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REPORTS

TO THE READER

The JOURNAL's first article is a comprehensive review of the Medical Device Amendments of 1976. Written by *Jay H. Geller,* Associate Chief Counsel for Enforcement for the Food and Drug Administration in Los Angeles, California, the article offers both an analysis of the significant features of the Amendments and a comparison of the Agency's authority over devices with its authority over foods, drugs and cosmetics. Mr. Geller not only sets forth the requirements of the major provisions of the law but also explains their reasons by citing legislative history. The article, which begins on page 424, is titled "The Medical Device Amendments of 1976—Major Features and Comparisons."

Food Update XV. The following papers were presented at the Food and Drug Law Institute's Food Update XV, which was held in Scottsdale, Arizona on April 25—29, 1976.

"Wanted—Plain Talk About Additives" expresses *William O. Beers'* concern over the constant and too-hasty criticism of the food-processing industry and its efforts in producing and improving the food supply. In his article beginning on page 448, the Chairman of the Board and Chief Executive Officer of the Kraftco Corporation states his belief in the safety of food additives and suggests specific programs for the industry to undertake to communicate this information to the public.

John C. Kirschman approaches the issue of food safety from a different viewpoint—that of a scientist. His article "Toxicology—The Exact Use of an Inexact Science" stresses the need for trained scientists to analyze carefully appropriate data in order to conduct an effective safety assessment. The article, which begins on page 455, also contains a discussion of the suitability of various test procedures and lists factors which must be considered in planning a toxicity testing program. Dr. Kirschman is Manager of Regulatory Sciences of General Foods Corporation.

Pharmaceutical Update VI. The following papers were presented at the Food and Drug Law Institute's Pharmaceutical Update VI, which was held in Cherry Hill, New Jersey on May 19 and 20, 1976.

The requirements of the Controlled Substances Act of 1970 provides the basis for *Thomas O. Henteleff's* article, which begins on page 465. Mr. Henteleff, a partner in the law firm of Kleinfeld, Kaplan and Becker, discusses that Act as it applies to manufacturers accustomed to regulation by the Food and Drug Administration. He cites recent cases of interest concerning the establishment of quotas, the distribution of new drugs and the dispensing of controlled drugs by doctors outside their practices. "Legal Developments Relating to Controlled Drugs" also contains summaries of regulations issued to enforce the Act.

In "Legal Implications of Good Manufacturing Practice Regulations," *Patrick V. Gibbons* raises the issue of substantive v. interpretive regulations in relation to the good manufacturing practice regulations of the Food and Drug Administration. Mr. Gibbons covers several aspects of the controversy, including the remedies provided for violations of the regulations. Mr. Gibbons, whose article begins on page 473, is Counsel, Domestic Manufacturing and Quality Control of the Schering-Plough Corporation.

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The Medical Device Amendments of 1976—Major Features and Comparisons

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THE "MEDICAL DEVICE AMENDMENTS OF 1976"[1] to the Federal Food, Drug and Cosmetic Act[2] provide the Food and Drug Administration (FDA) with important new regulatory tools with which to regulate medical devices. These new Amendments will significantly aid the FDA in carrying out its mandate to protect the public health. Through these Amendments, the FDA has been given exceptionally broad authority to regulate nearly every facet of the manufacture, distribution and sale of medical devices distributed in interstate commerce.

The purpose of this paper is to present the reader with an overview of the significant provisions of the Medical Device Amendments and to compare the authority the FDA has over foods, drugs

* This paper reflects the views of the author only and does not reflect the official views of either the Food and Drug Administration or the Department of Health, Education and Welfare.

[1] Public Law No. 94-295, 90 Stat. 539 (May 28, 1976). See H. R. Rep. No. 94-1080, 94th Congress, 2nd Session (1976). The Amendments were signed into law by President Ford on May 28, 1976 and became effective that day. See 41 *F. R.* 22620 (June 4, 1976). Many of the provisions of the Amendments that provide new regulatory tools for the FDA are patterned after provisions of the Consumer Product Safety Act, 15 U. S. C. 2051 *et seq.*

[2] (Hereinafter the Act.) 21 U. S. C. 301 *et seq.*

and cosmetics with the broad authority now provided over medical devices. As will be seen below, the Medical Device Amendments break much new ground in the realm of product regulation by the FDA. The creation of these new regulatory tools should serve notice on food, drug and cosmetic manufacturers that similar regulatory provisions may be applicable to them in the not too distant future.

Definition of Device

The Amendments significantly expand the statutory definition of the term device. Prior to these Amendments, a device was defined as an

"apparatus, instrument and contrivance, including their components, parts and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; or (2) to affect the structure of any function of the body of man or other animals."[3]

Under 21 U. S. C. 321(h) as amended, a device is now defined as an

"instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is—

"(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them.

"(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals, or

"(3) intended to affect the structure or any function of the body of man or other animals, and

"which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal purposes."

The broadening of the definition to include such articles such as *in vitro* reagents—for example, pregnancy diagnostics—reflects the awareness of Congress of both the need to have broad regulatory authority over such articles and the increasing difficulty of drawing the line between drugs[4] and devices.[5] That part of the definition which excludes articles that act chemically in or on the body or which are metabolized by the body is a further refinement of the

[3] See Title 21 USCA Sec. 1-800, p. 121.

[4] See 21 U. S. C. 321(g)(1).

[5] H. R. Rep. No. 94-853, 94th Congress, 2nd Session, 5—9 (Feb. 29, 1976). Especially significant here is the case *United States v. An Article of Drug... OVA III,* Civil No. 74-572 (DC NJ July 16, 1976), affirmed No. 75-2193 (April 21, 1976) in which the FDA sought to have a pregnancy diagnostic classified as a drug. The District Court held the article not to be a drug because it deemed pregnancy not to be a disease.

line drawn between drugs and devices. Also in this connection, the definition of device now includes articles named in the National Formulary and United States Pharmacopeia official compendia (as is the case with drugs).[6]

Another significant change in the definition of device is that it includes within its scope articles intended for use in the diagnosis of disease or *other conditions,* a departure from both the old device definition and the current definition of a drug.[7] This "other conditions" provision is obviously geared to articles intended for use in diagnosing conditions such as pregnancy, which may not necessarily be considered "diseases" in medical parlance.[8] The definition of drug, however, was not amended, and does not extend to any article other than one intended to diagnose disease, thereby creating a distinction between drugs and devices that conceptually should not exist. The legislative history offers no explanation as to why the device definition was broadened without a concomitant broadening of the definition of drug.

Presumption as to Interstate Commerce

The jurisdiction of the FDA over articles subject to the Act is predicated on the article having some connection with interstate commerce.[9] The Amendments provide that "in any action to enforce the requirements of this Act respecting a device the connection with interstate commerce required for jurisdiction in such action will be presumed to exist."[10] This rebuttable presumption relieves the government of its usual burden of proving the element of interstate commerce in civil and criminal actions, by shifting the burden of showing a lack of interstate commerce to the claimant or defendant. Too often trials have been lengthened unnecessarily and unnecessary costs have been incurred by the government in having to prove interstate commerce by bringing witnesses hundreds of miles to establish that an article was shipped across state lines on a common carrier, simply because a recalcitrant claimant or defendant would not stipulate to such facts. The legislative history indicates that Congress included this presumption because the usual requirement that the government prove at a trial that an article proceeded against was introduced into,

[6] 21 U. S. C. 321(g)(1)(A). Official compendia are defined at 21 U. S. C. 321(j) to include the United States Pharmacopeia and the National Formulary. These references contain standards of strength, quality and purity of medicinal products sold for medicinal use. U.S.P. XVIII, 1970, p. xxvi.

[7] 21 U. S. C. 321(g)(1)(B).

[8] H. R. Rep. No. 94-853, *supra,* at 9.

[9] 21 U. S. C. 321(e), 331—334.

[10] 21 U. S. C. 379a.

in, or held for sale after shipment in interstate commerce imposed a major evidence gathering burden on FDA inspectional personnel.[11] The Amendments, however, apply *only* to devices. Congress did not see fit to extend this presumption to foods, drugs or cosmetics even though the public policy considerations would clearly be the same.

Administrative Restraint

Perhaps the most revolutionary innovation in the Amendments is a provision which allows for detention of devices discovered during the course of an official investigation which appear to the FDA inspector to be adulterated or misbranded.[12] A detention order, which must be approved by an individual designated by the Secretary of Health, Education and Welfare,[13] may last up to twenty days, with an extension for another thirty days to allow for institution of seizure or injunction proceedings.[14] Upon request, an informal hearing is available to the person whose device is detained.[15] The detained device may be moved only pursuant to an order of the Secretary or by expiration of the detention.[16] It is now a violation of the Act to move a device in violation of a detention order or to remove or to alter any label identifying the device as detained.[17]

The concept of detention by an inspector during the course of an official inspection is a totally new concept in the Act. Never before have inspectors been able to seek detention of devices or other articles subject to the Act's jurisdiction during the course of an official inspection.[18] To insure that articles which appear to be in violation of the law are not moved, the FDA has had to rely on voluntary holds by manufacturers and distributors or on state officials to exercise their embargo authority,[19] if any, to detain devices until the FDA could institute court proceedings.[20] In the legislative history, Congress indicates that the detention authority is necessary because

"The public is sometimes unnecessarily exposed to *products* that violate the Act during the time period between discovery of a violation by an inspector

[11] H. R. Rep. No. 94-853, *supra*, at 15.

[12] 21 U. S. C. 374(g)(1).

[13] (Hereinafter the Secretary.) *Id.* The Secretary's authority under the Act and these Amendments has been delegated to the Commissioner of Food and Drugs. 21 CFR 2.120. See 41 *F. R.* 22620 (June 4, 1976). The individual to whom detention authority would be delegated could be either an FDA Regional or District Director.

[14] *Id.*

[15] *Id.*

[16] 21 U. S. C. 374(g)(2)(A).

[17] 21 U. S. C. 331(r).

[18] Detention authority is provided for articles offered for import into the United States. See 21 U. S. C. 381(a).

[19] See, for example, Cal. Health & Safety Code, Sec. 26830.

[20] 21 U. S. C. 332, 334.

and the completion of legal action resulting in seizure of a *product* or an injunction prohibiting a violation by a firm or individual. The Act provides no authority to detain temporarily *products* suspected or known to be defective."[21] (Emphasis supplied.)

Significantly, the legislative history indicates the need to detain *products,* yet the Amendment to the Act is limited solely to devices. Since the detention mechanism is such a powerful regulatory tool, it is difficult to understand why Congress limited its scope solely to devices while it could so easily have been made applicable to foods, drugs and cosmetics. The legislative history offers no explanations.

Classification of Devices

The Amendments provide for classification of devices for human use into three categories.[22] The first category, "Class I, General Controls," are those devices for which specific performance standards or premarket approval are not required to assure their safety and effectiveness,[23] and whose safety and effectiveness can be assured under the general provisions of the Amendments relating to devices[24] as well as under the adulteration and misbranding sections of the Act.[25] The second category is "Class II, Performance Standards" which includes devices for which general controls are insufficient and for which specific performance standards can be established in order to assure their safety and effectiveness.[26] The third category is "Class III, Premarket Approval" which covers devices that require premarket clearance because their safety and effectiveness cannot be assured through either the general controls or performance standards, and which are either intended for use in life supporting or sustaining situations or which present an unreasonable risk of illness or injury.[27]

This three-part classification is new to the Act. For human and animal drugs, the Act has only two categories: (1) those for which premarket approval is required, for example, new drugs[28] and new animal drugs;[29] and (2) those for which no premarket approval is required. The new drug and new animal drug provisions are based on a standard of general recognition of safety and effectiveness among qualified experts.[30] This general recognition standard is not applicable

[21] H. R. Rep. No. 94-853, *supra,* at 47.
[22] 21 U. S. C. 360c.
[23] 21 U. S. C. 360c(a)(1)(A).
[24] 21 U. S. C. 360f, 360h, 360i, 360j(a), (b), (e), (f), (j) and (k), 21 U. S. C. 374(a) and (e).
[25] 21 U. S. C. 351 and 352.
[26] 21 U. S. C. 360c(a)(1)(B).
[27] 21 U. S. C. 360c(a)(1)(C).
[28] 21 U. S. C. 321(p), 355.
[29] 21 U. S. C. 321(w), 360b.
[30] See footnotes 7 and 8, *supra.*

to devices. In the case of foods, only food additives[31] are treated in a manner different from other foods, and then only if they are not generally recognized by experts as safe. All cosmetics[32] are classified the same under existing law. Pesticide chemicals used in or on foods[33] and color additives used in or on foods, drugs, cosmetics and medical devices coming into contact with the human body[34] must be precleared for safety.

