especially difficult to manufacture or have been shown to have inherent characteristics which could result in bioequivalence problems. Most drug products in this category present potential rather than documented problems because they are closely related chemically to a drug product with a documented problem. While there is no direct evidence to implicate that drug specifically, the FDA believes prudence requires the position that an investigation to clarify any bioequivalence or special manufacturing question is essential to a determination of the safety and effectiveness of that drug product.

For several years the Agency has been working toward a system under which effective Drug Efficacy Study Implementation (DESI) drugs will be regulated under "old drug monographs." The delay in implementing this program has resulted from several factors, all of which are related to drug quality. Work on an old drug monograph program concentrated on devising a system with minimum but enforceable controls. It was felt that most DESI drugs could be given old drug status, but that such status should not result in an atmosphere which could lead to either a loss of quality control or to an inability to require the submission of needed records and reports to the FDA. Accordingly, it was determined that the "old" drug status should be contingent upon the manufacturer meeting certain conditions. Such status will be accorded so long as the manufacturer files records and reports which are specified and has the ability to produce a drug meeting all labeling, composition and manufacturing specifications necessary to assure product quality.

Quality Products

Prior to adoption of a program classifying certain drugs as old drugs, it was necessary to assure that all manufacturers of such drugs be capable of producing quality products. To aid the monitoring system of the FDA and to provide manufacturers with a comprehensive quality control standard, new regulations prescribing current GMPs had to be prepared.

Because the principles involved in determining the bioavailability of any drug product are central to the issue of abbreviated NDA approval, the FDA considered publication of bioavailability regulations to be a necessary forerunner of an effective enforcement program.

It is difficult to isolate the abbreviated NDA program for other related projects since GMP, bioavailability, bioequivalence, and old

drug regulations have been considered and treated as related parts of a more comprehensive regulatory program to assure drug product quality. Within a few weeks, there will be published in the *Federal Register* several documents related to this comprehensive regulatory program.

First, a statement of general policy under which drugs evaluated as effective in the drug efficacy study will be classified as "old" drugs as long as the drug products are manufactured pursuant to GMP requirements set forth in applicable regulations. They must be labeled consistently with the requirements set forth in applicable DESI notices and must meet any other applicable conditions specified for such drugs. Failure to observe the specified conditions for "old" drug status will result in the article becoming a new drug, which, in the absence of an approved application, will subject a drug to seizure and the manufacturer to civil and criminal proceedings.

Prescription Drugs

Second, there will be a notice of proposed rule-making and notice of enforcement policy for any human prescription drug product determined in the drug efficacy study to be effective for at least one indication or identical, similar or related to such a drug product. This notice will revoke and supersede the notice issued by the Commissioner of Food and Drugs, published in the *Federal Register* of July 14, 1970[1] which specified the conditions under which new drugs evaluated as part of the drug efficacy study may be marketed in accordance with the new drug provisions of the Act. It will also revoke and supersede the specific requirements for submission of a full or abbreviated NDA or bioavailability data contained in each DESI notice for an effective drug published in the *Federal Register* prior to the date of the notice except for those specific drugs and DESI notices listed. It will state the interim enforcement policy of the FDA that all effective drug products covered by a DESI notice may be lawfully marketed without submission or approval of a full or abbreviated NDA if they meet all of the requirements set forth in the applicable DESI notice (including any amendments) and in the notice. Finally, this notice proposes a new regulation to codify present enforcement policy in order to inform the public fully about these matters.

Under this notice and proposed regulation, the FDA will require an approved full or abbreviated NDA for a drug evaluated as effective in the drug efficacy study only where such drug presents a known

[1] 35 *F. R.* 11273 (July 14, 1970).

or potential bioequivalence or special manufacturing problem. Approximately 150 specific drugs will be listed as requiring premarketing approval because of a known or potential bioequivalence or special manufacturing problem. All other drugs evaluated as effective in the drug efficacy study may be marketed without premarketing approval providing the manufacturer submits certain records and reports, labels the drug product in compliance with the applicable DESI notice, and manufactures the product under GMPs.

Manufacturing Requirement

Where a bioequivalence or special manufacturing requirement is established for a drug product, all persons marketing the product will be required to submit and obtain approval of a full or abbreviated NDA. Approval of the NDA will be based on data demonstrating that the drug product meets the bioequivalence or special manufacturing requirement.

