VOL. 23, NO. 12 DECEMBER 1968

Food Drug Cosmetic Law JOURNAL

Current Good Manufacturing Practices Compliance—A Review of the Problems and an Approach to Their Management

. . . . . SEYMOUR B. JEFFRIES

Papers Presented at the Twelfth Annual Educational Conference of The Food and Drug Law Institute, Inc., and The Food and Drug Administration

A COMMERCE CLEARING HOUSE PUBLICATION
PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis, contributions and comments are invited.

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $20; single copies, $2. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

December, 1968
Volume 23 • Number 12

Second-class postage paid at Chicago, Illinois and at additional mailing offices.

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1968 FDLI — FDA Conference.—Some of the papers presented at the Twelfth Annual Joint Educational Conference of the Food and Drug Law Institute, Inc. and the Food and Drug Administration are featured in this issue of the JOURNAL. Additional papers will appear in a later issue. The Conference was held in Washington, D. C. on December 3, 1968. The theme of the Conference was "The Four C's of Consumer Protection: Communication, Collaboration, Cooperation and Compliance."

In his "Welcoming Remarks," beginning on page 604, *John C. Suerth,* Chairman of the Food and Drug Law Institute, gives a brief history of the origin of the Institute and of its work in conjunction with the Food and Drug Administration, and expresses the theme of the current Conference.

Charles C. Johnson, Jr. discusses the role of the FDA within the Consumer Protection and Environmental Health Service, of which he is administrator. Ideas for future programs that could possibly alleviate some of the environmental problems that we are facing in every facet of our national life are listed in his article "The Future of Consumer Protection" beginning on page 608.

In the article "FDA Today and Tomorrow," *Dr. Herbert L. Ley,* the new Commissioner of the Food and Drug Administration, deals with specific problem areas with which the FDA is now concerned, and the programs, both planned and presently in progress, by which industry and the FDA may combat these problems. Dr. Ley specifically mentions the problems of drug additives, the "generic-brandname" controversy, and microbiological contamination. The article begins on page 614.

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Food·Drug·Cosmetic Law
Journal

Current Good Manufacturing Practices Compliance— A Review of the Problems and an Approach to Their Management

By SEYMOUR B. JEFFRIES

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IF ANY SERIES of events could be said to mark the beginning of the need for new dimensions and scope in management guidance and information, process and quality control and communication systems in the pharmaceutical industry, the passage of the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act in 1962, and the subsequent promulgation of the Current Good Manufacturing Practice (CGMP) regulations in 1963, are those events. Adopted at the height of the Thalidomide incident, this legislation reflected the growing concern of government, the consumer and industry with the safety and efficacy of pharmaceutical products from their investigational stage all the way through to their sale to the ultimate consumer.

CGMP Regulations Designed to Insure Dosage Integrity

Among the most significant amendments was Section 501 (a)(2)(B) which classified as adulterated any drug not produced in conformity with

CGMP. The intent of the law was twofold: to *insure the dosage-integrity of drugs* by preventing the development, production and distribution of faulty drugs which invariably result from faulty manufacturing practices, and to provide the enforcement authority to correct faulty operations *before* drugs of questionable integrity result therefrom.

This amendment in substance, provides that a drug will be deemed to be adulterated if the methods or the facilities or controls "do not conform to or are not operated or administered in conformity with CGMP to assure safety, identity, strength, quality and purity." Thus, a drug would be deemed to be adulterated if the method or facilities or control (production and quality controls) do not conform to CGMP. What is indeed significant, is that a drug which is not in fact adulterated will be deemed to be so if it does not conform. In its intent, this requirement is certainly reasonable; as a sanctionable statutory standard which should define or establish a rule or required course of conduct, the statutory words *"Current Good Manufacturing Practice"* are no more definitive than an admonition to "be good or else." The words are vague in that they do not: (a) permit a manufacturer to define what is the standard of good industry practice, or (b) provide a basis for evaluating the state of operational compliance. And since industry production and quality control practices are in a state of constant change, the statutory standard is, itself, fluid—changing constantly.

What we have in effect, is the juxtaposition of a vague, constantly changing—fluid—statutory standard with an *absolute* standard of perfection (dosage integrity and zero-defects) imposed on the producer to assure safety, identity, strength, quality and purity—and anomalous regulatory and statutory posture which for all practical purposes, makes the manufacturer's task in achieving and testing statutory and regulatory compliance exceedingly difficult and, in many ways, unreasonably hazardous. Parenthetically, this legalistic anomaly makes counsel's role in evaluating his clients CGMP compliance both more important and formidable.

This legalistic anomaly is further complicated by the fact that absent a definitive, stable statutory standard, and because it is the only repository of information on industry practices (much of it being in the protected trade secret area) the Food and Drug Administration (FDA) alone is positioned to announce by sanctionable administrative edict what a "current" Good Manufacturing Practice (GMP) is.

Again parenthetically, one might ask how current FDA's repository of information on industry practices really is? The fact of the matter is that the FDA has long recognized the practical difficulties involved in determining, as of a given point in time, the level or character of GMP

acceptable and applicable to the manufacturer of a particular drug produced in its own environment, and in relationship to existing plant/facilities equipment and personnel.

Vague and fluid as the statute may be in its words, the intent is reasonable, and to implement both the intent of Section 501 (a)(2)(B), FDA promulgated the interpretive CGMP regulations providing industry with "general guidelines" setting forth minimum requirements or standards defining what *"current"* GMPs consist of, and these standards were supplemented by additional requirements imposed through new drug certification procedures.

Stripped of all niceties, the statute and its GMP interpretive regulations served notice on every producer and distributor of bulk or finished dosage forms of drugs that insuring the integrity of drugs meant that nothing less than a zero defects standard of operations would be considered acceptable in the development, production and distribution of drug products.

To the firm desiring to produce drugs in conformity with legal standards, this means that a drug—prescription, over-the-counter (OTC), and proprietary—must be so manufactured that it shall have *premarket assurance of quality and integrity, and that each individual unit (dose) must comply with what it purports to be.* It also means that the acceptable standard of GMP compliance may legally be construed to be "equivalence" with the best in the industry. Contrasted with FDA's former requirement of "batch" integrity, the practical effect of an operational standard such as "dosage-integrity," which makes the mixup of one tablet or label a violation, is to render obsolete most traditional production and quality control techniques and systems.

Modern Production Technology Creating Compliance Hazard Gap

The fact is, there is already a serious and growing "compliance hazard gap" between the industry's high-speed "dosage-form" production and packaging capabilities and its traditional quality control techniques and technologies. For example, management cannot hope to continue employing traditional physical and chemical assay methods and production controls if it expects to cope, effectively and economically, with the broadened "content uniformity" assay requirements proposed for the United States Pharmacopeia's (U. S. P.'s) 18th edition, the National Formulary's (NF's) proposed dissolution testing requirements, proposed microbiological control program for non-sterile drugs, or the FDA's expanded "unit-dosage" field testing program of important drugs.