Transitional Provisions for Devices Considered as New Drugs or Antibiotic Drugs

The Amendments set forth the procedures for handling devices for human use that previously have been classed as either new drugs or antibiotic drugs.[35] Each device which is the subject of an approved new drug application (NDA), an investigational NDA, a pending NDA, an order in which the FDA has declared such article to be a new drug, or in litigation arising under the new drug provisions of the Act is automatically deemed to be a Class III device unless the Secretary approves a petition placing such device in Class I or Class II.[36] The transitional provisions continue in effect the requirements of an approved NDA or investigational NDA for a device where applicable.[37] For a device with a pending NDA, such application automatically becomes an application for device premarket approval.[38] For the remaining types of devices classified in Class III, approved premarket applications must be sought.[39]

For devices that previously have been considered antibiotic drugs, prior regulations with regard to them remain in effect until such devices are placed into one of the three device classes.[40]

These provisions ensure continued strict regulatory controls over this type of article until implementing regulations under the Amendments can be promulgated. The Food Additive Amendments[41] and the Color Additive Amendments[42] applied to all such articles falling within their scope, regardless of how long they had been on the market. There is no "grandfather clause" exempting devices current-

[31] 21 U. S. C. 321(s), 348.
[32] 21 U. S. C. 321(i).
[33] 21 U. S. C. 321(q), 346a.
[34] 21 U. S. C. 376(a). The *definition* of color additive, 21 U. S. C. 321(t), was not amended to include medical devices.
[35] 21 U. S. C. 360j(c).
[36] 21 U. S. C. 360j(*l*)(1).
[37] 21 U. S. C. 360j(*l*)(1)(e)(A) and (C).
[38] 21 U. S. C. 360j(*l*)(1)(3)(B).
[39] 21 U. S. C. 360j(*l*)(1)(3)(D).
[40] 21 U. S. C. 360j(*l*)(1)(4).
[41] 21 U. S. C. 321(s).
[42] P. L. 86-618, Sec. 203 (July 12, 1960).

ly on the market from the premarket application provisions of the Act as there was with new drugs.[43] There is, however, a 30-month grace period for Class III devices on the market on the date of enactment of the Amendments within which to comply with premarket approval requirements.[44]

Classification Panels

Another innovation in the Amendments is the establishment of classification panels consisting of experts in the fields of clinical and administrative medicine, engineering, biological and physical science and related fields.[45] The duties of these panels include determining which devices should be subject to general controls, performance standards or premarket approvals, so that the FDA may notify manufacturers and importers of medical devices of the legal requirements to which they will be held.[46] The Amendments detail how the panels are organized and operate, procedures for implementing classifications, how changes in classification are to be made, and initial classification of devices not in interstate commerce prior to the enactment of the Amendments.[47] Such panels provide added legitimacy to Agency decisions because the panel members are generally impartial scientists who are not under the same Congressional, industry and public pressures as are the FDA's personnel.

Panels such as those established to classify devices are not specifically authorized for foods, drugs or cosmetics, *per se*. Certain activities with respect to color additives[48] or pesticide chemicals[49] may be submitted to advisory committees upon request of an adversely affected party. While the FDA makes great use of advisory committees, especially in relation to the establishment of monographs for over-the-counter (OTC) drugs,[50] the closest it has come to using panels such as these intended for devices were the expert panels contracted for review of the safety and effectiveness of new drugs when the 1962 drug amendments became effective.[51] Although these expert drug panels were not specifically authorized by the Act, the FDA's reliance on their recommendations and findings has been approved by the Courts.[52]

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[43] P. L. 86-781, Sec. 107(c)(4) (Oct. 10, 1962).
[44] 21 U. S. C. 351(f)(2)(B).
[45] 21 U. S. C. 360c(b)(1), (2).
[46] *Id.*
[47] 21 U. S. C. 360c(c)—(h).
[48] 21 U. S. C. 376(b)(5)(C) and (D).
[49] 21 U. S. C. 346a(e) and (f).
[50] See 21 CFR 330.
[51] See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U. S. 609, 614—615 (1973); *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U. S. 645, 647 (1973). 31 *F. R.* 9426 (July 9, 1966).
[52] See *Weinberger v. Hynson, Westcott & Dunning, Inc., supra; Weinberger v. Bentex Pharmaceuticals, Inc., supra.*

Providing for the use of such panels in the Amendments is a clear Congressional affirmation of the FDA's need to rely on competent outside experts to make recommendations to the Agency on important public health determinations. The reliance on such panels' recommendations usually bolsters the Agency's position in court where the subject matter of a panel's recommendations is an issue.

Performance Standards

The Amendments provide for the promulgation of performance standards for Class III devices[53] that "provide reasonable assurance of (the device's) safe and effective performance" including construction, components, power systems, testing, restrictions on sales and the form and content of labeling for proper use of the device.[54] A proceeding for the development of a performance standard is initiated by the Secretary by inviting any person, including any federal agency, to develop the standard.[55] The Amendments also provide that an already existing standard may be adopted as a formal performance standard.[56]

There is no provision in the Act for the Secretary to initiate an NDA or new animal drug application. Indeed, the legislative history expressly rejects any notion of the Secretary so doing.[57] However, either the Secretary or an interested person can petition for approved use of a food additive,[58] pesticide chemical[59] or color additive.[60] Some may argue that the OTC drug monographs are the drug equivalent of a device performance standard.

Premarket Approval

For the first time, the Act requires premarket approval for these devices placed in Class III.[61] The Act sets forth the mechanisms for applying for premarket approval, action on such application, and withdrawal of approval of an application.[62] All of these mechanisms

[53] 21 U. S. C. 360d(a). Authority for promulgation of performance standards is also vested in the Secretary for electronic products emitting radiation. 42 U. S. C. 263(f). Similar authority is provided to the Consumer Product Safety Commission for products it regulates. 51 U. S. C. 2056.

[54] 21 U. S. C. 360d(a).

[55] 21 U. S. C. 360d(b), (c).

[56] 21 U. S. C. 360d(d).

[57] See H. R. Rep. No. 2139, 75th Congress, 3rd Session, 9 (April 14, 1938); H. R. Rep. No. 2464, 87th Congress, 2nd Session, 3 (Sept. 22, 1962).

[58] 21 U. S. C. 348(d).

[59] 21 U. S. C. 346a(e).

[60] 21 U. S. C. 376(b)(5)(C)(i).

[61] 21 U. S. C. 360e.

[62] 21 U. S. C. 360e(c)—(e).

are substantially similar to those in effect for new drugs and new animal drugs.[63] The Amendments, however, for the first time, provide for a "product development protocol."[64] This procedure allows the development of a medical device and the data supporting its safety and efficacy at the same time. If the Secretary approves a notice of completion of a product development protocol,[65] it is tantamount to approval of a premarket approval application. There is no "product development protocol" counterpart for new drugs, new animal drugs, food additives or color additives.

The Amendments establish alternative administrative mechanisms for review of an order approving or denying a premarket application or product development protocol.[66] Upon a petition for review of any such order, the Secretary may either hold a formal administrative hearing *or* refer the matter to an advisory committee of experts.[67] No such alternatives are available for a review of the Secretary's action on a food additive petition, NDA or new animal drug application. With these latter three premarket approval products, the only administrative review mechanism is by way of a formal administrative hearing.[68] In the case of a proposed pesticide chemical tolerance regulation, referral to an advisory committee *must* be made on request, with a later opportunity for a formal administrative hearing.[69] Referral of a proposed regulation concerning a color additive *may* be made to an advisory committee upon request, if the Secretary determines that such a referral is necessary, with a later opportunity for a formal administrative hearing.[70] The Amendments incorporate a middle ground of existing procedures by providing alternative means of review that are mutually exclusive, thus allowing the referral mechanism not available for food additives, new drugs and new animal drugs, but denying the opportunity for *both* referral and an administrative hearing available for pesticide chemicals and color additives.

Banned Devices

The Amendments provide that when the Secretary finds, after consultation with the appropriate classification panel, that a Class I, II or III device intended for human use presents substantial deception or an unreasonable and substantial risk of illness or injury, "he

[63] See 21 U. S. C. 355(c)—(e); 21 U. S. C. 360b(c)—(e).
[64] 21 U. S. C. 360e(f).
[65] 21 U. S. C. 360e(f)(5)—(7).
[66] 21 U. S. C. 360e(g).
[67] 21 U. S. C. 360e(g)(1) and (2).
[68] 21 U. S. C. 348(g), 355(h), 360b(h).
[69] 21 U. S. C. 346a(e).
[70] 21 U. S. C. 376(b)(5)(C)(i) and (d).

may initiate a proceeding to promulgate a regulation to make such a device a banned device."[71] An informal hearing is available to interested persons.[72] Where the Secretary determines that the use of the device "presents an unreasonable, direct, and substantial danger to the health of individuals" and so notifies the manufacturer of the device, he may implement the proposed regulation immediately pending final Agency action.[73] While there is no specific "banning" counterpart for other articles regulated by the Act, it could be accomplished through the Agency's inherent power to issue declaratory orders under the Administrative Procedure Act[74] or under its general rule-making authority.[75]

Judicial Review

The Amendments provide for judicial review of final Agency orders concerning classification of devices, performance standards, reclassification of devices, premarket approval, banned devices, good manufacturing practice (GMP) regulations and investigational uses of devices.[76] Such review must be made by the United States Court of Appeals for the District of Columbia or the Circuit Court of Appeals where the person challenging the Agency action resides or has his principal place of business.[77] This provision is consistent with the review of similar types of orders affecting foods and drugs.[78]

A provision found in the Amendments which allows the Circuit Court to order the Secretary to reopen an administrative proceeding upon a petitioner's showing to the Court that he had reasonable grounds for failing to adduce additional data regarding the regulation[79] is available only for new drugs,[80] new animal drugs,[81] food additives[82] and pesticide chemicals[83] in addition to Class III devices.

[71] 21 U. S. C. 360f(a). The Consumer Product Safety Commission has similar authority to ban hazardous products subject to its jurisdiction. 15 U. S. C. 2057.

[72] *Id.*

[73] 21 U. S. C. 360f(b).

[74] 5 U. S. C. 500 *et seq.*

[75] 21 U. S. C. 371(a).

[76] 21 U. S. C. 360g(a).

[77] *Id.*

[78] See 21 U. S. C. 346a(i) (pesticide chemicals); 21 U. S. C. 348(g) (food additives); 21 U. S. C. 355(h) (new drugs); 21 U. S. C. 356(c) (insulin-containing drugs); 21 U. S. C. 357(f) (antibiotic drugs); 21 U. S. C. 360b(h) (new animal drugs); 21 U. S. C. 371(e) and (f) (standardized foods, special dietary foods, emergency permits, poisonous ingredients in foods, compendium drugs, narcotic-containing drugs and drugs subject to deterioration); and 21 U. S. C. 376(d) (color additives).

[79] 21 U. S. C. 360g(b).

[80] 21 U. S. C. 355(h).

[81] 21 U. S. C. 360b(h).

[82] 21 U. S. C. 348(g)(4).

[83] 21 U. S. C. 346a(i)(4).

This reopening mechanism has never been invoked by a Circuit Court in which review of a final Agency order has been sought.

Notification and Other Remedies

When the Secretary finds that a device intended for human use "presents an unreasonable risk of substantial harm to the public health" and that notification is necessary "to eliminate the unreasonable risk of such harm and no more practicable means is available" to eliminate such risk, he shall issue an order so notifying all health professionals who prescribe or use such a device and any person(s) who should properly receive such notification.[84] This provision also allows for notification to be provided to those to whom treatment with the device has been administered.[85] The notification procedure is determined by the Secretary.[86] There is no counterpart to this notification in the Act for food, drugs or cosmetics. This provision supplements the Secretary's general publicity authority to disseminate information regarding food, drugs, devices or cosmetics in situations involving imminent danger to health or gross deception of the consumer.[87] This section significantly augments the Secretary's authority to alert the public to potential and actual risks associated with the use of certain devices.

Another significant new remedy is the "repair, replacement or refund" feature of the Amendments.[88] If the Secretary determines that the notification procedure is insufficient and (1) the device presents an unreasonable risk of substantial harm to human users, (2) there are reasonable grounds to believe the device was not properly designed and manufactured, and (3) there are reasonable grounds to believe that the unreasonable risk was caused by the manufacturer, importer, distributor or retailer, the Secretary may order such manufacturer, importer or distributor to *repair* the device to eliminate the unreasonable risk, *replace* the device with one that complies with the Act and/or *refund* the purchase price of the device (less a reasonable allowance for use if the device has been used by the user for more than one year).[89] The purpose of this provision is to eliminate risks associated with devices and to provide consumers with economic

[84] 21 U. S. C. 360h(a). Similar provisions exist for electronic products emitting radiation (42 U. S. C. 263(g) and products subject to the Consumer Product Safety Act (15 U. S. C. 2064).

[85] 21 U. S. C. 360h(a).

[86] *Id.*

[87] 21 U. S. C. 375. See H. R. Rep. No. 94-853, *supra*, at 21.

[88] 21 U. S. C. 360h(b). See footnote 84, *supra*.

[89] 21 U. S. C. 360h(b)(1)(A).

redress for defective devices presenting unreasonable risks.[90] Congress contemplated that a notification order would suffice for devices that presented reasonable risks when manufactured but whose risks became unreasonable due to a change in technology.[91] There is no counterpart to this remedy provision for any other articles regulated by the Act. This provision is highly innovative for the Act and gives the FDA significant new powers to keep device manufacturers within the confines of the law.

A final remedy provided is reimbursement.[92] A replacement, repair or refund order may also require a manufacturer, distributor, retailer or importer to reimburse any other person similarly situated for expenses incurred in carrying out such order if the Secretary determines reimbursement is required to protect the public health.[93] The Amendments state clearly that such reimbursement orders will not affect the private rights one party may have against another.[94] This provision, which has no counterpart elsewhere in the Act, is another significant enforcement tool in the hands of the Secretary.

Records and Reports

The Amendments allow the Secretary to promulgate regulations which require manufacturers, distributors, importers and retailers of devices for human use to establish and maintain records, to make reports to assure that devices are not adulterated or misbranded and to otherwise assure the safety and effectiveness of the device.[95] The regulations must not be burdensome, must state the reason why records are requested, and must preserve the anonymity of patient identity except in exceptional circumstances.[96] The Amendments exempt from these requirements:

(1) licensed practitioners manufacturing or importing and using devices for use in their own practices;

(2) a person manufacturing or importing devices for his or her own use in research or teaching and not for selling; and

(3) anyone else the Secretary, by regulation, sees fit to exempt from the record keeping and reporting requirements.[97]

The records and reports provisions are intended to aid the Secretary in determining whether a device complies with other provisions

[90] H. R. Rep. No. 94-853, *supra*, at 23.
[91] *Id.*
[92] 21 U. S. C. 360h(c).
[93] *Id.*
[94] 21 U. S. C. 360h(d).
[95] 21 U. S. C. 360i.
[96] 21 U. S. C. 360i(a).
[97] 21 U. S. C. 360i(b).

of the Act as well as to assist in making determinations as to what regulatory action, if any, should be taken with respect to a device.[98] Under the Act, maintenance of specific records is required of all new drug[99] and new animal drug[100] application holders. Similarly, maintenance of records is required of all drug manufacturers[101] and some food manufacturers[102] under the GMP regulations. Since such GMP regulations limit the types of documents to be maintained, this new provision of the Amendments gives the FDA wide latitude and open-ended authority to enact whatever device record keeping requirements it deems necessary.