With respect to assuring drug quality, the FDA has concluded that, except for those drugs for which there is evidence or good reason to believe that a bioequivalence or special manufacturing problem exists, the Agency's surveillance and monitoring programs are sufficient to protect the public health. These programs include plant registration, drug product listing under the Drug Listing Act, plant inspections to enforce good manufacturing controls, systematic analysis of marketed drug products and a product defect reporting system.

The third document to be published in the *Federal Register* will be a final regulation promulgating bioavailability regulations which establish methods for testing *in vivo* the rate and extent of absorption of single drug products subject to NDAs. Basically, the regulations will require the testing to be conducted on new drug products containing chemical entities not previously marketed. Such testing will be in comparison with the pure drug substance in solution or suspension as a reference. Such data also will be required for new formulations of already marketed drug products using as a reference a drug which is the subject of an approved application.

In Vivo Testing

The fourth document will be a proposed regulation establishing procedures and criteria for the promulgation of bioequivalence requirements on specific drugs with known or potential bioequivalence

problems. Under the proposal, generic drug products for which there is a known or potential bioequivalence problem must be shown to be comparable in rate and extent of absorption to a marketed reference product through *in vivo* testing and/or *in vitro* testing as specified by the FDA. Drug products subject to a bioequivalence requirement will also be subjected to bioequivalence testing without regard to whether an NDA has previously been approved. Thus, if a bioequivalence requirement specifies an *in vivo* testing method that is more sensitive than the clinical trials contained in the approved NDA, the holder of the application must conduct further testing.

The FDA will propose to establish bioequivalence requirements for specific drugs or drug classes pursuant to the procedures and criteria set out in the proposed bioequivalence regulations. The first proposals will be aimed at establishing such requirements for the medically most important drugs on the list with known bioequivalence problems. Manufacturers of such drug products who do not have adequate data to support an approval of a full or abbreviated NDA will be required to remove such drugs from the market or face seizures of products and injunction or criminal proceedings.

The FDA will also propose to revise 21 CFR 314.1(f) to require the same information in an abbreviated NDA, with respect to the labeling, composition, facilities and controls used for manufacturing, processing, and packaging, and submission of samples, as is required in a full NDA. This proposed revision reflects the FDA's conclusion that, although the kinds of information required in an abbreviated NDA may differ from those required in a full NDA, the quality of such information should be the same.

GMP Regulations

Finally, the FDA will propose new GMP regulations under which improved quality control procedures necessary to assure drug quality will be set forth. Among other things, detailed record keeping, drug sampling, laboratory, labeling, and personnel requirements will be included to assure that responsibility for quality control is exercised independently and documented at every phase of the manufacturing process.

In summary, the change in concept regarding the abbreviated NDA is but part of an active enforcement program. Because of new procedures being developed to assure drug product quality, the FDA

has determined that full or abbreviated NDAs are required for effective DESI drugs only where there is a bioequivalence or special manufacturing problem. Such premarketing approval is not required to assure the quality of the majority of the effective DESI drugs.

Interim Enforcement Policy

The proposed use of the abbreviated NDA will be subject to the rule-making provisions of the Administrative Procedures Act (APA). All interested persons will have the opportunity to participate in such rule-making. However, in the interim, the FDA will not proceed against those drugs evaluated as effective in the drug efficacy study, and which do not present a known or potential bioequivalence problem, for failure to obtain premarketing abbreviated NDA approval. It is not necessary for the FDA to follow the rule-making procedures of the APA in order to adopt this interim enforcement policy. Had the DESI notice been adopted as final orders following publication of a proposal and evaluation of public comment, a rule-making procedure would be required to revoke the new drug declarations made in the DESI notices. This is not the case here. The DESI notices were not adopted through a rule-making procedure; the FDA's declarations of new drug status constituted statements of policy and not enforceable obligations. The FDA knows of no rule of law or common sense that would require revocation of an opinion, whether contained in a letter or in the *Federal Register,* by a procedure more formal than the one which created it. **[The End]**