Management will be compelled to employ more sophisticated, semi-automated, and computerized methods and systems, not only for monitoring and controlling processing and quality control operations, but also for dealing with the massive proliferation of administrative, marketing, technical, and quality control data generated in the course of regulatory compliance if it is to meet the legal demand for "dosage-integrity," and "zero-defects" operations.

The most significant effect the "dosage-integrity" and "zero-defects" standards have had on the industry is that they have, irreversibly, opened the door to "nuts and bolts" regulations of each and every aspect of manufacturing and quality control which could, in any way, affect the quality of the final drug product. These standards have imposed legally sanctionable responsibilities upon management for continuous monitoring, testing and evaluation of *current* GMP compliance performance.

And since, as indicated earlier, the minimum requirements or standards defined as "current" GMP are subject to change as experience and scientific and technological development indicate a need for redefinition, this means that as a manufacturer's products become more complex and his processing more complicated, so must his controls, in order to maintain his quality assurance objectives. In effect, it becomes the manufacturer's duty and responsibility to develop and establish the character and configuration of GMPs "currently" needed to achieve dosage-integrity for his product. It could, for example, mean that with the introduction of a new, ultra high speed tablet compressing unit or high speed packaging and labeling equipment, good manufacturing practices might require material modifications in applicable quality assurance control protocols and procedures to insure product integrity and establish an appropriate state of CGMP compliance.

Top management should be aware of the hazards involved in failure to meet GMP requirements even though, curiously enough, the requirements may have been made without notice to those who must comply. In failing to comply, management runs the risk of enforcement by publicity, costly product recalls, or even having its plant closed down upon immediate notice, when the violation is considered by FDA to be material to the public's health. The violation can turn up in a variety of ways: the framework of a drug recall, either voluntary or one ordered by FDA (which may also involve a seizure of goods in the field), in a factory inspection report disclosing "significant adverse conditions and practices," an FDA "potency survey," or as a result of a product complaint made to the FDA by a consumer, physician or pharmacist. Violations found by a state Board of Pharmacy inspector may also be forwarded to FDA for action. Most

compliance inadequacies, however, show up in the producer's own quality control laboratory prior to and sometimes after the product's distribution.

Penalties of Non-Compliance with CGMP Regulations

One manufacturer who failed to apply the GMP techniques established as "current" to prevent cross contamination by penicillin, had his plant closed, on notice, until the adverse conditions were remedied. A number of products were sample tested in the field, seized and destroyed, and criminal proceedings were initiated against the president and quality control director. The publicity almost ruined the company.

Another producer was compelled to recall drugs worth thousands of dollars because they were found to be Salmonella infected; he had failed to follow FDA's "current" GMP raw material quality control protocol.

Following a factory inspection, one producer was cited for "significant adverse conditions" involving poorly prepared and documented master formula and batch records. Tablet hardness and weight test data were found to be contrived on several batches. His plant and records were subjected to the most intensive inspection, immobilizing his operation for almost four weeks. The financial consequences were nearly catastrophic. Product recall and seizure problems arising from management's *ignorance* of substantive changes in assay requirements of the official compendia, or its *negligence* in communicating such changes to quality control personnel, or because assay records and laboratory record-keeping procedures were below standard, occur far more frequently than they should.

It should be noted parenthetically, that violations of the GMP regulations are by no means limited to the small and medium volume producers. Drug recalls occur in companies of all sizes. The real problem to the public and the FDA, is the producer to whom quality assurance is a nebulous, "tomorrow thing" to be handled only after the violation is disclosed.

Management's CGMP Regulations Compliance Burden Formidable

To really grasp the enormity and complexity of the operational and GMP compliance problems confronting management, the most serious consideration must be given to: (1) FDA's changing enforcement attitudes, (2) the impact of current scientific, social and economic developments in the health care field on the industry's regulatory and operational trends, (3) the difficulties management is faced with in making business and technical decisions and judgments necessary for a "state of compliance," and (4) the liabilities—civil and criminal—faced by the manufac-

turer, corporate officers and others burdened with the duties and responsibilities of compliance.

Management is expected to develop and employ "quality assurance" policies, organizational patterns, facilities, plant design, procedures, systems and methods in conformity with current guidelines or minimum requirements (standards) established by the CGMP regulations designed to *insure* dosage integrity, and *assure* an acceptable state of compliance.

The oddity implicit in the manufacturer's compliance *judgment problem* is that management, composed almost wholly of *non-legal people,* is expected to deal with sanctionable legal standards, where the legal and practical tests for such standards are by no means as definitive as they might be.

While it is comparatively simple for FDA to promulgate GMP requirements which call for *"adequate"* buildings, *"suitable"* equipment, *"appropriate"* personnel, a system set up in a *"manner to assure"* that raw materials shall be identified, stored—tested, inventoried, handled, and otherwise controlled so that they shall *"conform to appropriate standards"* of identity, strength, quality and purity, that *"appropriate"* records are maintained on components, that there be *"competent"* preparation of batch records, *"reasonable"* control procedures, *"adequately"* controlled labeling, *"adequate"* laboratory controls, *"adequate"* systems for facilitation of recalls, *"adequate"* stability data, and *"appropriate"* action on complaints, the *translation* of these standards into actual compliance *applications* is not nearly so easy, nor are the tests for the exercise of management judgment required to determine the state of compliance in each instance any less difficult.

Management is told, "here are the legal current GMP general guidelines and minimum requirements, subject to change as the needs indicate. You, Mr. Producer, translate them into manufacturing practices consonant with the regulations, your own production and quality control needs, and the changing demands imposed by scientific, social and economic developments in the industry. We (FDA) are not telling you specifically 'how or what' you are to do since your production and quality control problems may vary from those of other producers. You are, however, legally responsible and liable for evaluating compliance performance, that is, evaluating buildings and other facilities in terms of 'suitable' or 'adequate' etc., and judging whether you have achieved a satisfactory state of compliance. Anything less is sanctionable, and we will pass final judgment on your compliance activities by factory inspections, field tests of your products and other surveillance activities necessary to check your compliance performance evaluations and decisions."

Company and Personal Liability

Often overlooked, as well as frequently misunderstood in analyzing management's CGMP compliance problems is the nature and scope of corporate and personal liability sanctioned by the statute. Briefly stated we have seen that under Section 501 (a)(2)(B) a drug which may not be in fact adulterated, will be deemed to be if it does not conform. It would appear then that the act of producing a drug where the methods, facilities or control do not conform, is in itself a violation of the statute. As was noted earlier, where such violation or deficiencies in the matter of compliance with CGMP regulations create such a hazard that the public might be endangered were such practices permitted to continue, FDA could act to enjoin the manufacturer, that is, padlock the plant and prevent any shipments therefrom. And under certain circumstances, criminal charges could be brought against the corporate officers and employees—as, for example, where penicillin or steroid contamination is found to exist in a batch of finished dosage forms of drugs, particularly where quality control had already released such items for shipment. It is important to note that the manufacturer may be convicted of having violated the act regardless of intent, motive or even consciousness of wrongdoing. The courts held repeatedly that a person who brings a product covered by the Federal Food, Drug and Cosmetic Act into commerce is bound to see that the commodity does not violate the provisions of the statute.