General Provisions

The Amendments contain twelve general provisions, miscellaneous subject matters grouped under one heading for convenience.[103] The significant provisions are discussed here, with the exception of the transitional provisions which are discussed at pages 429 and 430.

A. Custom Devices.—A significant general provision is that which exempts certain devices, denominated as "custom devices," from the performance standard and premarket clearance provisions when the device:

(1) is made on the order of a *physician* or *dentist;*

(2) is intended either for a particular patient or for the practitioner's use in his or her own practice; and

(3) is not generally available to, or used by, other physicians and dentists.[104]

It is noteworthy that this section does not specifically include *chiropractors,* who are well-known users of medical devices. However, the Amendments provide that the Secretary may, by regulation, after an oral hearing, designate other persons qualified to receive the custom device exemption.[105] This provision is in accordance with the FDA's philosophy that neither the Act nor the FDA are intended to regulate how the individual practitioner conducts his or her medical practice.

[98] H. R. Rep. No. 94-853, *supra,* at 31.
[99] 21 U. S. C. 355(j).
[100] 21 U. S. C. 360b(e).
[101] See the GMP Regulations for drug products, 21 U. S. C. 211.101, 211.110, 211.115, 225.103, 225.110, 225.115, 226.-102, 226.110 and 226.115.
[102] See the food GMP Regulations, 21 CFR 128a (smoked fish); 128b (low-acid canned foods); 128c (cacao products); 128d (bottled water).
[103] 21 U. S. C. 360j.
[104] 21 U. S. C. 360j(b).
[105] *Id.*

B. Publication of Notices.—The general provisions also require that all proposed rule-making, or other actions, taken under the classification, performance standards, premarket approval, banned devices, notification, and records and reports sections appear in the *Federal Register*. The notice must state:

(1) the reasons for the action to be taken;

(2) the manner in which interested persons may examine the data upon which the proposed action is based; and

(3) the period of time for comment (to be not less than 60 nor more than 90 days).[106]

The FDA, through its detailed preambles to proposed regulations, has long followed these practices in rule-making procedures without such a specific requirement. It is significant again that this section applies only to rule-making to be conducted on *devices* and does not extend to foods, drugs or cosmetics.

C. Restricted or Prescription Devices.—The general provisions allow the Secretary to promulgate regulations requiring that certain devices be restricted to sale, distribution or use upon written or oral prescription of a licensed practitioner where there is a potentiality for harmful effect, or particular expertise is needed to safely and effectively use the device.[107] Prior to enactment of the Amendments, prescription devices were regulated under the misbranding provisions of the Act[108] and regulations promulgated pursuant thereto.[109] The restrictions may not be made solely on the basis of failure of a health care professional to be board-eligible or board-certified.[110] The Secretary may require statements of restriction on the label of any such device.[111] The provision also recognizes the skills of nurses and technicians in using such devices.[112] A somewhat analogous provision has been in effect for prescription drugs since 1938.[113]

[106] 21 U. S. C. 360j(d).

[107] 21 U. S. C. 360j(e).

[108] 21 U. S. C. 352(f)(1) and (2).

[109] 21 CFR 801.109. The FDA published a notice (41 *F. R.* 22621 (June 4, 1976)) stating that "Restricted devices include all prescription devices as now defined in 21 CFR 801.109... (See House Report No. 94-853, Medical Device Amendments, February 29, 1976, at 24—25)."

[110] A board-eligible practitioner is one who has the training or experience to make him or her eligible for certification by a certifying board recognized by the American Board of Medical Specialties. See 21 U. S. C. 360j(e)(1). A board-certified practitioner is one who has been certified by such a board of the American Board of Medical Specialties. *Id.*

[111] 21 U. S. C. 360j(e)(2).

[112] H. R. Rep. No. 94-853, *supra*, at 24.

[113] 21 U. S. C. 353(b).

The drug provision, however, does not require a regulation to be promulgated for a particular drug before it is considered to be a prescription drug as is the case with prescription devices. With devices, the Secretary must decide administratively whether a particular device is a prescription device. With drugs, he may establish prescription status either through an administrative proceeding[114] or by enforcement proceedings in a federal district court.[115]

D. Good Manufacturing Practice Requirements.—The general provisions allow the Secretary to promulgate regulations establishing GMPs for the manufacture, storage, packing and installation of devices to assure that the devices are safe and effective.[116] Regulations issued by the FDA for GMP of human and animal drugs[117] and medicated feeds[118] have been promulgated pursuant to the Agency's general rule-making authority[119] and not through a specific authority, such as that now provided for medical devices. Likewise, GMP regulations have been promulgated for the food industry as a whole (sanitation)[120] and specific segments thereof.[121]

An amendment to the adulteration provisions of the Act declares a device to be adulterated if it fails to comply with the GMP regulations.[122] Since 1962, a drug not manufactured in conformity with GMPs has been deemed to be adulterated.[123] There is no provision in the Act, however, deeming foods not manufactured in conformity with GMPs to be adulterated. Food not manufactured in conformity with GMPs is considered to be adulterated as having been prepared, packed or held under insanitary conditions.[124] There are no GMPs for cosmetics.

The device GMP provision allows the Secretary to exempt certain individuals from specific GMP regulations by granting a petition for a variance.[125] The statute details what information must be in the petition and how the petition is handled.[126] The purpose of the variance provision is to allow for flexibility for certain seg-

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[114] 21 U. S. C. 371(a). See *Weinberger v. Hynson, Westcott and Dunning, Inc., supra,* and *Weinberger v. Bentex Pharmaceuticals, Inc., supra,* where the Supreme Court held that the FDA has primary jurisdiction to determine administratively the status of particular drugs subject to regulation under the Act.

[115] 21 U. S. C. 331, 332 and 334.

[116] 21 U. S. C. 360j(f).

[117] 21 CFR 211.1 *et seq.*

[118] 21 CFR 225.1 *et seq.*

[119] 21 U. S. C. 371(a).

[120] 21 CFR 128.

[121] See 21 CFR 128a—128d.

[122] 21 U. S. C. 351(h).

[123] 21 U. S. C. 351(a)(2)(B). P. L. 87-781 (Oct. 10, 1962).

[124] 21 U. S. C. 342(a)(4).

[125] 21 U. S. C. 360j(f)(2).

[126] *Id.*

ments of a highly diverse industry.[127] Congress apparently felt that the device industry is more diverse than either the food or drug industries although the legislative history is silent on the point, since no other GMP provisions in the Act or its regulations have a variance provision.

Finally, the GMP section requires that the Secretary appoint advisory committees for advice and recommendations on proposed GMP regulations and petitions for variances.[128] No such advisory committees are, or have been, required for promulgation of food or drug GMP regulations.

E. Exemption for Investigational Use.—Another general provision permits an exemption from the statutory requirements in the case of human devices intended for investigational use by qualified experts.[129] The person seeking the investigational exemption must:

(1) submit a plan for clinical testing to a local institution review committee, which must be approved by such committee;

(2) assure, except in emergency cases, that informed consent is obtained from each human subject; and

(3) maintain certain records and reports.[130]

The legislation requires the Secretary to promulgate regulations setting forth the conditions under which the investigational exemption is to be pursued.[131] The purpose of this provision is "to encourage, to the extent consistent with the public health and safety and with ethical standards, the discovery and development of useful devices intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose."[132]

There are similar provisions in the Act for investigational exemptions for food additives,[133] new drugs[134] and new animal drugs.[135] Detailed regulations are in effect implementing the investigational food additive,[136] new drug[137] and new animal drug[138] procedures. It would seem logical that the investigational device regulations would be patterned after these regulations that already have been promulgated.

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[127] H. R. Rep. No. 94-853, *supra*, at 25.
[128] 21 U. S. C. 360j(f)(3).
[129] 21 U. S. C. 360j(g).
[130] 21 U. S. C. 360j(g)(3).
[131] 21 U. S. C. 360j(g)(2).
[132] 21 U. S. C. 360j(g)(1).
[133] 21 U. S. C. 348(i).
[134] 21 U. S. C. 355(i).
[135] 21 U. S. C. 360b(j).
[136] 21 CFR 121.75.
[137] 21 CFR 312.
[138] 21 CFR 511.

F. Release of Safety and Effectiveness Information.—The Amendments require the Secretary to promulgate regulations that provide for release of a detailed summary of the safety and efficacy data supporting approval or denial of a premarket application, protocol or exemption order[139] to be released to the public at the time the order is issued.[140] Similar regulations are to be promulgated that are applicable to advisory committee decisions on these matters.[141] A final caveat to this section to insure that a proprietary interest remains with the developer of the data is that no person may use information obtained under this section to establish the safety and effectiveness of another device.[142] This, however, would not apply to the person originally submitting the data to the FDA.[143] This data release provision resulted from Congressional sentiment that the "best interests of government, industry and the public are served by proper public scrutiny of actions of the Food and Drug Administration."[144] Congress felt that "this provision, coupled with requirements that the proceedings of advisory panels be transcribed and requirements that classification panels and the Secretary set forth reasons for recommendations and decisions, will help assure effective public scrutiny and Congressional oversight."[145]

No comparable provisions are found in the Act for pesticide chemicals, food additives or color additives, which must be approved for safety, or for new drugs or new animal drugs which must be approved for both safety and effectiveness. However, a provision is made in regulations promulgated pursuant to the Freedom of Information Act[146] for public disclosure of "a summary or summaries of the safety and effectiveness data" in new drug[147] and new animal drug[148] application files. Similar regulations presumably will be enacted for data in Class III device premarket application and protocol files. For food additives,[149] and color additives,[150] the regulations provide for public disclosure of "all safety and functionality data and information submitted with or incorporated by reference in the petition." These disclosure procedures were adopted by the FDA for the same reasons that Congress stated for including this specific disclosure provision applicable to devices.

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[139] 21 U. S. C. 360j(h)(1).
[140] *Id.*
[141] 21 U. S. C. 360j(h)(2).
[142] 21 U. S. C. 360j(h)(3).
[143] *Id.*
[144] H. R. Rep. No. 94-283, *supra*, at 51.
[145] *Id.*
[146] 5 U. S. C. 552.
[147] 21 CFR 314.14.
[148] 21 CFR 514.11(e)(2).
[149] 21 CFR 121.51(h)(1)(i).
[150] 21 CFR 8.9(a)(1).

G. Traceability.—Another general provision states that "No regulation under this Act may impose on a type or class of device requirements for the traceability of such type or class of device unless such requirements are necessary to assure the protection of the public health."[151] The legislative history suggests that this provision is intended to give the FDA a valuable regulatory tool "to trace a device through the various channels of commercial distribution" while balancing the expense required in tracing hazard,[152] citing the cardiac pacemaker as a type of device for which traceability should be required. While no such similar traceability provisions are elsewhere in the Act, several of the GMP regulations require product coding to facilitate recalls of articles from the channels of commerce.[153] This section appears to be superfluous since the Secretary could require traceability where necessary under the device GMP regulations.[154]

State and Local Requirements Respecting Devices

The Amendments provide that no state or local government may establish or continue in effect any requirement respecting devices for human use which are different from or in addition to applicable federal requirements and which relate to safety and effectiveness of the device or other matter included in a federal requirement.[155] However, the Secretary may exempt a state or local government from such preemption after an oral hearing on a state or local government application for an exemption when he finds that the state or local requirement is either more stringent than the federal standard or the requirement is mandated by compelling local conditions.[156] Nevertheless, compliance with local requirements must not result in the device being in violation of the Act.[157] The intent of this provision is to prevent undue burden of interstate commerce by different federal and state standards for medical devices.[158] The legislative history cites the California Sherman Food, Drug and Cosmetic Act[159] as both an example of state regulation of devices which the federal government previously had not actively regulated, and also as an example of the type of state or local requirements

[151] 21 U. S. C. 360j(j).
[152] H. R. Rep. No. 94-853, *supra*, at 52.
[153] 21 CFR 211.101(b).
[154] 21 U. S. C. 360j(f).
[155] 21 U. S. C. 360k.
[156] 21 U. S. C. 360k(b). The legislative history provides no examples of what such compelling local conditions might be.
[157] 21 U. S. C. 360k(b)(2)(B).
[158] H. R. Rep. No. 94-853, *supra*, at 45.
[159] Cal. Health & Safety Code, Sec. 26000 *et seq.*

the FDA should authorize to be continued under the exceptions portion of this provision of the Amendments.[160]

This provision is the first Congressional reference in the Act to direct federal preemption of state and local regulation of articles subject to the jurisdiction of the Act. Nevertheless, several older cases have discussed the preemptive effect of the Act on state regulation.[161] In addition, in 1913, the Supreme Court held that a state statute in conflict with the Act was void.[162] The legislative history is silent on why this provision is applicable only to medical devices.