The FDA's Acceptance of Foreign Clinical Data

By WILLIAM E. RAGOLIA

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THE SUBJECT FOR DISCUSSION is what the Food and Drug Administration (FDA) does in accepting foreign clinical data. Such data are submitted to the FDA when a statute requires a manufacturer to obtain approval before introducing its products into interstate commerce. The description "foreign clinical data" is very broad. By definition, "foreign" must include every country outside of the United States, although in effect it is limited to those countries which have developed more sophisticated scientific communities. These countries, because of technological advances, find that their scientists are generating data which is of interest to those who want to sell products in the United States. Further, as a matter of routine practice, in the area of pharmaceuticals, this may be limited to England, Sweden and Switzerland on a general basis. Some particular research facilities in other European countries may be included, although satisfactory work from other parts of the world would not be precluded from FDA acceptance. By clinical data, I include preclinical animal work as necessary to initiate Phase I studies, as well as clinical research leading to the subsequent phases. Primarily, centers on submissions of foreign data to the FDA relate to original new drug application (NDA) approvals or new indications for use of a currently marketed drug. I expect, however, in the future that, if the Old Drug Monograph System becomes a reality, foreign data may have to be considered for those drugs whose monograph requires bioequivalency studies.

I recall Marc Antony's remark at Caesar's funeral about how the evil men do lives after them, but good always seems to be forgotten.

I often wonder if conventional wisdom in the scientific establishment in the United States regards foreign biomedical research from

the same perspective. Too often one is left to conclude it is the scientific catastrophe of thalidomide and the ethical horror of prisoner-of-war camps that are remembered, rather than the benefits of scientific discoveries throughout the world.

The scientists and other individuals who have had the responsibility and experience in presenting data to the FDA in connection with investigational new drugs and NDAs have been dismayed by the continuing limitations the FDA places on acceptance of data generated outside of the United States unless it is supported by some work done in this country. In effect, this means that the data generated are accepted by the FDA for the purpose of establishing safety, but not efficacy. The FDA defends its position broadly on the basis of its statutory mandate to protect the health and well-being of the public. Those who take exception to this policy raise a variety of issues, including allocation of important research funds and facilities and return on an increasing investment by United States companies in foreign-based research. Also mentioned are the lack of availability of certain drugs to United States citizens when they are available in other countries and a general objection to what is described as scientific chauvinism by those who lobby for the conducting of additional clinical research in the United States. Finally, those interested in the protection of human subjects in research projects maintain that it is unnecessary to expose additional patient populations to clinical studies if there already exist adequate data to justify the use of the product.

Expenditures in Foreign Countries

The economic significance of foreign clinical data may be appreciated by reviewing the changing commitment of research expenditures in foreign countries by drug manufacturers having headquarters in the United States. A recent survey of these companies shows that the amount spent for research on drugs for human use in the United States in 1971 totaled $576 million. The amount spent by the same companies in that year in foreign countries totaled $52 million. Each of these expenditures, domestic and foreign, represented an increase of 11% over the amount spent during 1970. In 1972, domestic expenditures increased by 4% over the 1971 level to $600 million; foreign research expenditures, totaling $66 million, represented an increase of 26% over 1971. The most dramatic shift in research expenditures, however, occurred in 1973. During that year, marked by inflationary trends both here and abroad, expenditures in the United States increased by only 7%, while foreign expenditures by United States com-

panies in the survey increased by 64%. This figure—64%—represents a dramatic change over 1972 levels, even if one takes into account the factors of the inflationary spiral and the devaluation of the United States dollar on foreign currency exchanges. The shrinking ratios of expenditures between the United States and foreign countries were: 1971, 11 to 1; 1972, 9 to 1; 1973, 6 to 1.

Intellectual Community

In attempting to parse the problem before the FDA concerning its acceptance of foreign clinical data, I would like to refer, for the purpose of gaining an additional perspective, to a series of lectures by Charles Percy Snow. Lord Snow, an English scientist and novelist, after leaving government service, in 1959 began speaking about the problem of the two cultures which exist within the intellectual community. In "The Two Cultures and the Scientific Revolution," he perceived:

"Two polar groups: at one pole we have the literary intellectuals . . . at the other scientists . . . between the two a gulf of mutual incomprehension—sometimes (particularly among the young) hostility and disregard, but most of all lack of understanding. They have a curious distorted image of each other and attitudes are so different that, even on the level of emotion they can't find much common ground."