It is important to note as well, that corporate officers and employees may be personally prosecuted and convicted for illegal shipments of adulterated drugs by the corporation even if they had no direct part in the transaction. They may be held criminally liable merely on the basis of having had a "generally" responsible share in the act that took place. This concept of absolute liability is grounded on the theory that in this sensitive area of consumer protection penalties frequently serve as the most effective means of industry regulation. The only question is whether or not the regulations were violated regardless of intent, motive or consciousness of wrongdoing. This is predicated on the notion that in the interest of the larger good, it is reasonable that the statute impose the burden of acting at risk upon a person otherwise innocent, where such person stands in responsible relation to a public danger. That criminal prosecutions have not been pressed more energetically under this section of the act is not surprising in view of the admitted vagueness and fluidity of certain CGMP regulations standards and requirements coupled with its stated policy of encouraging "voluntary compliance." That the trend is towards more vigorous enforcement, as FDA moves more and more in the direction of greater specificity of GMP standards and requirements pin-

pointing individual responsibilities for performance in manufacturing and quality control, appears to be a certainty.

In the "private" liability sector, drug manufacturers, as a group, are faced with greatly expanded drug product liability litigation. In fact the Tort Law of product liability has been called "new bonanza." Not too long ago, most product liability cases involved foods, then the evolution of litigation involving a variety of other products including cosmetics and cigarettes began to push food product liability actions into the background. The greatest impact now is in claims for injuries allegedly resulting from the use of drug products.

What makes a drug product "defective" within the meaning of product liability law is not too clear. In some jurisdictions merely the capacity to cause "side effects" or harmful reactions to an "appreciable class of users" may render a product for intimate bodily use "defective." Some authorities state that the trend in product liability law, particularly litigation involving drugs, is to make the manufacturer the insurer of the product.

In a number of jurisdictions, the drug manufacturer's traditional defenses of lack of fault, or lack of privity between him and the allegedly injured consumer, lack of a sale or warranty, and the "idiosyncratic" or "allergic" defenses are of little or no avail.

In a growing number of jurisdictions it is being held that if a drug manufacturer in a negligence action is held to have violated the Federal Food, Drug and Cosmetic Act, and if acts constituting such violation are held to be the proximate cause of the injury, the manufacturer may be held strictly liable under the "negligence per se" theory, without proof of actual negligence. The implications of this trend in product liability law vis-a-vis the mandates and sanctions imposed upon the company, under Section 501 (a)(2)(B), should give pause for reflection by management at all levels of production and quality control on the growing complex of hazards and risks involved in corporate statutory compliance functions. Management might also reflect upon the importance of developing free and open lines of communication and liaison with informed, knowledgeable legal counsel who is prepared to assist management in the interpretation and application of statutory and regulatory requirements.

As a footnote to the comments on the development of product liability law in the drug field,—a subject which deserves separate treatment in depth—it might be interesting to note the significant views expressed by a growing number of casualty insurance underwriters to the effect that product liability insurance—a precarious form of coverage at best—might

eventually be denied to producers who as a result of federal and state GMP inspections are found to have a consistently poor and risky compliance record. One very prominent insurance executive noted that his casualty group was watching very closely the progress and results of FDA's Intensive Factory Inspection Program (IDIP) and its new Plant Evaluation System (PEV) for premium rating purposes. Since product liability coverage is so critical to any drug producer's marketing program, whether it be to the private consumer or to government, this is indeed an area that deserves careful consideration.

Management's compliance judgment, its liability and its administrative burden is indeed a formidable one. But any criticism of the position management is put in by the generality of GMP guidelines and standards, should take into account FDA's historic posture, *agreed to—in fact, insisted upon—by industry*, that, the large variety of materials used, the complexity of drug products manufactured, differences in plant facilities, and the various sizes and types of company organizations make it almost impossible, and certainly undesirable, to prepare a detailed, highly specific production and quality control system that will be universally applicable.

It might also be noted at this point, that the more pragmatic minded producers and legal specialists in the drug field have accepted, within reasonable limits, the following views: (a) that GMP regulations are going to be pretty much what FDA says they are going to be, (b) that the regulatory trend is definitely in the direction of greater specificity, standardization and universality in production and quality control systems applications, and (c) that management, to achieve and maintain a satisfactory state of compliance, will have to rely more and more on sophisticated managerial technologies and systems, together with *closer and continuous liaison with specialized legal counsel* and external, "objective" quality assurance consultants.

Vagueness of CGMP Guidelines a Problem in Evaluation of Compliance

A practical illustration of the problem posed by the generality or vagueness of the GMP guidelines or minimum requirements, is the case of X drug company, a major producer that is in the process of developing a totally computerized management-information system, a critical segment of which is the maximum computerization and automation of production and quality control functions.

A question arose in designing the raw materials handling and control applications as to what specific data elements should be included in the file, and what the input and output specifications should be to assure not

only conformity with the current requirements of the "Components" section of GMP (133.6), but also anticipated regulatory and business demands.

On its face, the problem appeared simple, yet each member of the Management Information Committee consisting of the Vice President of Plant Operation, the Vice President of Manufacturing, the Quality Control Director, and legal Counsel, offered a different view of what the file data should consist of, *what CGMP regulations controls, were required,* and how they should be handled to meet both management's and the regulation's requirements.

Each executive saw and tested the regulatory standards differently, ostensibly because of different background experience, and functional responsibilities, but fundamentally, because *detailed specificity as to what compliance consisted of is lacking in the regulations themselves.* In fact, the committee members were not even able to come up with a unanimous view as to the actual state of compliance of the company's raw materials handling and control methods and system.

Result: the company decided to resolve the Committee's dilemma by bringing in an external, completely objective quality assurance consulting group not only to inspect and audit compliance performance and come up with an evaluation of "state of compliance," but also, to assist the company's EDP Systems Group in designing and programming the data and control specifications for this and other production and quality control computer applications which would also conform to CGMP regulations.

It was mentioned earlier, that to grasp the enormity of management's compliance evaluation and decision-making responsibilities consideration had to be given not only to FDA's current enforcement attitudes (which were characterized as hard-nosed) but also to the key scientific, social and economic changes which have taken place in the health care fields. Both critically affect the industry's present activities and its plans for future growth and profitability; and both call for definitive management judgments and decisions along lines indicated earlier.

Loss of Patience at FDA

With respect to enforcement of GMP regulations, the Food and Drug Administration has made it abundantly clear that it has lost patience with sub-standard manufacturing practices in the drug field, and that it is disappointed in the results of its three years of effort at "voluntary compliance." "The law" said the Commissioner recently, "is there to be enforced and it calls for compliance with the practices which will result in good

drugs . . . and field offices have been told to recommend seizure, prosecution or injunctions when they find violations." The FDA has also taken the position that those manufacturers who cannot achieve compliance "will not be able to stay in the drug manufacturing business."

One of the tests applied by the FDA to measure the degree of compliance with GMP regulations is the incidence of drug recalls due to manufacturing errors. "The incidence of drug recalls" says FDA, "is increasing sharply and analysis shows that close to 80% were for reasons which could be related to a failure to observe GMP regulations including: potency variations, cross contamination, non-sterility, label mixups, decomposition and adulteration, and in many instances failure to meet all the requirements of the official compendia." What is significant, is FDA's statement that it is not ready to accept the recall as a satisfactory means to be relied on for protecting the public from defective drugs.