Informal Hearing

The Amendments add a new definition to the Act, that of "informal hearing." The term means a hearing which is not a formal administrative hearing as contemplated by the Administrative Procedure Act.[163] This section sets forth the informal hearing requirements:

(1) designation of the presiding officer;

(2) the right to have an attorney present;

(3) reasonable notice of, and comprehensive statement about, the matters to be discussed at the hearing;

(4) the right to hear the Secretary's proposal, conduct reasonable questioning and present written or oral information;

(5) preparation of a written report of the hearing; and

(6) transcription of the proceedings in certain cases.[164]

While there are no provisions for comparable informal hearings *per se* elsewhere in the Act, such hearings are available under the Emergency Permit regulations,[165] and are apparently available in the case of drugs and devices offered for import by firms that are not registered as required by the Act.[166]

The legislative history indicates that the informal hearing definition was added because so many informal hearings are contemplated by the device amendments, for example, prior to reclassification of a "new drug" as a device, amending performance standards,

[160] H. R. Rep. No. 94-853, *supra*, at 45.
[161] See Annot., 21 USCA Sec. 301, note 5, pp. 118—219 (1972).
[162] *McDermott v. Wisconsin*, 228 U. S. 115 (1913).
[163] 21 U. S. C. 321(y). See also 5 U. S. C. 554, 556, 557.
[164] 21 U. S. C. 321(y).
[165] 21 CFR 90.
[166] 21 U. S. C. 381(a).

and before banning a device.[167] However, the language in the definition is *not* limited solely to device matters. Thus, this informal hearing procedure could, and probably will, become a major new regulatory tool for the FDA in this era of proliferating consumer products and limited government resources.

Amendments to Current Law

A. Prohibited Acts.—The Device Amendments significantly augment many sections of the existing law. Thus, the following additional acts are prohibited:[168] failure to comply with notification, repair, replacement, refund and/or reimbursement orders;[169] failure to maintain required records or reports;[170] and failure to comply with investigational use requirements.[171] The prohibited act of disclosing trade secrets[172] is amended to include pertinent device material.[173] The prohibited act of failure to maintain records[174] is amended to include failure to establish or to maintain required premarket approval reports[175] or records.[176] Finally, as with new drugs,[177] it is prohibited to mention FDA approval of premarket application[178] or investigational use exemption[179] on the labeling of a device.

B. Seizure Authority.—The seizure authority[180] with respect to devices is greatly expanded. Under the new law, an adulterated or misbranded device "is liable to be proceeded against at any time on libel of information and condemned in any district court of the United States."[181] This method of proceeding civilly is only applicable otherwise to counterfeit drugs, their containers and articles associated with the making of counterfeit drugs.[182] All other civil forfeiture proceedings involving new drugs and adulterated and misbranded foods, drugs and cosmetics require the article or its components to have moved in interstate commerce before federal district court jurisdiction attaches.[183] The legislative history indicates that Congress felt that the FDA inspectors spend too much time documenting interstate shipment when "whether or not a medical

[167] H. R. Rep. No. 94-853, *supra*, at 52.
[168] 21 U. S. C. 331, 333.
[169] 21 U. S. C. 331(q)(1)(A).
[170] 21 U. S. C. 331(q)(1)(B).
[171] 21 U. S. C. 331(q)(1)(A).
[172] 21 U. S. C. 331(j).
[173] *Id.*
[174] 21 U. S. C. 331(*l*).
[175] *Id.*
[176] *Id.*
[177] *Id.*
[178] *Id.*
[179] *Id.*
[180] 21 U. S. C. 334.
[181] *Id.*
[182] 21 U. S. C. 334(a)(2). See 21 U. S. C. 321(g)(2).
[183] 21 U. S. C. 334(a)(1).

device actually crosses state lines has nothing to do with the principle" of assuring safe and effective medical devices.[184] Since these considerations obviously carry over to foods, drugs and cosmetics, it is difficult to understand why Congress relieved the government's burden of establishing interstate commerce only in device seizure actions.

C. Adulterated Devices.—The device adulteration provision of the Act[185] is expanded to include: devices which are represented to conform with performance standards and which, in fact, do not;[186] Class III devices without premarket, protocol or investigational approval;[187] banned devices;[188] devices not manufactured in conformity with GMP;[189] and investigational devices that are improperly used.[190] These additions to the adulteration provisions are extensions of Congressional action in recent years that define adulteration to mean more than contamination.[191]

D. Misbranded Devices.—The device misbranding provision of the Act[192] is amended to include the following: false or misleading advertising[193] on restricted devices;[194] restricted devices whose advertising and labeling fails to bear the established name of the device and a statement of the intended uses and directions for use;[195] devices subject to performance standards which fail to bear labeling prescribed by such standards;[196] and devices in cases where there has been a refusal to comply with a notification, repair, replacement, refund and/or reimbursement order[197] or record keeping and report order.[198]

E. Export Provisions.—The export provisions of the Act[199] have been amended for devices. The export provisions require that, prior to export, all foods, drugs, cosmetics and devices deemed to be misbranded or adulterated under any provision of the Act must conform with the specifications of a foreign purchaser, not be in conflict with the laws of the country to which export is intended, be labeled for export shipment, and not be sold or offered in domestic com-

[184] H. R. Rep. No. 94-853, *supra*, at 15.
[185] 21 U. S. C. 351.
[186] 21 U S. C. 351(e).
[187] 21 U. S. C. 351(f).
[188] 21 U. S. C. 351(g).
[189] 21 U. S. C. 351(h).
[190] 21 U. S. C. 351(i).
[191] See, for example, 21 U. S. C. 351-(a)(2)(B), 351(a)(5), 361(e).
[192] 21 U. S. C. 352.
[193] This provision is significant in that it gives the FDA jurisdiction over device advertising. Advertising of foods, drugs and cosmetics is regulated by the Federal Trade Commission. However, advertising may be used in FDA misbranding cases to determine intended uses of articles regulated by the Act.
[194] 21 U. S. C. 352(q).
[195] 21 U. S. C. 352(r).
[196] 21 U. S. C. 352(s).
[197] 21 U. S. C. 352(t)(1).
[198] 21 U. S. C. 352(t)(2).
[199] 21 U. S. C. 381.

merce.[200] In addition, for Class II, Class III, investigational and banned devices, the Secretary *must* determine that exportation is not contrary to public health and safety and has the approval of the country of intended export.[201]

While these latter two provisions do not apply to foods, drugs or cosmetics, they are more liberal than the export provisions for new drugs and new animal drugs that expressly forbid the export of medicated feeds containing new animal drugs.[202] No authorization is provided for export of any new drug. There is now an unexplained difference between the export provisions for devices requiring premarket clearance and drugs requiring premarket clearance.

Registration of Device Manufacturers

The Amendments provide for the registration of device manufacturers and listing of all of their products with the FDA as is now required for all drug manufacturers.[203] The new law adds provisions applicable only to devices which allow the Secretary to prescribe a uniform system for the identification of devices intended for human use.[204] In addition, the provisions require a manufacturer or distributor, at least 90 days prior to introduction of a device for human use into interstate commerce, to inform the Secretary of the Class into which the device falls and what action, if any, has been taken to comply with any applicable performance standard or premarketing application.[205] The criminal,[206] misbranding[207] and import[208] provisions concerning registration have been amended to include devices.

Inspections Relating to Devices

With the enactment of the Device Amendments, FDA inspectional authority of all things in a factory, warehouse, establishment or consulting laboratory where prescription drugs are manufactured, processed, packed or held[209] is extended to cover restricted devices.[210] In an inspection of an establishment where prescription drugs and restricted devices are *not* manufactured, processed, packed or held, FDA inspectors are restricted to examination of equipment, finished and unfinished materials, containers and labeling.[211] In the case of

[200] 21 U. S. C. 381(d).
[201] *Id.*
[202] 21 U. S. C. 381(d).
[203] 21 U. S. C. 360.
[204] 21 U. S. C. 360(j).
[205] 21 U. S. C. 360(k).
[206] 21 U. S. C. 331(p), 333.
[207] 21 U. S. C. 352(o).
[208] 21 U. S. C. 381(a).
[209] 21 U. S. C. 374(a).
[210] *Id.*
[211] 21 U. S. C. 374(a)(2).

prescription drugs and restricted devices, inspectional authority is extended to *all* things in the establishment, including records, files, papers, processes, controls and facilities, and excludes only financial, sales and price data, and some types of personnel and research data.[212] Since restricted devices are, for all practical purposes, the device counterpart of prescription drugs, augmenting inspectional authority for restricted devices was a logical extension of the "prescription" concept.

Under a new inspectional authority provision applicable only to devices,[213] FDA inspectors are permitted access to all records required to be kept pursuant to the general records and reports provision of the Amendments[214] and the investigational use exemption provision.[215] Thus, even though it would initially appear that record examination would be limited to restricted devices and prescription drugs only, the Secretary could, under these new powers, promulgate detailed regulations which would have the effect of equating accessibility to records for all nonrestricted and restricted devices. This additional inspectional authority gives the Secretary significantly greater authority over devices than is currently available for foods, drugs or cosmetics.

Assistance to Small Manufacturers

The Secretary must establish "an identifiable office to provide technical and other nonfinancial assistance with the requirements of the Federal Food, Drug and Cosmetic Act, as amended by this Act."[216] The provision stems from Congressional cognizance of the "potentially detrimental economic impact implementation of this legislation might have on small device manufacturers."[217] Congress stated clearly that it did not intend the assistance office to be a "hollow shell" but expected the office "to have sufficient resources and staff to provide a meaningful and effective vehicle for technical advice and other assistance."[218] Such an office has already been established.[219]

Congress exhibits a noble purpose, recognizing that such pervasive regulation of the medical device industry may have devastating

[212] 21 U. S. C. 374.
[213] 21 U. S. C. 374(e).
[214] 21 U. S. C. 360(i).
[215] 21 U. S. C. 360j(g).
[216] 42 U. S. C. 3512.
[217] H. R. Rep. No. 94-853, *supra*, at 57.
[218] *Id.*
[219] The FDA has already designated an office to render assistance to small device manufacturers. 41 *F. R.* 22620 (June 4, 1976).

financial and economic impact on small device manufacturers. However, such a noble purpose was not exhibited in the 1962 New Drug Amendments[220] or the 1969 New Animal Drug Amendments[221] when small manufacturers of such articles were likewise confronted with burdensome new responsibilities that had substantial economic and financial impact on them. This provision represents a significant new direction for the FDA which should inure to the benefit of the FDA, the industry and, most important, the consumer.

Release of Confidential Information

A provision of the Amendments which extends to foods, drugs and cosmetics as well as to medical devices is one authorizing the Secretary to release to persons under contract to the Secretary confidential information and trade secrets which relate to administration of the Act as long as the Secretary is not prohibited from using the information.[222] This provision was enacted to allow the Secretary to use contractors for computerization of new drugs and to allow the same to be done for devices.[223] Why a provision such as this was made to apply to all such articles subject to the Act's jurisdiction, when, for example, the administrative detention,[224] device record inspection,[225] assistance to small manufacturers[226] and interstate presumption[227] provisions are applicable only to devices, is not explained.

Conclusions

It is clear from this review of the Medical Device Amendments and other provisions of the Act that Congress has adopted a piecemeal approach to regulating foods, drugs, cosmetics and medical devices. While the Amendments confer significant and substantial new authority to the FDA, regulation of foods, drugs, cosmetics and medical devices remains nonuniform. Perhaps in future legislation, Congress will provide for uniform application of regulatory procedures to all products covered by the Act. However, if the past is any guide to the future, Congress will continue to augment the authority of the FDA with piecemeal legislation which results from a compromise of the competing interests of the Congress and the affected industry. **[The End]**

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[220] P. L. 87-781 (Oct. 10, 1962).
[221] P. L. 90-399 (July 13, 1968).
[222] 21 U. S. C. 379.
[223] H. R. Rep. No. 94-853, *supra*, at 50.
[224] 21 U. S. C. 374(g).
[225] 21 U. S. C. 374(e).
[226] 42 U. S. C. 3512.
[227] 21 U. S. C. 379a.

Wanted—
Plain Talk About Additives

By WILLIAM O. BEERS

Mr. Beers Is Chairman of the Board and Chief Executive Officer of the Kraftco Corporation.

I WOULD ENJOY spending the time allotted to me in this program discussing the food processing industry's outstanding record of product safety and describing some of the contributions made by its scientists and engineers toward improving our food supply by the use of additives. However, I have been asked to speak on the subject of improving the image of the food industry. This is a more slippery, less tangible topic but, in today's social climate, one which has assumed a disproportionate significance of its own. I will begin with a comment on the nature of current social criticism and then move on to the issues as I see them.

The prevailing mood in America, as most of us well know, is one of distrust and suspiciousness. In a figurative sense, institutions and organizations across the land have drawn their wagons into a circle and are living under siege. The health care and healing professions are whipped for rising costs and isolated charges of malpractice. Industry is castigated for not immediately restoring an environment which has been neglected by campers, tourists, governments and homeowners, as well as by corporations. Vietnam and Watergate have taken their toll of government officials, lawyers and public relations experts alike.

The food processing industry has become another target in this broad-scale attack. Triggered by rising prices at the beginning of this decade, the criticism has spread to a general inquiry into everything the industry does. Some of you may have noticed, as I have, that it sometimes seems that criticism has become an end unto itself in America. Once having told the world what is wrong with a particular institution or industry, our critics tend to fall

silent or turn on new targets, leaving the solutions to others. It seems almost as though the act of criticism itself is more significant than some of the changes which, in fact, may be needed.

The food processing industry, some claim, is guilty of recklessly introducing a variety of harmful additives into its products. When hard facts do not support the charges, the focus of the attack may well shift to the assumed reasons for the use of additives. The chief purpose of additives, we are told by our critics, is to increase the convenience and profits of the manufacturer. Such attacks are largely based on assumptions—generally unfavorable—about the other fellow's motives. This is somewhat like accusing a public official of doing a good job in office simply in order to get re-elected. It fails to take into consideration the human desire to do a good job for its own sake. This kind of cynicism is at the heart of our national problem.

Criticism of the food processing industry is likely to be a continuing problem for years to come. It will take a long time to complete the painstaking tests needed to provide definitive answers to the questions raised by allegations against additives. Meanwhile, we must deal with public questions openly, honestly, and constructively, and not simply by reacting defensively to each new food scare as it comes along.