The scientific intellectual wishes to generate data which are useful to the benefit of mankind. The literary intellectual—and I would ask you to keep in mind the fact that Snow uses the designation of literary intellectual only in the broadest generic sense—perceives a responsibility to protect his fellow man from the onslaught of those who would do him harm. One group wishes to provide benefits to mankind; the other group wishes to protect its members. The regulator, perhaps unhappily, is left with the responsibility of arbitrating the dilemma between these apparently conflicting interests which often are expressed with force and vigor by men of very different temperaments. In the sequel, "The Two Cultures: A Second Look," Snow speaks of an emerging third culture which:

"When it comes some of the difficulties of communication will at least be softened: for such a culture has, just to do its purpose, to be on speaking terms with the scientific one.

"Some social historians, as well as being on speaking terms with scientists, have felt bound to turn their attention to the literary intellectuals or more exactly to some manifestations of the literary culture at its extreme."

First-Hand Knowledge

Thus, the FDA acquires the identity of the third culture. However, in this relationship the FDA is advanced into what Snow described in a later lecture, "Science and Government":

"One of the most bizarre features of any advance industrial society in our time is that the cardinal choices have to be made by a handful of men: in secret: and, at least in legal form, by men who cannot have a first-hand knowledge of what those choices depend upon or what the results may be."

We can see, then, that Snow is talking about the polarization between the humanities and the sciences and between those who, in attempting to execute the mandates of a political body, must choose, sometimes largely at their own discretion, between and among those interests which they believe to be most important to the population at large. I think it is possible to appreciate the difficulties which exist in regard to the FDA's acceptance of data—and I limit that not only to foreign clinical data—if one first perceives the underlying conflicts between the polarized cultures outside and inside the FDA, and even within the communities which develop the data which the FDA must evaluate.

At present, we have the beginnings of a policy. The Agency, through *Federal Register* notices, has begun to articulate the terms of its policy by establishing guidelines which implicitly concede the validity of a diversity among the balancing of ethical considerations for the protection of human subjects. Hopefully, in the future, this will expand to include the evaluation of scientific data.

Clinical Research

I am referring, of course, to the FDA's recent addition to its regulations. Subpart (C), "International Research," otherwise known as 21 CFR 312.20. This regulation relies to a large extent upon the Declaration of Helsinki, which established recommendations for guiding doctors in clinical research. This statement of ethics was formally adopted by the World Medical Association (WMA) in June of 1964. The WMA, founded in 1947, is an international amalgamation of national medical associations. In the early 1970's, included among its members were the medical associations of over 60 nations. Its leaders have characterized it as an organization of physicians dealing with the concerns of the medical profession.

The Declaration of Helsinki, adopted by the WMA at its 18th annual meeting, was conceived in the 1950's in a project initiated under the direction of Dr. Hugh Clegg, the former editor of the *British*

Medical Journal. Dr. Clegg's project was completed under the guidance of Professor Antonio Spinelli of Italy, the Chairman of the Committee on Medical Ethics of the World Health Organization. The Declaration of Helsinki supports the concepts of the International Code of Medical Ethics and the Declaration of Geneva, which bind the physician's primary concern to the needs of his patient in contradistinction to the broader benefits that the research might have to the community at large. The Declaration of Helsinki, prior to adoption, was the subject of comment and criticism from many national medical associations and followed a series of recommendations on the entire subject of the ethical considerations of clinical research.

Declaration of Helsinki

The Declaration itself is rather simple in form. It first discusses basic principles, and then principles applying to clinical research associated with professional care and to clinical research where no therapy is involved. The basic considerations include:

(1) establishing adequate data as to the drug function by laboratory and animal experiments;

(2) the use of qualified individuals in conducting the research;

(3) a balance of benefit to risk;

(4) a foreseeable benefit to the general community; and

(5) special caution in the use of psychotropic substances.

In distinguishing between therapeutic versus nontherapeutic research, the Declaration of Helsinki advised that the attending physician has more discretion concerning informed consent in the case of a therapeutic situation than in the nontherapeutic situation, where informed consent should, as a rule, be obtained in writing.

The principles in the Declaration of Helsinki should be understood to establish, for the purpose of FDA compliance, only a minimal ethical standard for the protection of human subjects and clinical research. In countries which have laws and regulations that offer a great protection to the individual, it is these more exacting standards to which the clinical investigation must adhere.