Another test was FDA's so-called "potency survey" in the early part of 1966 as a result of which approximately 8% of the 4600 samples examined, were found to be significantly *over* or *under* the declared potency. That there may be considerable validity to the criticism by industry of the results of this survey, is not the point. The fact is that there were variations from the accepted reference standards, and the industry is presently faced with a broad based field sample testing program which contemplates as many as 300,000 sample tests from products picked up in the field.

A third, and very critical test, is analysis of factory inspection reports which, FDA said, "showed that inadequate manufacturing control procedures were at the top of the list of poor conditions which were observed in one out of four of the drug plants inspected." The analysis showed poor control procedures occurring in the following order: (1) packaging and labeling, (2) master formula and batch records, (3) components or raw material controls, (4) laboratory controls, (5) non-existent distribution records, (6) production controls, (7) buildings, (8) complaint files, (9) stability, (10) product containers, (11) equipment, and (12) personnel qualifications.

As a result of these and other tests, FDA recently announced that it was initiating an intensified drug inspection program of all prescription drug plants in order to achieve its goal of "complete assurance" of the quality of prescription drugs on the market. It can be expected that the results of FDA's factory inspection will inevitably become a part of its computerized Recall Monitoring and, Drug Firm Registration programs which will be used to check compliance history, and its Established Intelligence Pro-

gram, which includes accountability information from all firms and individuals producing and handling controlled drugs.

The FDA tests described, clearly revealed a broad variety of weaknesses and shortcomings in traditional product and quality control methods, systems and technologies, and in many instances, less than effective management quality assurance attitudes, orientation and organization—all of which FDA considers unacceptable.

In practical terms this means that management must (a) re-examine its compliance policies, (b) evaluate its present compliance "action programs" at each operational level, and (c) structure a practical self-inspection audit program designed to measure and achieve a state of compliance.

FDA's "IDIP" and "PEV" Programs a Move Towards Self-Certification

FDA's Intensified Drug Inspection Program (IDIP), perhaps more than any other enforcement plan, reflects the government's determination to zero top management in on the critical importance of production and quality control functions in assuring product integrity and "zero-defects" operations, and its legal responsibilities with respect to achieving and maintaining a satisfactory state of CGMP regulations compliance.

In moving forward on its current IDIP effort, FDA has adopted a "non-adversary" enforcement approach, reflecting, as we shall see later, the beginning of a basic change in its regulatory philosophy from that of the "cop on the beat" concept of enforcement to that of an agency setting standards and providing assistance to industry to help industry meet those standards.

FDA's switch in enforcement tactics is clearly consonant with its long range plans for more effective regulation through a formalized quality assurance self-certification (self-inspection) program. In principle, FDA's new regulatory frame of reference appears to be most promising. Operationally and legally, however, it raises a host of questions which deserve the most careful consideration. For example: Is industry ready to accept the practical consequences involved in an FDA "partnership" in achieving the level of self-regulation that would assure quality integrity and CGMP compliance?—particularly when the IDIP treatment contemplates an "in-resident" advisory type of project with a team of inspectors who are expected to stay in the plant until their version of compliance is achieved. The "big brother" IDIP theory also raises the question as to the liability of the manufacturer when something goes wrong where the plant has been

given the "full treatment." Can the government be held jointly liable with the manufacturer? Can the manufacturer set up as a defense in a product liability action, or a citation procedure the government inspector's compliance mandate (recommendation) carried out under his supervision?

And hardly to be overlooked in evaluating "self-inspection" as a mechanism for maximizing "voluntary compliance" is the posture FDA proposes to take on the matter of the privacy of the company's internal documentation and files on its own audit of itself. Since the objective of any self-inspection program is to search out errors or potential errors in production and quality control procedures, FDA's insistence on the right of access and review of self-audit documentation could in a practical, and possibly a legal sense amount to self-incrimination. Clarification on these, and other points, is called for.

However complicated these problems may be, voluntary self-certification is likely to become the operational keystone of FDA's compliance enforcement philosophy. Certainly such a self-regulatory program in the drug industry will be needed to more effectively expedite certain Health, Education and Welfare (HEW) public assistance programs under Titles 18 and 19 (Medicare and Medicaid).

Such a self-certification program could involve: (a) company quality control tests and other inspections to insure that standards are being met, and (b) a comprehensive reporting system to make certain that FDA learns promptly of any company quality assurance shortcomings and the corrective steps taken—based on a system similar to, but more definitive and feasible, than FDA's present Plant Evaluator program (PEV).

A reporting system under a drug industry self-certification program would require utilization of a *standardized, computerized GMP compliance inspection and audit program to permit continuous compliance monitoring and evaluation of the companies participating in the program.* It is also likely that FDA will find it necessary to recommend the adoption by industry of a *more detailed, standardized production and quality control system with common nomenclature* which would lend itself readily to *universal application* in a number of company operational areas.

Though standardization of production and quality control systems, particularly in the area of data design and record keeping procedures, might well represent a substantial departure from its traditional posture described earlier, any regulatory move towards greater *specification* of the GMPR's compliance requirements should be advantageous to management. Certainly management's "state of compliance" judgments and decision-

making problems will be easier to solve, and it would represent a substantial step forward in *equating* the quality assurance responsibilities and obligations among all companies, be they large, medium or small.

Expanded Welfare Programs Means Tighter GMP Regulation

Public and legislative criticism of drug prices and profits has long been a source of irritation to industry. It was the passage of Titles 18 and 19 (Medicare and Medicaid), and the authorization, under Title 2 of the Child Health Act, to the Secretary of HEW to set "a reasonable cost range" for drugs, that set in motion regulatory trends and pressures that have already, and will for sometime in the future, reflect themselves in a host of new management regulatory compliance responsibilities and business problems. Let us take a closer look at some of the problems created, their causes and their ramifications.

Legislative reaction in Washington and in many state capitols to the burgeoning costs of supporting the various federal and state health care programs has resulted in tremendous pressures on the agencies responsible for their administration to keep the lid on the costs of sustaining "vendor" drug programs.

It has been suggested for example, that one of the ways of keeping the cost of drugs down in federally supported public health assistance programs, might be to move the government into the drug dispensing business and centralize procurement under a government agency that will operate on a vendor-vendee basis to purchase drugs needed by competitive bidding—such bids to be on a generic name basis, regardless of whether branded products are, in fact, involved. The likelihood of such a development taking place in the immediate future is slim. However, should medical care costs continue to skyrocket, this could happen. The operational and profit consequences flowing from such a development should not be difficult to visualize, particularly by the producer who has (a) tried to qualify his plant and his products with, for example, Defense Supply Personnel Center (DSPC) and failed, or (b) *failed* to qualify because of price, or, (c) been unable to demonstrate the quality of his product, including in some instances, clinical efficacy.