Debate on Food Additives

In spite of the witch-hunting aspects of this controversy, the debate on food additives, in my opinion, is in fact a significant aspect of legitimate concern. As new substances find their way into food products and into the food chain, it is possible that the effects of their interaction may not be understood fully for many years. There is a synergism at work in these relationships which requires careful study. Furthermore, as scientific equipment and analytical procedures are refined, we are discovering the presence of previously unsuspected potential hazards in purely natural foods and substances now on the generally recognized as safe (GRAS) list. These, too, will need further testing to determine their fitness for human consumption.

For example, what does the future hold for spinach and rhubarb? Both of these foods contain oxalic acid, which builds kidney stones. Lima beans contain cyanide, and prussic acid occurs in almonds. Cabbage can help to cause goiter. Onions can cause anemia.[1] Nutmeg can be a powerful hallucinogen.[2]

[1] Tannahill, Reay, *Food In History*, Stein & Day (1973), p. 380.

[2] Hall, Richard, Ph.D. and Valley, Hunt, M. D., "Food Additives," *Nutrition Today* (July/August 1973), p. 27.

Consider, if you will, the coming ordeal faced by one of man's oldest staples, the potato. Far from being the simple food it appears to be, the potato actually is a complex chemical aggregate. Among the distinct chemical substances which so far have been identified in its makeup, one can find solanine alkaloids, oxalic acid, arsenic, tannins, nitrates and over a hundred other items of no known nutritional significance to man. In case my reference to solanine slipped past anyone in this room, let me remind you that this a relative of the poison found in deadly nightshade. The average consumer, who eats about 120 pounds of potatoes each year, thus ingests enough solanine to kill a horse, if taken in a single dose.[3]

Food Faddists

Clearly these foods are perfectly safe when consumed as part of a balanced diet. But food faddists, on one hand, urge us to eat unbalanced diets, with all the attending dangers of malnutrition. On the other hand, consumer activists condemn both natural and artificial ingredients which have no adverse effects unless they are taken in abnormally high quantities under laboratory test conditions. The truth is that our food supply is safer now than it ever has been.[4] It may also be true that artificial coloring, flavoring and texturizing are sometimes used when they needn't be. We must consider the hazards of additives seriously, but we must use good judgment, too. When the risks which were present in our food years ago are compared with the safety of our present supplies, the hazards from additives seem small indeed.

Nevertheless, testing should and will continue until the long-term effects are known. Meanwhile, the criticism of additives will not disappear by itself. Also, regardless of how carefully we explain our position, some individuals will never be convinced. As an example, the Kraft Foods Division of Kraftco Corporation produced a very fine booklet on additives as part of a broad "Consumer's Right to Know" program. Responses show that our message is getting across, but a disproportionate amount of time is taken up in continuing correspondence with readers who seem unwilling to accept facts. As it happens, these are the most vocal, articulate readers but not necessarily the best informed. We must not ignore these isolated

[3] Institute of Food Technologists Expert Panel, "Naturally Occurring Toxicants in Foods," *Food Technology* (March 1975), p. 68.

[4] Commissioner of Food and Drugs Schmidt, quoted in *GMA Delaney Update* (April 14, 1976).

cases but, at the same time, we must concentrate on reaching opinion-molders and the large majority of individuals who are seeking information and not arguments.

The problem facing the food processing industry in this regard boils down to this: Although much of the public's anxiety about the danger of food additives is not supported by the available evidence, the anxiety itself is real. We live in a period of heightened anxiety, by which I mean general feelings of apprehensiveness and fearfulness about everybody and everything. It can be a negative, disruptive element in our lives, for the very reason that it is vague and nonspecific. However, once the facts about a particular issue are put on the table for all to see, anxiety tends to lose its destructive force. Our most effective weapons, then, are facts openly shared and widely distributed.

Communication

We need not be afraid to share information with the public because, in the majority of cases, the facts reflect favorably on our industry. The other side of the coin is our willingness to accept and make changes in situations where changes appear to be needed. This kind of conversation, or consultation, with our critics and with the public will require special communications efforts from all of us. These communications must be above and in addition to regular advertising and public relations activities that are a normal part of doing business. Let me suggest a few examples of the kinds of communications I have in mind.

First, I would like to see a revival or a second round of the special press seminars which were sponsored by the Grocery Manufacturers of America (GMA) in 1973—1974.[5] For those of you who are not familiar with the program, let me briefly describe what happened. During a period of about 18 months, special one-day briefings were held in major cities for food writers of newspapers and consumer publications. Scientists of GMA member companies gave short oral presentations on current developments in areas of consumer interest. The oral presentations were backed up by written materials and followed by question and answer sessions. The agenda covered the toughest and nastiest questions then facing the industry, including botulism and additives. The candid, head-on approach was successful as far as it went. There was an initial flow of interest and

[5] Project described by Dr. Robert Harkins of the Grocery Manufacturers of America.

enthusiasm. Some of the media became familiar with qualified resource persons in the food industry to whom they could turn when new questions arose. This liaison can be invaluable in accurately reporting the food processing industry's position to the public. But it must include key general assignment reporters and science writers, because a ban on cyclamates, for example, will be reported by these writers, and not on the food pages. Another reason for strengthening and follow-up is the fact that many new writers have come on the press scene since 1973. We should get to know them.

Open Door Policy

Second, I believe the food manufacturing industry could take positive steps to establish an open door policy toward consumer activist groups. I realize this may require us to subordinate our legitimate desire for privacy and confidentiality in our company operations to the larger interest of rebuilding credibility in the public mind. Last fall, executives in my own company heard a leading consumer advocate suggest how such an activity might be structured.[6] He described a continuing program of discussion and interaction now in progress between management of an eastern supermarket chain and groups of consumer activists. The activists meet to address their questions to management and contribute their own input to the corporate decision-making process. The program seems to satisfy the needs of both sides to be heard and to be understood. It is participatory and it involves many people. The very act of exchanging information and opinions alone is a big help in breaking down resistance and putting cooperation in its place.

Third, the formal assignment of employees within our own companies to challenge the way we use additives could have a positive effect on relations with the public. Sometimes the best of us suffer from tunnel vision when we try to push a particular piece of technology to achieve a given goal. A good antidote might be the questioning by an individual within the company who is required to view things in the round, from a broader perspective, from the outsider's point of view.

In some companies, this function could be included in the duties of the director of quality assurance.[7] The position would then be that

[6] Address by James S. Turner, author of "Chemical Feast," Kraftco Conference, Oct. 29, 1975, Palm Beach, Florida.

[7] Suggested in article by Richard D. McCormick, Editorial Director of *Food Product Development* (April 1976), p. 7.

of a kind of corporate ombudsman. The assignment would include design and implementation of control systems to guide management on questions of food safety, ingredients, regulatory affairs, quality audits, consumer complaints and corrective actions. In the hands of an individual with good communication skills and the ability to relate to consumers—in addition to technical training—the position could be a focal point for achieving significant improvements in our public image.

Finally, while we in the food industry are working to improve our own image, it would be helpful to have the Food and Drug Administration (FDA) do the same for itself. As a businessman, I am not in one hundred percent agreement with everything the FDA does. Still, it must be acknowledged that, since 1907, the FDA and its predecessor organizations have performed yeoman service for the nation. Despite inadequate staffing and limited resources, the FDA has functioned effectively as a public watchdog.

Nevertheless, there are two immediate areas in which improved communications, with the help of the FDA, could contribute significantly to the image we seek. First of these is ingredient labeling. Unquestionably, a food product package should provide a description of its contents but the current emphasis on technical language and scientific terminology defeats the purpose. It is my conviction that the average consumer is more frightened than helped by language he or she does not understand.

Let me describe a simple food with which you all are familiar. In a partial listing of its principal components, we would find the following ingredients, listed in language which would be approved by the FDA. In the carbohydrate group are lactose and lactulose. In the protein category, we find casein, lactalbumin, lactoglobulin, beta-lactalbumin, createne, ribonucleic acid and valeine. In the fats group are cholesterol, lecithin and ten separate fatty acids. Minerals include calcium, monomagnesium phosphate plus a dozen more, ending in zinc and bromine. Vitamins, of course, are represented, including A, Carotene, C, D, E, K, biotin, riboflavin, thiamine and B-12. And this, remember, is but a very short partial listing of the ingredients.[8]

[8] Partial list of ingredients furnished by Dr. Jerry Proctor, R&D.

Ingredient Listing

Do you think the average consumer would purchase this product on the basis of the ingredient listing I have just read? Do you think the average consumer would recognize the product as the ideal food, human breast milk? For that is what it is.

Good judgment is needed in establishing a level of information on ingredient labels which truly communicates without confusing the reader. The industry needs cooperation from the FDA to achieve that.

The second area in which the open sharing of information plainly stated would help involves the manner in which our regulatory agencies function.[9] In recent years, the independent federal agencies have emerged as a major factor in our system of government. But many of their decisions are made without benefit of the legal due process which is such an important part of our government. In this area, the concept of due process traditionally meant that a regulatory body could be made to appear under oath and be effectively cross-examined as to the facts on which the regulation was to be based.

Today we have moved away from that concept. Instead, we receive regulations handed down by individual officials, often based on data which cannot be challenged in public hearings or in courts of law. And our courts regularly bless too many purely administrative actions as based on true expertise, which they are not. In the opinion of many, these desk-top determinations represent a peril to our freedom. By moving them back into the sunshine of open sessions, we can significantly help to restore public trust in the governmental decisions which are so important to confidence in our food supply.

These modest suggestions are just a start. I am confident every individual in this room could contribute workable and useful ideas on how to improve the image of our embattled industry. Your ideas are needed, for we are the ones who should be providing leadership in resolving questions about additives which trouble the public. We have the technical skills, the experience and the day-to-day involvement needed to express the probabilities which are more to be trusted than the prejudiced absolutes of critics who speak from alarm and not from certain knowledge. We must not hold back. We have little to lose and much to gain by speaking out during the critical years of testing which still lie ahead. **[The End]**

[9] From Breakers Conference, author requested to remain anonymous.

Toxicology—The Exact Use of an Inexact Science

By JOHN C. KIRSCHMAN

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THE SUBJECT OF TOXICOLOGY is a matter consuming more of our time and resources than we ever imagined several years ago. All of us and the public at large are hearing and reading more today than ever about selected activities in the field of toxicology. As a result, there appears to be increasing uneasiness, confusion and concern in the consumer's mind about the safety of the food supply and environment. It is most important that more knowledge and understanding be developed, not only for the public but for scientists as well, regarding safety assessment. While toxicology might be considered the exact study of poisonous effects based on inexact biological sciences, safety evaluations too often have been the inexact use of inexact sciences.

If toxicology deals with poisons, why are we in the food industry concerned? We sell foods, not poisons. The reasons are:

(A) all foods are chemicals;

(B) our bodies themselves are made of chemicals and serve as chemical processing factories—food being converted into tissue, energy and/or waste; and

(C) since we supply foods to the public, we hold the responsibility to know the toxicological profiles of our products in order to assure the public of their safety.

Thus, foods themselves, as well as the other millions of chemicals in our universe, can cause biological problems if exposure to them becomes excessive.

The key to safety assessment, therefore, must be reason, reason developed by responsible, experienced and knowledgeable authorities working with the benefit of appropriate and adequate data.

What has brought on this recent and continuing increased activity and concern for the safety of our food and environment? Questions of safety seem to gather from either:

(A) the development of novel and/or improved tests for evaluating biological effects of materials;

(B) the development of new analytical techniques with increased sensitivity which find the presence of potential toxicants where they previously were not found;

(C) unusual levels or different patterns of a substance's use unanticipated when first evaluated for safety; or

(D) laboratory trials with inappropriate tests in the hands of a novice scientist.

GRAS Survey

Since the passage of the 1958 Food Additive Amendment, enough such changes have taken place so that it is prudent now to re-evaluate the safety of not only regulated food additives, but also of those ingredients generally recognized as safe (GRAS). The food industry is just beginning to feel the impact of the first GRAS survey by the National Academy of Sciences (NAS) and its review by the Federation of American Societies for Experimental Biology (FASEB) scientists with the resultant requests for more safety data. There has been tremendous activity recently with colors. Indications are that flavors will soon be receiving a similar wave of attention. The same types of needs are developing with respect to cosmetics, drugs, consumer products and heavy industrial chemicals.

I will review briefly the toxicity test procedures which fall into six broad categories.

(1) *Acute Tests.*—These assess the immediate adverse effects of short-term exposures to toxic material. These generally involve the use of both sexes of three species in mature and weanling animals.

(2) *Subchronic Studies.*—These studies define the impact of repeated dietary dosing, generally involving exposure of 20 males and 20 females per group in each of two species at three dose levels, plus controls, for about ten percent of their life-span. These studies help to characterize the toxic manifestations and also to establish the maximum tolerated dose (MTD) level to be used in chronic tests. Measurements are made in food intake, growth, mortality, blood chemistry, urine analysis, hemotology, organ weights, gross behavioral effects

and histopathology as well as special studies dependent on the material being tested.

(3) *Metabolism Studies.*—Such studies should be done early in the course of toxicological evaluation, most properly after the subchronic work has been done. These experiments, often with the use of radioisotopes, determine the distribution kinetics and biochemical fate of the substance. Such data are most important for the purpose of comparing the mode of action and the metabolism of the compound between the test species and man. The species then selected for the chronic study should metabolize the test substance in a manner as similar, quantitatively and qualitatively, to man as possible.

Inappropriate Test Species

I am sure that many of us at this meeting have been concerned about some positive findings from studies resulting from the use of inappropriate test species. We must always remember, however, that our purpose is to protect the consumer and that selection of a species which would give negative findings of toxicity when the material is indeed toxic to man should be of greater cause for concern. For example, in the Middle East in biblical times, people became ill after eating lean green quail which had fed on hemlock seeds. The quail themselves were unaffected by this potent human poison. Short of having experience with the chemical in man, comparative metabolism studies as mentioned above offer a major opportunity to determine the most appropriate animal species for use in toxicological testing of potential toxicants.