Qualifications of Investigator

The FDA regulation on international research also addresses itself to the qualifications of the individual investigator, the facilities for performing the study, and necessary record keeping. In the case where

institutionalized subjects are used, frequently it is more difficult to evaluate the modicum of freedom in consenting. After information regarding the research is provided to the subject, it is recommended, but not required, that the protocol be subject to what is known as peer review. In the case where such a review committee is established, the investigator may not vote with the committee in regard to his protocol.

The regulations as discussed apply not only to new drugs subject to Section 505 of the Federal Food, Drug and Cosmetic Act, but also to the biomedical products subject to Section 351 of the Public Health Service Act. The major significance of the regulation established by the FDA is that it is a declaration by that Agency that the objective of protecting human subjects in clinical research may be obtained, notwithstanding certain differences in the procedures for instituting and conducting such research.

Regulation Falls Short

However, the regulation as promulgated falls short of achieving full recognition of foreign research standards. Section 312.20(c) provides that, under appropriate circumstances, data from foreign sources may render conducting Phase I and Phase II studies unnecessary. However, the foreign data from Phase III studies may be utilized only to supplement Phase III studies to be performed in the United States. By this statement, I conclude that under no circumstances will the FDA approve an NDA based solely on research done outside the United States. I find this position inconsistent with the general objectives of the regulation and appeal to my professional colleagues and counterparts within the FDA to bring this limitation to its appropriate demise.

Still lurking on the horizon is the even more difficult question dealing with the quality and quantity of scientific data that are required by the FDA to meet the statutory requirement of adequate and well-controlled studies. I find it difficult to believe that the cadre of government drug regulatory agencies around the world is out of step, as our own FDA marches in cadence. I am told that this view is an exaggeration and, in fact, there are regulatory agencies in other countries whose stringency equals that of the FDA. Whatever the case, there remains the undisputed fact that the standards for establishing the efficacy and safety of drugs based on adequate and well-controlled studies do differ in some countries which have highly re-

garded scientific institutions. Drawing again upon Lord Snow, I bring to your attention this observation in "The Two Cultures and the Scientific Revolution":

"There is no evidence that any country or race is better than any other in scientific teachability: there was a good deal of evidence that all are much alike: tradition and technical background seem to count for surprisingly little.

"The main issue is that the people in the industrialized countries are getting richer, and those in the nonindustrialized countries are at best standing still: so that the gap between the industrialized countries and the rest is widening every day. On the world scale this is the gap between the rich and the poor."

Limited Acceptance

In summary, I think it is fair to observe that the FDA is articulating what is becoming its policy for limited acceptance of foreign clinical data. One would hope that a perception of the conflicts which exist between various segments of the intellectual community would mellow into a tempered acceptance of each other's respected positions and of the positions held by different members within the polarized community. The FDA cannot be expected to permit the marketing of drugs for which it has no basis in concluding that the product is safe and effective. On the other hand, intellectual magnanimity can contribute to the more efficient employment of the world scientific resources.

[The End]

TCE FINDINGS INCOMPLETE, FDA DELAYS ACTION ON PETITION

Preliminary findings by the National Cancer Institute that the solvent trichloroethylene (TCE) produces liver tumors in mice were cited by the Health Research Group in a petition filed with the Food and Drug Administration (FDA) to ban the use of the substance as a food additive, but the Agency will not act until final test results are submitted. TCE is currently used to extract caffeine from decaffeinated coffee and in certain spice extraction processes, and residues are permitted at levels of 25 p.p.m. in decaffeinated coffee grounds and at 10 p.p.m. in decaffeinated instant coffee and coffee extracts. Tests conducted by the National Cancer Institute have shown that, among mice fed TCE at levels ranging from 500 to 2400 mg. per kg. of body weight, liver tumors occurred in 30 percent of the animals fed low doses and 44 percent of those fed high doses. Similar tests in rats did not produce any tumors.

The FDA noted that the tests did not involve feeding the animals coffee containing TCE and that the dosage levels were many times higher than the levels of TCE residues permitted in food. The Agency is reviewing preliminary data and will base regulatory action, if any, on the final test report.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,417

Devices to Control Devices

By JOSEPH R. RADZIUS

Mr. Radzius Is Food and Drug Counsel of the Dow Corning Corporation.

THIS IS THE SECOND SUCCESSIVE YEAR that the conference has included a workshop on medical devices. In light of regulatory events impacting upon the manufacture, distribution and use of medical devices, this panel will probably continue to be a part of the program for years to come.