Industry would indeed be remiss if it ignored the significance of the "straw-in-the-wind" move by the federal government to establish an O. E. O. (Office of Economic Opportunity) community health center in Montgomery, Ala. It might be added, parenthetically, that in looking into the possibilities of government dispensing practice and centralized

procurement of drug supplies, questions have been asked in congressional and state legislative hearings as to why double standards of quality assurance should exist as between FDA's CGMP regulations which are relatively vague and minimal, and Defense Personnel Support Center's more definitive, more stringent DPSC standards for pharmaceutical manufacturing and packaging.

Another aspect of the problem that should not be overlooked, is the strong possibility that The American Medical Association (AMA) and the American Hospital Association (AHA) accredited quasi public, voluntary and proprietary institutions may establish "acceptability as a supplier" by such quality demanding agencies as the Directorate of Medical Material (Defense Personnel Support Center) *as a basis for vendor qualification.* The fact is, that many large volume institutional drug buyers are already making their own "in-situ" quality assurance plant and product evaluations to qualify a vendor drug producer and his products. How much drug volume a manufacturer can afford to turn his back on in order to avoid the moderate cost and profit benefits involved in employing effective, prophylactic quality assurance production and quality control practices, procedures and systems is a question that management will have to face sooner than later.

Perhaps the most significant drug cost control programs expounded by the federal and state welfare administrative agencies, and supported by jittery legislators is the "drug formulary" concept. Federal legislation proposing the establishment of a formulary listing the drugs available for the treatment of needy individuals is now pending. One federal bill would make the receipt of federal funds under Title 19 and other health care titles, contingent upon the state's adoption of a drug formulary for all of its welfare programs. Other proposals would make the formulary listing and dispensing of so-called generic name equivalents of brand name drugs compulsory. Some states already have formularies restricting drug therapy to generic drugs (equivalents) except where there is none, in which case the physician is required to obtain prior approval.

The drug formulary concept has long been an accepted operational aspect of institutional medical and pharmaceutical practice. In terms of its new frame of reference—use in federal and state public assistance drug vendor programs—it raises regulatory, business and legal problems which management should understand. Their importance can best be understood by visualizing the effect such a qualifying requirement as "proof of therapeutic effectiveness" could have on a product and plant seeking listing.

Were the therapeutic effectiveness requirement to be construed narrowly by HEW's Formulary Committee to apply to each individual drug product submitted for listing, manufacturer A's "dextro amphetamine sulfate"—a generic item—would be excluded from listing until its therapeutic effectiveness was established "by substantial clinical evidence or, when appropriate, by assays in man that demonstrate the biological availability of the active ingredients." Drugs with effective New Drug Applications (NDAs) would apparently have little difficulty meeting this requirement.

Producers of *excluded* products would have the choice of either risking the financial consequences flowing from exclusion from this market place, or qualifying their products as indicated above. To compete for a share of the "welfare" drug market it would have to undertake and underwrite qualifying *clinical research programs* on every product produced together with facilities and personnel required for implementation. Production and quality control technologies and procedures would have to be reviewed and upgraded to achieve maximum efficiency and cost savings. In order to cope with the enormous added quantity of research, quality control and production data needed to expedite its product-qualifying objectives, management would have to integrate the most efficient, cost-benefit information and communication systems available.

Realistically, such a strict construction of the therapeutic effectiveness requirement would clearly be *inconsistent* with the immediate objective of the welfare administrators to reduce the cost of drugs. Since the therapeutic effectiveness of most individual versions of generic drugs ("old" and "official") has never been established, a narrow construction by a formulary committee would not only limit the list to very few items, but also make compulsory generic prescribing professionally impractical.

It would be foolhardy for any manufacturer to brush off the importance of public assistance drug volume—most of which will be tied to "formulary practices"—since it is the fastest growing segment of the drug market. Approximately one out of every four prescriptions are today being dispensed under some form of federal and/or state public health assistance program; by 1970, it is estimated that this will increase to one out of every three prescriptions dispensed. The penalties of exclusion from formulary listing speak for themselves.

Product and Plant Federal Licensing Proposal

Of tremendous significance to management in all companies, regardless of size, are the suggestions recently made by a major drug producer

(and HEW's Task Force on Rx Drugs) that every drug manufacturer should be *licensed* by the FDA, and *inspected annually,* and that no manufacturer should be permitted to market a drug product, whether new or old, until its therapeutic effectiveness has been satisfactorily established. The rationale underlying these proposals is that there are many drug producers whose existing manufacturing practices and facilities fall far below the requirements established by the CGMP regulations, and there are also countless numbers of drug products on the market which have never been cleared by FDA for safety and effectiveness—and on the "old" drugs, there is no legal compulsion to do proper testing before marketing. With respect to therapeutic effectiveness, what *is really being proposed is that any drug entity not heretofore cleared by FDA for safety and effectiveness shall become subject to some form or type of NDA certification procedure,* a condition tantamount to the licensing of all marketed drugs.

While the thrust of the proposals appears to be in the direction of providing greater protection to the consumer, the real objective is to zero in on the purported inequities inherent in the government's insistence on setting prices for drug programs on the basis of the existing low prices of the marginal, low cost producers of the so-called generic equivalents, most of which *have not* been burdened with the cost of establishing therapeutic effectiveness. Any manufacturer who has taken a product from its research and development stage to an effective NDA status, is more than familiar with the problems and costs involved. Regardless of how the qualifying procedure for establishing the therapeutic effectiveness of a recognized "old" drug might be tailored by FDA, the operational and cost burdens involved would result in higher generic drug prices.

It is extremely doubtful that FDA or its cost-conscious parent, HEW, would consider a move in this strong regulatory direction at this time. There are, however, indications that industry can expect FDA action in these regulatory areas in the very near future. FDA's proposed GMP self-certification program rings clearly in the direction of plant licensing and periodic monitoring of GMP compliance, and it has been hinted that proof of therapeutic effectiveness on certain "old" prescription drugs characterized as "life-and-death" preparations, should be subjected to some certification procedure not unlike the antibiotic drugs. Certainly the massive drug efficacy study being conducted for the FDA by the Drug Research Board of the National Academy of Sciences/National Research Council (NAS/NRC) is an indication of the government's regulatory thinking. Here the federal government is footing the bill to determine the efficacy of some 3,000 drug products which were cleared by FDA through its NDA licensing system between 1938 and 1962 which have not been subjected to

formal review or efficacy data. This number could be raised to 15,000 drug products covering "me too" duplicates by brand name, as well as "generic" manufacturers. Whether the government is ready to undertake the cost of testing the efficacy of these additional products is a big question.

Another aspect of the FDA drug efficacy study is the fact that the agency has set up a procedure which will result in the release of many products from NDA "licensing" control once they have been declared effective by the NAS/NRC Group. This will make it possible for any manufacturer to market the product—in the absence of patent restrictions —without going through the NDA clearance procedure. However, in order not to lose control over drugs released from the NDA system, and because FDA obviously recognizes that two drugs containing essentially the same active ingredients will not, in all cases, produce the same clinical effect, it contemplates publishing regulatory monographs on each released product in the *Federal Register*. The monograph will outline all the regulatory conditions with which a manufacturer must comply if he wants to market any of the released drugs. Where special circumstances are required to demonstrate therapeutic as well as chemical (or generic) equivalence, the regulatory monograph will so state.