(4) *Reproduction Studies.*—In recent years, since the thalidimide tragedy in the early 1960's, increasing attention has been brought to reproduction toxicology. Such tests now are routinely required for evaluation of food additives and drugs. Observations are made on fertility and general reproductive performance, perinatal and postnatal toxicology and teratology. Present protocols require testing over three generations with the teratological workup on one of the litters after *in utero* exposure to the test material.

(5) *Mutagenicity Studies.*—The most unsettled area of this soft science of toxicology, however, is testing for mutagenic effects. Studies include tests for chromosomal breaks, dominant lethal mutations in male germ cells, and host mediated assay. Much has been accomplished in these predictive tests over the last three to five years. They are, however, not yet reliable enough to give assurance that we do not have

false negative or false positive results and, in turn, are inadequate for use as the basis for regulation. While it appears as though all carcinogens are mutagenic, the converse has not yet been established and there is reason to doubt that all mutagens are, in fact, carcinogens.

As great as the need is for a quick and inexpensive test to replace the time-consuming and costly chronic animal tests, we dare not allow such procedures to be used as definitive indicators until their reliability and relevance to human health is adequately established. Until this state is achieved, such tests—exemplified by the widely touted Ames *in vitro* bacterial plate methodology—are recognized as valuable only for screening the yet untested compounds in order to priorize those needing chronic testing in animals.

(6) *Chronic Toxicity Studies.*—These studies aim to define the maximum dose producing no injury, particularly cancer, when administered to animals over major portions of their life-span. The procedure is similar to subacute studies but larger numbers of animals, usually rodents, are used with 50 to 100 animals per sex per group. The doses are selected with guidance from the subchronic data with the lowest treatment level relating to the proposed human intake, preferably 100 times higher. A 100 safety factor is generally applied to the highest dose level fed the most sensitive test species over the life-span without inducing an adverse effect. This is then taken as the acceptable daily intake (ADI) for man. One factor of ten is applied to transpose the observation from the test species to man. The second factor of ten is to allow for variation of sensitivity from one individual to another. Smaller safety factors have been used, and can be used properly, when much more is known about the material, such as knowledge of the metabolism of the substance in man as well as some experience retrospectively with human exposure to this type of material, for example, normal cellular components.

Threshold Level

Toxicologists are in agreement that toxicity is a dose-related phenomenon and that threshold limits exist below which the toxic manifestations do not appear. The Delaney clause to the 1958 Food Additive Amendment does not recognize the existence of a threshold level relative to carcinogens and, accordingly, disallows the use of any additive which has been shown to produce cancer in any animal species no matter what the level of administration. As laudable as this objective is—namely, to keep carcinogens out of the food supply—the

science has advanced in the last 18 years to the point that makes this provision inappropriate as a regulatory tool. The prowess of the analytical chemist has increased in this time so that the detection limits of most chemicals have been increased many orders of magnitude, making administrative zero much smaller than it was in 1958. While in the 1950's microgram quantities were barely detectable, some compounds today are quantifiable in the femtogram range, 1/1000 of a picogram or 1 times 10^{-15} grams. During the same period, we also have learned that not all carcinogens are of the potency of things like benzopyrene, benzidine and b-naphthalemine, which are readily determined to be carcinogens by testing methods used in the 1950's, 20 to 25 animals per group observed for 24 months. Other materials have since been found to have much lower carcinogenic potential, or to act only as cocarcinogens, enhancing the potency of the true carcinogens. Expanded testing procedures are necessary to detect the carcinogenic potential of such compounds. The lower the potency of the material, the larger population of test animals required to detect the effect, the greater the dose needed and the longer the time before cancer appears.

Safety Tolerances

Extension of the Delaney-type restriction to teratogenicity and mutagenicity would also be completely unrealistic in light of the scientific evidence that safety tolerances can be applied properly to such experimental observations. For example, vitamin A is teratogenic in the guinea pig at less than 20 times man's daily requirements for that vitamin.

The length of time that such chronic animal studies take slows down the rate at which improvements in methodology are developed. Of course, all changes that are tried do not turn out to be improvements. Therefore, it takes years to accept improvements in test protocols as valid, and harder still, to drop poor or meaningless practices. For example, the Food and Drug Administration (FDA) went to the seven-year dog studies for some time to determine whether this would generate improved information over two-year dog and rat studies. It found this not to be the case and so now is requiring only two-year studies in dogs. On the other hand, in recent years through improved animal supply and care, experimental rats have been living an average of 30 months compared to 24 months during the 1950's and 1960's. It is reasonable, therefore, if the material is to be tested throughout the average life-span of test animals, that 30

months should be used now, rather than an arbitrary 24-month cut-off. This, of course, raises the question as to the necessity for re-testing of materials for 30 months if 24-month studies were used originally. I personally feel that, while there is no need to retest arbitrarily for 30 months everything already tested for 24 months, today's rat studies should go longer than a two-year period. Mouse studies now are extending beyond the original 80-week length.

At the crux of today's confusion in making safety and regulatory judgments relative to carcinogenicity lies the fact that we have not had available a nationally agreed upon working definition of a carcinogen. Only recently was this matter addressed by a subcommittee within the National Cancer Institute. We need to establish a scientifically sound and acceptable set of criteria for toxicity testing and safety evaluation.

Not all toxicity tests are appropriate for use in safety evaluation of a material. Many toxicity tests in the past have been run solely for the purpose of determining what the qualitative characteristics were of the toxic manifestations elicited by the particular material, rather than to determine the lowest dosage or threshold level at which the adverse effects could be noted. When planning a toxicity testing program or using the data from toxicity tests for the purpose of making a safety evaluation, consideration must be given to the following six factors.

(1) *Numbers of Animals.*—Adequate populations of test animals must be used in order to give results that are statistically adequate for at least 95 percent confidence in the results. Twenty years ago, an acceptable protocol for chronic feeding studies was deemed to include 25 animals per sex per group. More recently, this number has been increased to 50 animals per sex per group. At the present time, some investigators are starting with 100 animals per sex per group in order to yield 50 animals per group at the end of the study of 30 months in rats. Many scientists today are also including a minimum of two separate and distinct untreated control groups with each study.

(2) *Administration.*—Food additives should be tested by the oral route of administration since other routes, while not completely irrelevant, are inappropriate for the evaluation of food additives.

(3) *Dosage.*—Enough dose levels, usually three, should be used in order to establish a dose response relationship for helping in determining the threshold or no observable effect level of the test material.

(4) *Test Species.*—The choice of the species of animal for testing will vary depending upon the material being investigated. Selection of species should be done with the aid of knowledge regarding the metabolism of the material. The species chosen should include that which most closely relates to man in its metabolism. Generally, even with such direct knowledge of metabolism, a minimum of one rodent and one non-rodent species is used.

(5) *Purity of the Material.*—Purity of the material tested must be established and known before the relevance of the test results to items of commerce can be relied upon. Let me also emphasize the added importance of holding a sample of that test material for possible later chemical analysis.

(6) *Quality of the Study.*—The experimental design is of no more value than the quality of the work performed, which is dependent upon the experience and diligence not only of the senior investigator but of every person on the team involved in performance of the study. It is a characteristic of the mundane and tedious tasks involved in long-term toxicity tests that often the lowest paid man on the staff, that is, the animal caretaker, has a most critical job.

Red No. 2

The recent episode with FD&C Red No. 2 exemplified the poor state of affairs on the present regulatory/safety scene in the United States. This color, one of the most heavily tested (36 studies reported) food additives, was finally delisted on the flimsiest of reasons. Red No. 2 was exonerated from the charge that it was embryo- and fetotoxic only after five years of some testing and continuing *ad hoc* Advisory Committee reviews. This issue revolved around the adequacy of numbers of untreated control animals needed to establish the normal background incidence of resorptions.

Now, after thorough evaluation with two mouse, two rat and one seven-year dog study, each deemed appropriate, acceptable and reliable, the color was "done in" by a test known to have been "goofed up," the results of which the investigators themselves do not wish to rely upon. In any case, these researchers saw no indication in the study to suggest that the color is carcinogenic. However, the statisticians got their oar in and suggested that, if looked at in one particular way, the results indicate that three percent Red No. 2 induced cancer in rats. One, in fact, stated that the purpose is to see what information can be gotten out of the results and not whether the study is valid or invalid. If the research toxicologist/biologist is now

removed from the assessment of test results and their validity and interpretations made solely and finally by statisticians, we are in for real trouble on more than just Red No. 2.

Still another fundamental issue was involved in the Red No. 2 case: that is, what is the definition of a carcinogen? One scientific camp holds that all tumors, benign as well as malignant, must be considered as cancerous or potentially cancerous. On this basis, the Environmental Protection Agency proposed banning the pesticides chlordane and heptachlor. Using these criteria, FD&C Red No. 2 would not have been found to be a carcinogen since the total numbers of tumors in the animals receiving three percent Red No. 2 were the same as in the untreated controls. However, other scientists hold that certain benign tumors never become malignant and so should be removed from the tally of malignancies, as was done with the recent FDA study on Red No. 2.

Definition of a Carcinogen

The absence of an accepted working definition of a carcinogen, adequacy of testing and interpretation of results is of such a dimension, both directly and indirectly to the benefit and risk of the consumer, that it can be classified as a national crisis situation. Accordingly, we in the food industry must get involved to a greater extent in the deliberations involved in these scientific matters by participating through our own scientists and no longer relying on someone else to assume these responsibilities.

Paracelsus once stated that only the dose makes the poison. Now that we have touched on toxicity testing, we come to the aspect of exposure which is every bit as important as the intrinsic toxicity of a material when assessing its safety of use. Once the toxicity of a material has been established and the ADI established, means must be established to assure that exposures do not exceed this acceptable intake. With new materials not yet in the marketplace, the regulatory officials will control the use by establishing concentration limits and product type restrictions on the particular additive. With other materials already in commerce, retrospective information is required. Information of this sort was published by the World Health Organization in 1970. Seventeen of the food additives included in that survey were found to have their potential daily intake (PDI) exceeding the ADIs. In the recent GRAS survey performed by the NAS, there were 5 additives out of 53, for which ADIs have been established, whose PDIs exceeded their ADIs.

Recognizing the inadequacy of these consumption data, the NAS has adopted a new method for calculation of consumption of food additives to be used in its GRAS III survey for regulated direct and indirect additives. The Codex Alimentarius Food Additive Committee is also in the process of generating new data on six additives whose PDIs in 1970 were found to exceed their ADIs. They are sulfites, phosphates, BHA, BHT, gallates and tartrates. The importance of these surveys is apparent when one realizes that regulatory officials are already considering restrictions on those items for which consumption significantly exceeds the ADI. So when your company is asked for use data, it is to your benefit to give as accurate information as possible. Whenever data are lacking, the experts make the most conservative assumptions, which can be disastrous in matters pertaining to safety assessments. For example, several years ago there was great concern about the consumption of phosphorus being too high relative to the intake of calcium in the United States. The original data indicated that three to four times the amount of phosphorus was being consumed compared to calcium consumption, and that this ratio was in the toxic range. This got industry's attention and as a result more recent review of better data suggests that the ratio is actually closer to 1.5-to-1, the nutritionally appropriate level, than the toxic ratio of 3- or 4-to-1.

Rules of the Road

Once the scientific criteria, the rules of the road, are established and we know what needs to be done and how it is to be done, there are other issues which need to be addressed. These include the following five considerations.

(1) The items requiring testing are so numerous and the testing costs so high that the supplier industries are not ready or able to underwrite such costs themselves. In many cases, the user companies will somehow have to join with the suppliers to accomplish the necessary testing. Such technical consortium efforts must be recognized as necessary by the involved industries and the government and then be given sanction under the law.

(2) The numbers of individuals within the food industries with the training, experience and expertise to perform and evaluate toxicity studies are completely inadequate to perform the tasks already at hand. Also, present training programs are not generating the new

cadre of biological scientists necessary to properly staff the toxicity testing centers.

(3) The flow of toxicological information and data on a national and international basis needs to be improved. It would be of great value to have within the private sector a clearing house to prevent excessive duplication of efforts, as well as to minimize the chance for inadequate and inappropriate work to be undertaken.

(4) More toxicological testing facilities will be needed to handle the increased amount of testing that will be required. The availability of well-staffed quality testing facilities, both in the United States and worldwide, is critically inadequate.

(5) Active research programs must be promoted to advance the state of the art of toxicity testing and, in the process, establish relevant and efficient methodologies to be used in safety evaluation programs upon which regulatory action is to be based.

Joint Venture

The United States chemical industries have made a start toward this end by forming the Chemical Industry Institute of Toxicology (CIIT). I call on you to give consideration to the formation of a similar joint venture within the consumer product industries to include foods, drugs, cosmetics, and their ingredient suppliers.

Whatever system is established in the United States for such testing and safety evaluation, it must have the stature necessary to command the respect of the public and the international scientific community. The food industries will not be able to look after themselves unless they help to develop their own cadre of scientists with the knowledge and experience to be recognized as experts by their scientific peers in the community at large.

Nature abhors a vacuum, and vacuums tend to be filled in a rapid and uncontrolled manner. If we allow vacuums to continue in the area of safety assessment, science and regulation, we can only expect that someone else will fill them. It is time that we participate in the establishment of the ground rules that will be controlling not only our technical destinies but total businesses, more so in the future than they ever have in the past. **[The End]**

Legal Developments Relating to Controlled Drugs

By THOMAS O. HENTELEFF

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THE IMPACT of the Controlled Substances Act of 1970 upon the pharmaceutical industry is already substantial and it is likely to increase as new substances are added to the list of controlled substances and as controlled substances are transferred from a less restrictive schedule to a more restrictive schedule. It is estimated that approximately three out of ten prescription drugs dispensed in the United States are subject to controlled status.