For several decades, the principal objective of the Food and Drug Administration (FDA) was to assure the introduction of safe and effective drugs (as well as foods) to the consuming public. With respect to medical devices, the Agency has exercised minimal controls. Unlike new drugs, there are no preclearance mechanisms to assure safety and efficacy prior to sale and use. Under provisions of the current Federal Food, Drug and Cosmetic Act, remedial action is authorized only if the Agency can sustain a burden of proof that the device is misbranded or adulterated as delineated by sections 501 and 502 of the Act. For the past 20 years or more, administrative and judicial actions concerning medical devices have been virtually restricted to prohibitions and seizures of quack devices.

This is rapidly changing, and the Bureau of Devices and Diagnostics is imposing more and more regulatory controls intended to protect the public from injury due to the use of unsafe, ineffective and unreliable medical devices. Depending upon one's point of view, these actions are either a blessing or a disaster. There are many who consider such regulations long overdue.

There are an equal number who feel that additional restrictions are unnecessary—that incidence of injury associated with defective products is so low statistically that to suggest further regulation will serve only to inhibit new product innovation. They also feel that the public will be exposed to injury—and more risk will be created—because the device is not available.

I have selected four topics which are timely and, to some extent, controversial. They amply illustrate the expanding orbit of regulatory requirements which are constantly confronting the medical device industry. The topics are product recall, *in vitro* diagnostic regulations, activities involving devices classification and medical devices legislation

Product Recall

The Federal Food, Drug and Cosmetic Act provides the Agency with no statutory authority to require product recall. The remedies which the Agency can exercise are seizure, injunctive relief or criminal prosecution. If the Agency wishes to prevent the distribution and use of a product, any one or a combination of these remedial criteria is undesirable because they offer no means for removing the violative product quickly or efficiently. Offending products have been known to remain in commerce for years while such remedies were pursued.

Under Section 705(b) of the Act, the FDA has explicit authority to issue publicity about devices which, in its opinion, present an imminent danger to health or represent gross deception of the consumer. Through this section of the Act, the Agency has achieved manufacturer acquiescence to establish "voluntary" product recall as the customary measure for removing products from the market. The mere threat of adverse publicity with attendant destruction of trademark credibility coupled with potential product liability implications permits the manufacturer little choice.

However, "voluntary" recall does not necessarily insulate the manufacturer from adverse publicity. For example, a weekly "recall list" is issued, normally containing a paucity of information. As a result, the news media will publicize the information in a misleading and/or erroneous fashion. The Agency has publicly stated for several months that the concept of recall and the "recall list" should be modified to properly reflect recall situations. Unfortunately, to date, the Agency, with its usual alacrity, has done nothing.

The Agency frequently issues the "recall list" weeks (and often months) after the recall has been completed and the problem resolved. I am aware of one occasion where the news media publicized a product recall several weeks after completion. The lay reader and the uninformed public could be left with the impression that the problem was immediate and, in some cases, that there was a second recall involving the same manufacturer. Is this in the public interest?

I also would like to explore the most fundamental of issues—is the Agency "recall list" necessary? Presumably, the immediate response is

that it is needed to fulfill the obligation of disseminating public information, an obligation to which all government bodies are beholden. However, the truth of the matter is that the list is probably used most frequently by manufacturers to establish a competitive advantage. It serves no real purpose for individuals, groups or institutions interested in the public welfare. If there is a rule, there should be a reason and if there is no reason, there should be no rule.

Finally, what is a recall? A situation may most effectively be corrected by on-site labeling, a physician letter or the like. Even in the absence of an actual product recall, the Agency still defines it as a recall.

In Vitro Diagnostic Regulations

The March 1973 *in vitro* diagnostic regulations initiated significant impetus for support of a medical devices law. For those intimately involved in the field of diagnostics, the regulations were a classic example of Agency action which, in effect, treated a "medical device" as a "new drug." To many, this was the beginning of the end; the catastrophic experience of the drug industry with the 1962 amendments was to be repeated and would encompass the medical devices industry. A devices law became an attractive alternative.

I hope to discuss the regulatory ordeal confronting diagnostic manufacturers. The regulations have posed problems, and there will be an attempt to place these problems in proper perspective, delineating their present and probable impact upon the industry, the profession and the patient.