If the unlikely happened and legislation were enacted requiring proof of therapeutic effectiveness as a condition precedent to marketing all drugs, the formulary committee's job would be simple. It could, on an open-end-basis, leave the choice of the generic drug (by manufacturer) dispensed up to the vendor pharmacist—which would mean that the department's computer bank would have to contain a product file on *every version* of the particular generic drug being marketed.

Except for legal questions involving substitution, such a pre-market requirement would, for all practical purposes, reduce the brand name-generic drug equivalency issue to a skirmish of scientific semantics and a competitive scramble for share of market. Authorities have observed that it would be difficult to make an issue about whether manufacturer A's brand of papaverine hydrochloride, or manufacturer B's generic name version should be prescribed and dispensed when both manufacturers have established the therapeutic effectiveness of their products to the satisfaction of the FDA.

Since most generic drug manufacturers have *not* established therapeutic effectiveness of their products, the formulary committee could adopt the view widely held among worried welfare agency administrators and

legislators that a showing of "chemical equivalency" (by in-vitro chemical assay) is a sufficient demonstration of equivalency as between two products containing the identical active ingredients in identical quantities. While this is an economically convenient posture, and while it might appear to offer short-term advantages to the small generic manufacturer, the great weight of opinion in FDA, in HEW, among physicians and pharmacists, and even among the generic drug manufacturers themselves, is that the basic issue of "generic equivalence versus clinical equivalence of drugs" is a long way from being resolved.

It is doubtful whether physicians are ready to entertain the professional and personal liabilities and risks implicit in relinquishing control of patient drug therapy where the scientific community is so evidently split on the issue of generic versus clinical equivalence. Pharmacists, faced with similar professional and personal liabilities and risks have stated that, "the drug manufacturer, or the government must guarantee the product marketed to the retailer under a generic name, and the producer must be required to offer proof of quality of certification of each particular drug *sold* to the pharmacist for resale to the public." Certainly the message to management is clear.

Greater Specification of Production and Quality Procedures Indicated

It was mentioned earlier, that a spokesman for the major producers in the industry had suggested proof of therapeutic effectiveness as a condition precedent to marketing for all drugs. It was also mentioned that many smaller drug manufacturers also were very much aware of the need to resolve the doubts as to generic equivalencies versus clinical equivalencies of drugs. This group suggested that the HEW Task Force on Prescription Drugs appoint academic institutions with pharmaceutical manufacturing facilities to formulate complete master formulae, considering the pharmacology of drugs for all official preparations, such master formulae to include: (a) active ingredients, (b) inert excipients as fillers, (c) binders and granulating compounds, (d) disintegrants, (e) anti-oxidants or anti-reducing agents, and (f) lubricants, vehicles, ointment bases, etc.

It was also suggested that the *master formulae should spell out the entire manufacturing procedure including mixing time, drying time, moisture content, sieve sizes, hardness of tablets, ph of solutions, ointment basis, etc., and the type of equipment to be employed,* including all applications required by the GMP regulations. It was further suggested that method-

ology of assay protocols for these formulae as formulated and manufactured should be established; that the drugs so formulated, manufactured and assayed be subjected to clinical availability studies; that parallel clinical studies should be conducted simultaneously on existing products containing the same active ingredients but manufactured in accordance with master formulae which may differ permitting the manufacturer to establish his own formula and method of procedure and making available to said manufacturer the facilities for clinically equating his product versus the standard.

It was also recommended that upon the completion of these studies, the Task Force on Prescription Drugs establish a *Medicare Drug Formulary* which would include the accepted master formulae and procedures of manufacturing, and the requisite protocols for control which might eventually be incorporated as an integral part of the U. S. P. and the N. F. "The standardization of formulae, manufacturing methods and quality control procedures, as outlined," they said, "will encourage true competition and should satisfy the federal government concern with achievement of the lowest possible cost consistent with high quality."

What is interesting to note is the fact that major companies advancing the concept of pre-market proof of therapeutic effectiveness for all drugs, and the smaller generic drug manufacturers advancing the notion of a formulary which would provide a comprehensive recipe for manufacturing a drug, are both, for their own economic reasons, seeking to establish an operational concept which involves a "locking-in" and a greater specification of the production and quality control systems, techniques and protocols required to *maximize product quality and clinical reproducibility*—not unlike the concept basic to an effective NDA.

FDA's Changing Enforcement Philosophy

Interesting too is the fact that in moving in the direction of greater delineation of specification of the production and quality control functions and operations and reproducibility of product quality (integrity) and clinical effectiveness, industry is simplifying FDA's unavoidable shift in GMP regulatory enforcement philosophy from a *negative*, "thou shalt not" (allow such and such adverse conditions to exist) policing approach, tied to fluid, vague regulatory admonitions and requirements, to a more *positive*, "thou shalt" regulatory approach ("here is what is wrong; this is the way it should be done"), founded on more definitive GMP regulations which *specify in detail*, basic standards and requirements applicable to production

and quality control functions and operations which producers would have to meet to achieve a state of GMP compliance.

As a practical matter, the change in FDA enforcement philosophy suggested above should come as no great surprise since it is clearly crucial to successful implementation of its present "Intensive Factory Inspection" and "Plant Evaluation" programs, and basic to the long-range development of FDA's manufacturer's "Self-Certification" program. And if the reader will pause and reflect a moment upon the high level of plant, processing, quality control and product integrity specificity (standards) the Department of Defense has already established for its drug vendors (DPSC Standards for the Manufacture and Packaging of Drugs, Pharmaceuticals and Biologicals), is it really so unreasonable to expect that HEW and FDA should move in the same GMP "rigidifying" direction where the government's public assistance drug programs are emerging as one of the industries' largest consumer groups? Certainly FDA's year-long project for revising the GMP regulations in order to pin-point individual responsibility via greater specification of standards and requirements reflects HEW's deep concern about optimizing consumer protection on the quality of medication marketed by the drug makers.

It would seem that since both the major and smaller drug producers are thinking in the direction of some form of national licensing of products and plants which would extend FDA's role even further as a central repository of product and industry manufacturing practices, the agency should establish a comprehensive computerized data monitoring system which would be designed to draw from industry *certain key product, manufacturing and distribution data needed for regulatory evaluation and judgment purposes* which it would digest, process and feed out to the various welfare drug program administrators for their use by their formulary committees. As indicated earlier, an information system of this kind will eventually have to be developed by FDA in the course of implementing its producer self-certification program.

Considering the developments which are taking place in the drug field, it is patently clear that management will, sooner or later have to develop, and have available and readily accessible for transmittal to FDA and other regulatory agencies, in some predetermined computer compatible format, certain product quality (chemical and clinical), production, processing, quality control and distributional data evidencing full and systematic regulatory compliance. Radical notion? Not at all. Adverse reaction

data, accountability information on firms and individuals producing and handling controlled drugs (including Investigational New Drugs (INDs), NDAs and antibiotics, etc.), product recall monitoring and company registration and compliance history are already computerized by FDA. And with the introduction of its Computerized Drug Code Directory which will list each and every drug product marketed alphabetically and by its unique computerized identifying code number, FDA will have dragged every producer, labeler and distributor into the computer age creating, as we shall see, a host of new problems for management, the government and for Food and Drug attorneys.