Thus, it is imperative for all segments of the pharmaceutical industry to have a thorough understanding of the requirements, controls *and* protections provided by the Controlled Substances Act and the implementing regulations, and of the agency charged with the responsibility of enforcing the Act. As reflected by its name, the Drug *Enforcement* Administration (DEA) is essentially a police-oriented agency whose primary objective is to identify and prosecute persons who violate the Act. The role of DEA as a policeman influences the attitude of its officials and creates a regulatory environment which may differ significantly from that which the pharmaceutical industry is accustomed to as a consequence of its dealings with the Food and Drug Administration (FDA). The DEA inspector, who, in the James Bond tradition, prefers to be identified as "Agent so and so," rather than as an inspector, is charged with the responsibility of monitoring the activities of legitimate manufacturers and distributors of controlled drugs, as well as the smuggler, the pusher and the illegal manufacturer of controlled substances. As a result, the DEA agent may tend to equate the motives and actions of the latter with the former. Moreover, some agents who have a first-hand knowledge of the plethora of horrors of drug abuse and of the unscrupulous tactics

of the persons who seek to profit from the miseries of the drug addict tend to develop a philosophy that the end justifies the means. In view of these tendencies, it is especially important that the members of the pharmaceutical industry attempt to dispel any erroneous beliefs as to their legitimate intentions by cooperating fully with the DEA in its attempt to control drug abuse. Yet, at the same time, they must be fully aware of their rights under the Act and the Constitution.

Primary Role

The primary role of the DEA as an enforcer, rather than a regulator, is reflected in the fact that the overwhelming majority of cases litigated in the courts involving the Controlled Substances Act arise in the context of a criminal prosecution of an individual charged with the illegal distribution or dispensing of controlled drugs. A recent exception was a case[1] decided last January by the United States Court of Appeals for the First Circuit involving the allocation of the 1975 individual manufacturing and procurement quotas for phenmetrazine. In that case, the Court upheld a method of computing the quotas in which the National Prescription Audit (NPA) projections as to the amount of phenmetrazine dispensed by retail pharmacies in the continental United States in 1974, rather than the manufacturers' actual sales to their DEA-registered customers, were used as the basis for assessing the quantity needed to satisfy the legitimate medical and inventory needs for the drug in the United States. The Court in reaching this decision was apparently not bothered by: (1) the fact that the NPA projections do not represent actual retail sales but rather constitute a statistical estimate based upon a sampling of the prescription filled by 800 of the approximately 56,000 pharmacies located in the continental United States; (2) the fact that the NPA projections are not intended to project the amount of drug dispensed in retail pharmacies in Hawaii, Alaska, Puerto Rico and the Virgin Islands, while the DEA is required to establish a quota which is adequate to provide for the legitimate medical and inventory needs for all places subject to the jurisdiction of the United States, including Hawaii, Alaksa, Puerto Rico and the Virgin Islands; (3) the fact that NPA projections normally do not include legitimate dispensing by hospital pharmacies, doctors, private clinics or government installations; or (4) the fact that the Administrative Law Judge and the Acting Administrator of the DEA found that certain data projecting the amount

[1] *Western Fher Laboratories et al. v. Levi,* CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 38,051, 529 F. 2d 325 (CA-1 1976).

of phenmetrazine purchased by drug stores in 1974, which were relied upon by the DEA at the administrative hearing and which were obtained from the same company which is responsible for the NPA projections, "were unreliable." The Court's acceptance of the DEA formula in which the NPA data, rather than the manufacturers' actual sales, were used to determine medical and inventory needs, was predicated upon the Court's conclusion that "substantial amounts (of the drug) are being illicitly diverted somewhere along the pipeline." It is significant to note that this conclusion of the Court was not based on the evidence of reported thefts or losses of phenmetrazine along the pipeline, which the Court in its opinion recognized as being "very small," but upon the testimony of a DEA official that the drug is a popular and abused drug and that illicit sales of it are very profitable. It is also significant that several of the DEA officials who were involved in the case have indicated that, in their opinions, the decision of the Court tended to overemphasize the evidence as to the amount of phenmetrazine which was being abused.

Phenmetrazine Quotas

Moreover, what the Court apparently did not appreciate was that even if one could assume that the testimony as to the popularity and profitability of phenmetrazine could be translated into evidence of a substantial amount of abuse, the testimony did not necessarily support the Court's conclusion that substantial amounts were being illicitly diverted along the pipeline nor did it justify the quota established. This is because the diversion of controlled drugs often takes place at the end of the pipeline, rather than along the pipeline, through the use of stolen scripts or scripts written by unscrupulous doctors. The formula used by the DEA in establishing the phenmetrazine quotas; and approved by the Court, does not take into account this source of diversion. In fact, the greater this type of diversion, the larger the quota under the DEA's formula, since diversion through stolen scripts or unprofessional dispensing normally would be reflected as legitimate dispensing by the NPA data and, thereby, be included in the DEA's estimate as to legitimate medical needs.

In my opinion, the use of the NPA projections as the measuring rod for determining what constitutes the legitimate medical or inventory needs for a controlled drug is, for the reasons previously discussed, subject to substantial and real limitations. It makes more sense from both a factual and a legal viewpoint to use the manufacturer's actual sales to its DEA-registered customers as the basis for

determining the legitimate medical and inventory needs. If the controlled drug is being diverted illegally by any person in the chain of distribution, the DEA should use its enforcement tools, including the revocation of the person's license to handle controlled drugs and the imposition of civil and criminal penalties, to eradicate or prevent the diversion. It is important to note that the quota system, at most, acts only indirectly to prevent diversion and carries with it the risk that persons who need or desire the substances for legitimate medical and scientific purposes will be deprived of the substances. Except in those situations where the quota is set at zero by reducing the quantity of the controlled substance available, a possibility exists that those who desire the substance for illicit use will continue to obtain it while those who desire it for legitimate scientific or medical needs will be deprived of the availability of the substance.

While the Court of Appeals of the First Circuit in its decision recognized that "there might be situations in which, because of the interest of serving the nation's legitimate medical needs, reducing procurement quotas to make the pipeline more lean could be too crude an instrument," it concluded that in order for "such a situation to arise there would have to be, at the very least, a clear and definite showing that legitimate medical needs were not being satisfied." It is submitted that the decision of this Court was based not so much upon the failure of the petitioners to show that the legitimate medical needs were not being satisfied or upon the actual evidence of abuse, but upon the Court's hesitancy in overturning the DEA in a case involving a drug which is subject to abuse. The lesson to be drawn from this case, in my opinion, is the difficulty of prevailing in litigation with the DEA no matter how strong the facts or law on your side appear to be and, concomitantly, the importance of attempting, wherever possible, to resolve controversies with the DEA at the administrative level.

New Drug Provisions

In addition to this First Circuit case, there have been a couple of other recent developments in the courts involving controlled drugs which deserve mention. Probably the one which is of the greatest interest to the pharmaceutical industry is a United States Court of Appeals for the District of Columbia Circuit's decision[2] upholding a

[2] *American Pharmaceutical Association v. Mathews*, CCH FOOD DRUG COSMETIC LAW REPORTER ¶ 38,048, — F. 2d — (CA DofC 1976).

District Court decision[3] that the FDA does not have the authority under the new drug provisions of the Federal Food, Drug and Cosmetic Act to restrict the channels of distribution of an approved new drug subject to control under the Controlled Substances Act. The issue in this case was an FDA regulation which purported to restrict the distribution of methadone to direct shipments from the manufacturer to approved maintenance treatment programs, approved hospital pharmacies and selected community pharmacies. In this case, the FDA attempted to argue that it had authority under the safety requirements of the new drug provisions of the Federal Food, Drug and Cosmetic Act to condition the approval of a new drug not only upon a showing that the drug is "safe" for its intended uses, but that it will be distributed in such a manner so as to reduce significantly the hazards associated with its intentional misuse. The District Court concluded, however, that in the context of the Federal Food, Drug and Cosmetic Act the term "safe" was intended to include only the inherent safety of the drug when used in the manner intended. The District Court felt that Congress intended for the FDA to have the primary responsibility for controlling the manufacture and preapproval distribution of drugs, including controlled drugs, and for the DEA to have the primary responsibility for the distribution of approved controlled drugs. According to the Court,

"Once a drug is cleared for marketing by way of NDA-approval, for whatever uses the Commissioner deems appropriate, the question of permissible distribution of the drug, *when that drug is a controlled substance*, is one clearly within the jurisdiction of the Justice Department [DEA]. The District Court in rendering this opinion stated that the "unique problems of medical judgment, law enforcement and public policy [associated with methadone] . . . cannot justify a federal agency of specifically delimited jurisdiction from implementing equally unique control solutions not authorized by Congress."

This admonition of the District Court undoubtedly will be cited frequently by attorneys representing the pharmaceutical industry in cases with the FDA or the DEA in their attempts to get the courts to focus on the legal and factual issues involved, rather than merely accepting the judgment of the agency in the name of public health or public policy. Yet, I suspect that even the District Court which decided the methadone case might have been inclined to interpret the Federal Food, Drug and Cosmetic Act differently if there had been a gap with respect to federal regulatory control over the distribution of methadone. The Court in its opinion observed that not only did the DEA have the

[3] *American Pharmaceutical Association v. Weinberger*, 377 F. Supp. 824 (DC DofC 1974).

authority to control the distribution of methadone under the existing statute, but that Congress had recently passed a new act[4] which significantly increased that authority. Thus, in my opinion, it is still possible that another court, or even the District Court involved in the methadone case would be willing to uphold an attempt by the FDA to limit the distribution of an approved new drug, where the bases for that attempt centers around a misuse other than abusive misuse and where another federal agency does not have sufficient authority to control the misuse.

Prosecution of Doctor

Another interesting case involving controlled drugs is the recent Supreme Court decision[5] in a case involving the prosecution of a doctor for dispensing controlled drugs outside the usual course of his professional practice. The importance of this case insofar as the pharmaceutical industry is concerned is that it overturned a prior Court of Appeals' decision which held that Congress intended to reserve the "severe" penalties imposed by Section 841 of the Controlled Substances Act to persons who sought to avoid registration entirely by not registering and that persons who were registered could only be subject to the "modest" penalties provided for in Sections 842 and 843 of the Act. The Supreme Court, however, held that only the lawful acts of registrants are exempt from the "severe" penalties imposed by Section 841.

The fact that the DEA is primarily an enforcement agency, as opposed to a regulatory agency, is also manifested in the relatively few final and proposed regulations emanating from the DEA during the course of a year. During the last 14 months, there have been four final or proposed orders or statements of policy published by the DEA which I consider to be of general interest to the pharmaceutical industry. Two of these orders dealt with the security controls which should be implemented by manufacturers and distributors of controlled drugs in order to help prevent illicit diversion. In April of 1975,[6] the DEA published a final regulation setting forth recommended procedures for the screening and hiring of employees for positions which necessitate that they come in contact with controlled drugs. This regulation provides that the employer should make inquiries

[4] 88 Stat. 125 (May 14, 1974).

[5] *United States v. Moore*, CCH Food Drug Cosmetic Law Reporter ¶ 38,043, 423 U. S. 122 (1975).

[6] 40 *F. R.* 17142 (April 17, 1975).

concerning the potential employee's prior criminal convictions and unauthorized activities in controlled drugs. This regulation does not establish mandatory procedures but rather "guidelines to assist non-practitioners in implementing realistic drug security programs."

In April of 1976,[7] the DEA published a final order establishing new and more restrictive security requirements for the handling and storage of Schedules III—V controlled drugs. In the proposal which preceded this order, the DEA had proposed that the secure storage areas contain only Schedules III—V controlled substances to the exclusion of all other drugs, material and controlled substances in other schedules. The final order, however, allows Schedules III—V controlled substances to be stored with Schedules I and II controlled substances under security measures required for Schedules I and II controlled substances. It also provides for a procedure through which the manufacturer or distributor can obtain permission from the DEA to store noncontrolled drugs and other material with Schedules III—V controlled drugs. The action taken by the DEA with respect to this order demonstrates a willingness on the part of the Agency to consider reasonable comments and to incorporate changes in the final order where the changes are justified by the comments.

"Contingency" Import Registrations

In September of 1975,[8] the DEA announced that, in the absence of an emergency in which domestic supplies of a controlled substance are shown to be inadequate or the domestic competition is shown to be inadequate, the DEA will discontinue its practice of granting "contingency" import registrations. According to the Agency, the issuance of these regulations is "unnecessary and also administratively burdensome." In this announcement the DEA, in my opinion, has incorrectly commingled the statutory and regulatory requirements for an import permit with the statutory requirement for registration. While a showing of inadequate domestic supplies or inadequate domestic competition is a prerequisite to the issuance of an import permit, under the Act, the issuance of an import registration is not dependent upon either of these showings. The fact that such a registration might be administratively burdensome does not justify the DEA's refusal to register. It is submitted that the import registration of a qualified applicant on a "contingency" basis is in the public interest within the meaning of the Act, since it allows for the prompt importation of a

[7] 41 *F. R.* 16458 (April 19, 1976).

[8] 40 *F. R.* 43745 (Sept. 23, 1975).

controlled substance in the case of an emergency in which domestic supplies of that substance are inadequate. It is important to remember that the granting of a registration to import a controlled substance does not authorize the registrant to import that substance since a separate import permit must be obtained from the DEA for each consignment of the controlled substance to be imported.

Finally, in April of this year,[9] the DEA issued a proposal to require that all orders from a finished dosage form manufacturer of a Schedule I or II controlled drug placed with the manufacturer of the bulk raw material be preceded or accompanied by a written certification that the quantity of raw material ordered does not exceed the finished dosage form manufacturer's procurement quota for that calendar year. Under the proposal, the manufacturer of the bulk raw material would be prohibited from filling the order in the absence of receiving the certification from the finished dosage form manufacturer.

In conclusion, let us hope that the courts and the regulatory agencies will adhere to the admonition of the District Court in the methadone case so that the abuses of controlled drugs will not, out of expediency, result in any abuses in the judicial or the administrative process. In my opinion, one of the best ways to help assure this is for the pharmaceutical industry to cooperate with the DEA and the courts in their legitimate attempts to control the abuse of controlled drugs.