Many questions deserve exploration. For example, there is a body of specialists who believe that the Agency had no authority under the Act to issue such regulations, thus raising the fundamental issue of legality. If the Agency was *in delicto,* should the question have been reviewed by the courts?

As expected, when breaking new ground, the FDA tends to rely upon past experience. Because the Agency is drug oriented, has there been a failure to distinguish drugs from diagnostics in finalizing and implementing the regulations?

There are countless "small" diagnostic firms operating on fixed overhead, subject only to cyclical business costs—and these firms produce perfectly safe and effective products. What effect, if any, will this have on currently available diagnostic products? Will it impede the introduction of new diagnostics in the future? One cannot ignore the economic issues.

Product Classification

Under proposed legislation, contemporary products would be categorized and classified. The products would be classified as:

requiring "scientific review" (a charming term which simply means "premarket clearance");

requiring the setting of standards;

requiring nothing more than general controls which are now being exercised.

In anticipation of a law, the Bureau of Devices and Diagnostics established panels, and the effort has been in operation for over a year. There are 14 panels which have been convened. The 14 categories of devices being reviewed are:

(1) anesthesiology;
(2) cardiovascular;
(3) dental;
(4) ear, nose and throat;
(5) gastroenterological-urological;
(6) general and hospital and personal use;
(7) neurological;
(8) obstetrical-gynecological;
(9) ophthalmic;
(10) orthopedic;
(11) physical medicine (physiatry);
(12) general and plastic surgery;
(13) diagnostic products;
(14) radiology.

The first panel to complete its task was the cardiovascular panel, and relevant deliberations and conclusions are expected to be made public shortly.

It is my personal impression that the activities of the classification panels have been largely ignored. This is extremely dangerous. These panels exercise enormous powers and can affect the delivery of health care. Existing products could be removed from the marketplace, and reconsideration may be in order for certain products under development. It is essential that the deliberations of these panels be carefully followed and reviewed. If pertinent facts are not brought to the attention of the panels, the results could be disastrous. (Be prepared before you learn of it through the *Federal Register*.)

Certain issues must be addressed; I will list but a few:

What is the conflicts of interest situation for panel members?

Why does the industry member serve in a non-voting capacity?

How were the industry members selected?

Should the panels be open?

What is the relationship of Freedom of Information regulations to panel activities? How and to what extent can information be obtained?

Are there any plans to extend industry input to the panels?

Perhaps the Agency can enlighten us on these issues. It is quintessential that all parties pay close heed to these activities. If not, an insurmountable dilemma may prevail.

Medical Devices Legislation

The final topic is medical devices legislation. Recently, the question most often asked is when will there be a devices law? I think it now safe to say that the odds for a law in 1975 are excellent.

During November, extensive efforts were made to "mark up" the House bill. The substance of those efforts may be confidential; however, at the very least, a generalized review to bring us current would be valuable.

Mr. Steve Lawton of the House Staff publicly stated that what has been seen in the past and what will be seen after "mark up" will not be recognized—an obviously alarming comment. It merits some discussion.

Certain aspects of the Senate-passed bill remain in dispute; such as, the concept of custom devices, substantive as opposed to interpretive "current good manufacturing practices," the question of lot certification for some devices, and others.

In discussing the concept of recall earlier, there was specific reference to the Agency's lack of authority to require product recall. Proposed legislation will change that. The probing issue is whether proposed legislation is as favorable as many think.

I would like to repeat an amusing story which I have heard Mr. Alan Kaplan relate from time to time. Mr. Kaplan has stated that legislation necessarily is fraught with ambiguities. A medical devices law will prove no exception. Upon passage of the Food Additive Amendments of 1958, a knowledgeable person whom Mr. Kaplan knew referred to them as the "lawyers full employment Act of 1958." If and when a medical devices law is enacted, it will be interesting to note if essentially the same subtitle will apply. **[The End]**

For Everyone with Australian Business Interests

An Introduction to Trade Practices and Consumer Protection in Australia

Australia's Trade Practices Act of 1974 makes doing business in Australia a "whole new ball game." Sweeping changes in the rules governing trade practices and consumer protection, coupled with stiff penalties for breaches of law, make a thorough understanding of the Act a "must" for any U. S. company with business interests "down under."

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