Computerized Drug Code to Have Far-Reaching Consequences

The National Drug Code Directory was developed by the Science Information Facility of the FDA to assist the HEW and state welfare agencies in handling the staggering volume of paper work involved in processing an estimated 275 to 300 million vendor drug claims annually by the use of electronic data processing techniques. It might be noted that HEW's Prescription Task Force estimates that the annual volume of drug claims will increase to 400 million by 1975.

Each manufacturer has already been requested to submit to FDA complete product data to be included in his product's computer file, including: product name (and identification number), established or common name, product form, legal status, container size and type, active ingredients and quantities of active ingredients on the label, and inactive ingredients as they appear on the label.

The consequences flowing from this development are most interesting. To management it represents not only a significant elaboration of FDA's computerized company compliance and product intelligence programs, but establishes a new character and line of communications between industry and FDA.

As a practical matter, management will find it necessary to review and renumber its master formulae substituting the new product identification code number in order to avoid the confusion of numerical profusion. Management may also have to review and revise its quality control and production work sheet formats and its batch numbering practices; record-keeping procedures and protocols will also need modification. And raw material procurement handling, inventory and record-keeping procedure will have

to be reviewed and revised. Product labels will have to be re-designed to include the product's unique computer identifying code number required for vendor billing and other control purposes.

Still another aspect of this development is the possible use of these computer product identification numbers by the Bureau of Narcotics and Drug Abuse and the FDA in expanding their surveillance, accountability and control activities with respect to the production and distribution of dangerous abuse drugs. Closely monitored production and quality control surveillance does not appear to be too far off.

The intensification of regulatory and legislative activities resulting from the government's increasing fiscal and social involvement in the public health care field, plus the mounting tide of price and profit criticism has imposed upon management the burden of generating growth and profits in the face of a continuously rising cost trend in the drug research and development, production and marketing functions (*particularly the "regulatory compliance" aspects* of these functions). Most realists in the industry are not counting on price-profit relief as long as the taxpayer's share of the drug industry's output continues to climb. They see relief in the form of an all out attack on operating and *compliance* costs employing management techniques, technologies and systems designed to maximize efficiency and economy in the utilization of men, machinery, materials and money.

Regulatory Compliance Costs on Upswing

Regardless of the form it takes, regulatory compliance must cost the manufacturer money. The benefits, tangible and intangible, come later. The suggestions, for example, that producers be licensed by the FDA, that they be inspected once a year, and that pre-market therapeutic effectiveness be made compulsory, translated into compliance action, could mean expenditures for new quality control laboratory equipment, additional processing and quality control personnel, new plant construction and modernization. It could mean new processing equipment and more elaborate environmental controls to prevent drug-on-drug cross contamination. And to establish the therapeutic effectiveness of each product marketed by some special "short form" NDA type of procedure developed by FDA could involve setting up a clinical research program including substantial expenditures for professional, technical and clerical personnel.

Role of Legal Counsel Expanding in CGMP Regulations Compliance

Conceptually and practically, FDA's CGMP regulations are, by law, the basic building blocks management, at every level and in every company, must be guided by in structuring: (a) its technical production and quality control procedures, techniques, protocols and systems, (b) its control and regulatory reporting data format, and (c) its production and quality control communications network.

Because industry can expect no abatement in price, profit or regulatory pressures, it is apparent that management has little choice but to seek out and adopt bold, new managerial approaches, techniques and solutions if it is to continue operating effectively, profitably and legally within the constantly narrowing confines of government regulations and the broadening base of publicly supported health care programs.

The law requires that management comply with, and that the government enforce, "current" standards of manufacturing. Because non-legal personnel are, as a practical matter, expected to deal with and interpret legally sanctionable CGMP guidelines and requirements which are vaguer than they should be, and statutory standards more fluid than they should be, it follows that management's compliance obligations can best be served by enlarging legal counsel's role and involvement in its compliance activities and problems. Counsel should, in evaluating, guiding and assisting his client's compliance activities, review management policies, attitudes and decisions, communications and organizational patterns.

With regulatory emphasis on the qualification of *key* production and quality control personnel, counsel might very well assist management in evaluating education and experience standards and compliance, personnel training procedures, job definitions and assignment of responsibilities and functions. Management should review with counsel his state of compliance with respect to facilities, procedures, systems, and methods. Counsel should also be consulted with respect to the development of routine production and quality control inspection and audit procedures. And it is vitally important for management to consult with and involve counsel in all FDA contacts, particularly on GMPR inspection matters.

So far as counsel is concerned, it need hardly be said that as a non-technical person, he has an overriding responsibility to become as familiar with the "nitty-gritty," practical aspects of his client's production and quality control activities as appears necessary to perform his consultation functions comfortably and effectively. **[The End]**

Welcoming Remarks

By JOHN C. SUERTH

The Following Was Presented As the Opening Address at the Food and Drug Law Institute, Inc.—Food and Drug Administration's Twelfth Annual Educational Conference at Washington, D. C. on December 3, 1968. Mr. Suerth Is Chairman of the Food and Drug Law Institute. Succeeding Articles in This Issue Were Presented at the Same Conference.

AS THE NEWLY-ELECTED CHAIRMAN of the Food and Drug Law Institute (FDLI) it is a special privilege for me to welcome you to this important educational conference. As a representative of industry, I can assure you that we value highly these conferences. They offer not only the opportunity to share knowledge and information, but also provide the personal contacts between industry, government, and consumer representatives, which lead to mutual respect and understanding.

The theme of this 12th Annual Joint Educational Conference is "The Four C's of Consumer Protection—Communication, Collaboration, Cooperation, and Compliance." These aptly chosen words, along with providing a basis of departure for our program this week, also provide the guidelines for our activities throughout the year. As with all laws and regulatory decisions, compliance is a natural result of understanding through communication and cooperation within our mutual areas of concern.

This program from the start has enjoyed the complete support of the officials of the Food and Drug Administration (FDA). For this the officers and members of FDLI are deeply grateful, as their support indicates that they share our enthusiasm about its benefits.

Don't we really share basic goals and responsibilities in our important job of serving the consumers of America? Admittedly, we are working in areas of ever-increasing complexity; it requires the best efforts of us all to keep up; nevertheless, the ultimate aim is

unchanged—we are to get what we produce into the right hands in the right form and quality at the right place, at the right time.

To discuss the best ways to carry out these responsibilities will occupy our thoughts for the next few days.

The formation of the FDLI was inspired by the conviction of responsible people in both government and industry that wider knowledge of the food and drug law would lead to the needed respect for that law. The Institute is an agency on a public basis which reflects for industry the highest sense of acceptance of primary social responsibility. Its activities are soundly based on the premise that the federal and state food and drug laws need to be better understood in the interests of the consumer, industry, and government. These laws, and their effects, are of fundamental importance to the commerce of our nation—and, inseparably, to the consumer.