[The End]

AGENCIES AGREE ON NARCOTIC PROGRAM POLICIES

The working arrangements for the approval and registration of treatment programs for narcotic addiction have been set forth in a Memorandum of Understanding agreed to by the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA). According to the agreement, each agency shall obtain prior approval of the other before a new application for a treatment program is approved by the FDA or registered by the DEA. The agreement is aimed at coordinating any denial or revocation proceedings and providing for the disposition of narcotics if a program is terminated.

CCH FOOD DRUG COSMETIC LAW REPORTER, ¶ 41,671

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[9] 41 *F. R.* 14398 (April 5, 1976).

Legal Implications of Good Manufacturing Practice Regulations

By PATRICK V. GIBBONS

Mr. Gibbons Is Counsel, Domestic Manufacturing and Quality Control of the Schering-Plough Corporation.

I RECENTLY ATTENDED A SEMINAR in Washington where the proposed Good Manufacturing Practice (GMP) regulations were discussed. As you might imagine, we got into a dialogue on the legal character of the regulations. The dialogue ended rather abruptly when one of the Food and Drug Administration (FDA) representatives, rather testily I thought, told the multitudes that whether the regulations are substantive or interpretive is no longer open to question: Commissioner Schmidt had spoken on that point in the February 13 preamble.

I presume one of his peers instructed the fellow during the luncheon for we heard no more on that point from him. But one hopes that the love of the troops for the Commissioner does not lead to other indiscretions concerning the law and regulations, particularly until we lawyers get a further chance to muddy the waters or clear the air, depending upon your environmental penchant.

The law on the point is rather clear. Section 501(a) (2)(B) of the Federal Food, Drug and Cosmetic Act provides that a drug shall be deemed to be adulterated if:

". . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. . . ."

The first regulations implementing that section were published in 1963. But the current proposal attempts very far-reaching revisions, some of which, in my opinion, exceed any kind of "currency" in the industry.

But, you say, what of it? The lawyers, you believe, once again are counting the dancing angels on the head of that Twelfth Century theological pin. Let's look at the substantive-interpretive controversy more closely.

Administration agencies have authority to promulgate two kinds of regulations:

(1) Substantive regulations have the force and effect of law. A violation of such a regulation is the same as a violation of the Act itself, and carries the same penalties. Thus, if the current GMP regulations are substantive, a violation of them could result in a jail sentence for the persons responsible.

(2) Interpretive regulations do not have the force and effect of law, but simply describe the Agency's explanation of what the statute means. A violation of an interpretive regulation does not subject the violator to any penalty *per se,* although he should realize that the Agency may prosecute him, or seize his goods, since it has forewarned him that it interprets his act (or non-act) to be a violation of the statute. For example, if the current GMP regulation is interpretive and if a manufacturer does not comply with a particular provision of the regulation, he should know that the FDA may charge him with a violation of Section 501 (a)(2)(B) of the Act since he is not following what the FDA considers to be current GMP as required by the Act.

Interpretive or Substantive

Industry has taken the consistent, and I believe sound, legal position that the current GMP regulations are interpretive and not substantive. The FDA has concurred at least tacitly in this view by charging a violation of Section 501(a)(2)(B) of the Act any time it brings a legal action. The particular section of the regulation in question also may be mentioned in the complaint filed by the government but, to the best of my knowledge, it always has been accompanied by a specific reference to the statute, which would not be necessary if the regulation were substantive.

As a practical matter, in the trial of a lawsuit, the FDA cannot merely introduce the regulation in evidence and rest; it must go forward and establish that the particular act or non-act complained of is in fact a violation of current GMP. This requires expert testimony, usually by an FDA official. The manufacturer can then come forward with experts of his own.

Where does all of this leave us? Sterling Drug, based on recent experience, might opine "up the creek without a paddle." It discovered that failure to follow current GMPs means that the finished product is adulterated and in violation of the Act even though the finished dosage form is, in every respect, all it is supposed to be.

But, and I hate to put it this way, the converse is also true—merely following current GMPs does not guarantee that you will get a correctly manufactured product. Defects can creep into a finished product in spite of the most careful adherence to any kind of GMPs.

We must examine one more important area before we can lay down this awful burden; we must look at the statutory language itself. Perhaps Congress said something in those 1962 amendments that our artful friends, the jurists, can explain.

Due Process

In order to meet the test of due process of law required by the Fifth Amendment to the United States Constitution, a statute must not be vague and indefinite. Are the words "current" and "good" so vague and indefinite as to deprive a citizen of the United States, person or corporate, of due process of law? One case in which a federal court has written an opinion on this subject is *U. S. v. Bel-Mar Laboratories, Inc.* Bel-Mar challenged the constitutionality of the statute on the ground that it violated the Fifth Amendment, always a good start. The court held with the government, however, and said:

". . . the constitution does not require an impossible degree of specificity. Rather '(t)he test is whether the language conveys sufficiently definite wording as to the proscribed conduct when measured by common understanding and practices.' . . . Moreover, a strong presumption of validity attaches to an act of Congress, and '. . . statutes are not automatically invalidated as vague simply because difficulty is found in determining whether certain marginal offenses fall within their language.' . . . No more than a reasonable degree of certainty, viewed in light of the conduct charged, can be demanded. . . .

"Section 351(a)(2)(B), the particular provision in issue, was enacted as part of the 1962 amendments to the Food, Drug and Cosmetic Act of 1938, a piece of legislation that touches '. . . phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection.'"

That is known as the motherhood, cherry pie and Old Glory justification. The Seventh Circuit Court of Appeals came to the same conclusion in a challenge to GMP by a pharmaceutical firm which made the following points in its favor:

"Dictionary definitions confirm Senator Kefauver's opinion that 'current' and 'good' are ambiguous and imprecise words. In *Webster's New World Dictionary,*

four adjectival meanings are listed for the word 'current' and at least eleven are listed for the word 'good.' The dictionary only underscores what is obvious: 'current' and 'good' are, standing alone, and in the phrase 'current good manufacturing practice,' words which are so elastic, so imprecise, as to defy measure. Language is indeed an unwieldy tool. . . . But still it must be used with sufficient precision to warn those who might violate a statute and thereby subject themselves to loss of their property, injunctions, or even criminal sanctions. It is not enough to tell those subject to the statute to do 'good,' or to be 'current.' "

Unfortunately, the Circuit Court did not agree, saying,

"The Constitution requires only a reasonable degree of certainty in statutory language.

"We have no trouble with the use of the word 'current' in the GMP section of the FDA law. It fixes the point in time when the acceptability of the relevant production practices must be determined.

"Thus, the statute does not permit prosecution for failure to follow safety practices which were not recognized prior to the production of the subject drugs."

In addition, the Court said,

"The GMP provision is as precise as necessary under the circumstances; it is not unconstitutionally vague.

"We hold that the defendant violated reasonably stable, definite, and ascertainable standards of good manufacturing practice designed to insure the production of unadulterated drugs.

"We conclude that the term '*current good manufacturing practice*' adequately defines a standard which the administrator was authorized to particularize in interpretative regulations."

With quality opinions like those, upholding the right of the FDA to fling you in jail for not signing your batch records the same way as your pay check, one wonders why the Commissioner would want to issue the substantive spectre at all, particularly when the FDA, as I mentioned before, always cites the Act when bringing an action involving GMP violation.

So you have been found wanting. What can they do to you?

Three Remedies

Failure to comply with the Act's requirement that a manufacturer use current GMP may result in any one of three remedies provided by the Act:

(1) seizure of the goods which were manufactured out of compliance;

(2) an injunction against the firm or its officers restraining them from any one of several acts, including shipment of goods manufactured not in compliance or restraining them from manufacturing other goods not in compliance; and

(3) a criminal prosecution of the firm and/or its responsible officials.

To these three remedies, which are spelled out in detail in the Act, the FDA has added a remedy of its own, and one with which you may be more familiar, at least as effective as any of the other three: a recall. Let's discuss each of the three statutory remedies, plus recalls, in a little more detail.

Seizures are the most common remedy sought by the FDA. A seizure is an action against a particular quantity of goods. No individual and no corporation is involved, no fines may be levied against anyone, no one can go to jail, and the court has no power except to order some kind of disposition of the specific quantity of goods seized. The seizure does not directly affect any goods not seized, even goods from the same lot as those which were seized, although a manufacturer probably ought to get a pretty clear message, if the FDA seizes part of a lot.

Joel Hoffman, of the Wald, Harkrader and Ross law firm, enunciated a theory on seizures at the March Food and Drug Law Institute enforcement conference which I commend to your attention.

" 'The Decree Goes Against the Mushrooms'

"When a regulated company discovers or is informed by the FDA that violative goods are on its premises, and seizure is feared, there is one course of aotion that almost always commends itself: Destroy the goods immediately. This serves both the purposes of the statute and the interests of the company.

"Since the statutory objective is to remove offending goods from the channels of trade, their prompt and voluntary removal obviates legal action to remove them. From the FDA's viewpoint, one would hope, compliance has been achieved. The company has also demonstrated its commitment to protection of the public.

"It is sometimes possible, however, that the FDA would prefer the dramatic impact of a seizure as a means of impressing its seriousness of purpose on both the company involved and the trade generally. Here, too, the company's interests are well-served by prompt destruction of the offending goods. For the seizure action is an *in rem* proceeding, that is, it is a suit against the goods themselves. And if there are no goods, there can be no suit."[1]

The second remedy provided by the Act is an injunction, a remedy also sought by the FDA in cases involving alleged violations of current GMP. Usually, the FDA reserves this remedy for a situation in which a pharmaceutical firm is disregarding the Agency's repeated suggestions and warnings concerning manufacturing practices.

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[1] Hoffman, Joel E., "Enforcement Trends Under the Federal Food, Drug and Cosmetic Act—A View from Outside," 31 FOOD DRUG COSMETIC LAW JOURNAL 338 (June 1976).

The third remedy, a criminal prosecution, may also be used in situations involving manufacturing practices. The FDA has tended to use this extreme remedy with careful discretion, and generally only in those instances in which it believes there has been a blatant disregard of the requirements of the law.

The Federal Food, Drug and Cosmetic Act does not mention the word "recalls" or spell out procedures by which recalls may be required or requested by the FDA. Nevertheless, where the FDA finds a reasonably serious violation of current GMP, a recall is frequently suggested.

Regulatory Letter

And, just to prove it is not losing interest in the regulatory process, the FDA has come up with a regulatory letter concept which, underhanded though it may seem, attempts to drag the president of your company into the GMP controversy.

Do our FDA brethren really believe that regulations containing words like "reasonable," "adequate" and "scientifically sound" can "become binding specific requirements that must be complied with." I know that lawyers get ribbed once in a great while for using seemingly archaic language, but nobody ever went to jail for not understanding what "Know All Men by These Presents" meant. I hope we can all convince Commissioner Schmidt with our "Dear Alex" letters that he already has enough arrows in his regulatory quiver without substantive GMPs. **[The End]**

SENATE PASSES COSMETIC SAFETY BILL

Legislation that would give the Food and Drug Administration (FDA) major new authority to regulate cosmetics through safety testing, registration and labeling was passed by the Senate on July 30, 1976. The main purpose of S. 1681, the "Cosmetic Safety Amendments of 1976," as expressed in the Senate Committee report, is to ensure that uniformly high standards for safety substantiation through testing are applied to all cosmetic companies. The bill would require every manufacturer of a cosmetic to substantiate the safety of the cosmetic before placing it on the market by performing specific tests on animals or humans to determine the cosmetic's potential for toxicity, sensitization, and irritation. These reports would have to be retained and submitted to the FDA upon request or as provided by regulation. Other provisions of the bill would require the registration of processors of cosmetics and the alphabetical listing of ingredients, except flavors and fragrances, in the labeling of cosmetics. S. 1681.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,682

SELF-POLICING OF CONTROLLED SUBSTANCE PROCUREMENT

Regulations have been issued by the Drug Enforcement Administration (DEA) that require manufacturers who order a basic class of controlled substance in Schedules I or II to certify in writing that the quantity ordered does not exceed the person's unused and available procurement quota of such basic class for the current calendar year In its response to comments on the proposed regulations, the DEA pointed out that, because the manufacturers and not the Agency retain the certification, the procedure creates a method of industry self-regulation.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,672, 80,362, 80,472

HEARING SCHEDULED ON SAFETY OF RED NO. 2

A public hearing for the presentation of evidence on the factual issues related to the Food and Drug Administration's (FDA's) denial of a petition for "permanent" listing of the artificial coloring FD&C Red No. 2 will be held on September 13, 1976. Earlier last month, the FDA's ban on the color additive was upheld by a federal appeals court. The petition requesting the "permanent" listing had been submitted in November of 1968 and was denied by the Agency in April of 1976 on the ground that the existing evidence could not assure the safety of the coloring for any of its suggested uses.

Objection to the FDA's denial of the petition and a request for a hearing on the matter were submitted by the Certified Color Manufacturers Association (CCMA), whose predecessor had been one of the sponsors of the petition. The hearing will provide an opportunity for the CCMA to demonstrate that, contrary to the findings of the FDA, Red No. 2 is safe for use, requires no further testing to establish its safety, and raises no serious questions of carcinogenicity. The CCMA will be allowed to present evidence supporting its objections to the studies upon which the FDA relied in making its determination that Red No. 2 is unsafe and a possible carcinogen.

In a partial objection to the FDA's decision, the Cosmetic, Toiletry and Fragrance Association advised the Agency of its intention to file a petition for the listing of Red No. 2 for use in cosmetics that are applied topically, as contrasted with cosmetics that may be ingested. The FDA stated that, because the issues raised by the Association do not warrant a separate hearing, the September evidentiary hearing will address the question of whether the coloring, if not approvable for all petitioned uses, may be approvable for certain limited uses.

CCH FOOD DRUG COSMETIC LAW REPORTER, ¶ 41,674

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