The Institute is dedicated to the belief that education, coupled with understanding will secure the highest degree of compliance through cooperation. An important aspect of the Institute program is its soundly based activity encouraging the teaching of all branches of law relating to food and drugs in the law schools of four distinguished universities—New York University, the University of Southern California, George Washington University, and Northwestern. In this connection I must mention the caliber of the men who are teaching these courses. They bring to their classes a professional capability and competence which marks them as outstanding in their field. Their interest in the law, and in teaching it to the students, contributes that undefinable quality to a course which stimulates the curiosity of the pupil and leads to both an understanding of the law and, more important, a feeling for it. In the teaching of a law which is unique, this is of utmost importance.

Furthermore, the Institute has made available to the profession, to law students, and to many others, a body of distinguished writing in this important field. The Institute's series of research books make up a comprehensive working reference library on food, drug, and related laws. The FOOD DRUG COSMETIC LAW JOURNAL provides timely articles and research studies on current legal problems throughout the world.

We are especially indebted to President DePew who oversees the publications and educational programs, and to Frank T. Dierson, secretary-treasurer of the Institute, who edits the JOURNAL. Along this same vein, I

should like to recognize the long and valued cooperation of Commerce Clearing House and its president, Robert Bartlett.

The Federal Food, Drug and Cosmetic Act of 1938 constitutes the basic regulation of the affected industries. It has operated to assure the American consumer of the most wholesome, nutritious and useful foods and the safest drugs in the world by providing guidelines for industry in the public interest. Although industry has not always agreed with the actions and recommendations of the FDA there has been created through the years an atmosphere of good faith between them which the pressure of the times has failed to diminish.

The recent revaluation of the FDA's mission has adopted the view long advocated by the Institute that compliance assurance is a responsibility shared by the regulated industries, state food and drug officials, and the FDA. The Bureau of Voluntary Compliance is pledged to devote its efforts to working with industry in promoting voluntary compliance, developing voluntary compliance programs, administering FDA's program for self-certification, and providing technical assistance on quality control.

Plant inspection is undergoing significant changes. FDA is restating its mission as one of total consumer protection in which law enforcement is only one approach. It is emphasizing that its goal is compliance through corrective action rather than by way of prosecution. Inspectors stress evaluation of a firm's quality controls with the objective of improvement. Last March, FDA began a program of providing a report to top management of food and drug firms on significant adverse conditions or practices observed on inspection or identified in a subsequent interview. One of FDA's major purposes in inaugurating this new report is to inform top management in a letter sent by certified mail of conditions in its plant, or plants, some of which may be a distance removed from the head office. It is hoped that those who have the decision-making power can act promptly to correct any adverse conditions reported. Thus, violations may be corrected and future ones prevented through increased understanding, trust, and respect.

If this voluntary cooperation program is to work, those in industry must take full advantage of the educational tools made available through FDA. I believe they may be expected to do so as they have shown throughout the years, with few exceptions, a recognition of the unusual responsibility our nation ascribes to those who produce and handle our foods and drugs. This is in accordance with the fundamental belief in freedom of action whereby example and self-regulation, rather than more legal restrictions, bring about the needed respect for law.

Let us, then, consider our mutual activities within the framework of Communication, Collaboration, Cooperation, and Compliance. We have done much together in the past and have a strong basis of accomplishment on which to build a continually successful future. You will have the opportunity to hear many worthwhile speeches delivered during this conference. It is my hope that these talks will stimulate some worthwhile informative exchanges during the question and answer periods.

In behalf of the Institute, I express thanks to all who have worked so hard to make this conference a success, and I also look forward to working with the officers and members of the Institute in strengthening its program and enlarging its industry support. **[The End]**

U. S. SUPREME COURT UPHOLDS OREGON LABELING OF HALIBUT

A decision upholding the constitutionality of an Oregon statute (ORS 616.217) that prohibits the labeling of flounder as Greenland Halibut was affirmed per curiam, without an opinion, by the U. S. Supreme Court. The Oregon statute prohibits the labeling of a fish product as halibut unless the fish is of the species *Hippoglossus hippoglossus* (Atlantic Halibut) or *Hippoglossus stenolepis* (Pacific Halibut).

Although the term "Greenland Halibut" is accepted in scientific circles to describe flounder *(Reinhardtius hippoglossoides)*, it is not a commonly understood name among the general public, the U. S. District Court in Oregon had declared. Likewise, the consumer is not aware that Greenland Halibut contains seven times more fat than halibut and twenty-five percent less protein. Consequently, the U. S. District Court had ruled that the Oregon statute was a permissible exercise of the state's police power to protect consumers from deceptive labeling of halibut. Furthermore, the statute made a rational classification that was consistent with a legitimate regulatory interest.

The U. S. District Court had rejected an argument by the fish processors and importers that Sec. 12 of the Fair Packaging and Labeling Act preempted this area of regulation. The Court said, "The Fair Packaging and Labeling Act only supersedes State 'Net Contents' regulations. Congress, by omitting an express limitation on the State's power to regulate product names [Sec. 12], did not intend to preempt this area of regulation."

Subsequent to this decision, the Food and Drug Administration issued Regulation § 3.70 prohibiting the labeling of flounder as Greenland Halibut if introduced into interstate commerce.

Atlantic Ocean Products, Inc. v. Leth, U. S. Supreme Court,
CCH FOOD DRUG AND COSMETIC LAW REPORTS ¶ 40,332

The Future of Consumer Protection

By CHARLES C. JOHNSON, JR.

Mr. Johnson Is Administrator of Consumer Protection and Environmental Health Service, U. S. Department of Health, Education and Welfare.

YOU HAVE HEARD THE NAME OF THE ORGANIZATION which I head, the Consumer Protection and Environmental Health Service (CPEHS). I will discuss with you the background against which our new agency was established; the nature and mission of the agency, and something of the shape of the future as I see it for CPEHS, for the Food and Drug Administration (FDA), and for industry.

CPEHS was created last summer in a time when our nation had reached—or at the very least was rapidly approaching—an environmental crisis. That urgent state of affairs is with us as we meet here together today. In the year 1968, the greatest nation in the world must face a harsh and frightening fact: In spite of our tremendous advances in medicine, science, engineering and technology; in spite of a lengthening span of human life through improved health services and victories over communicable disease; in spite of affluence and high standards of living; in spite of all these things—perhaps indeed *because* of these very things—we have not succeeded in creating a physical, social and cultural environment in which we can find that satisfaction for the "whole man" which was surely the purpose of all our strivings.

We have only to look around us to see evidence of crisis in our physical environment. Every year, pollution gets worse, rather than better; the problems of insuring safe food, drugs, water, and a variety of consumer products are increasing; the quality of American life, particularly urban life, is deteriorating in a morass of environmental problems so complex as to appear almost beyond remedy.

Environmental Problems

Let me briefly mention a few of the environmental problems that confront us here and now, in December 1968:

(1) Toxic matter is being released into the air over the United States at a rate of more than 142 million tons a year. That is three-quarters of a ton for every American. This outpouring comes from 90 million motor vehicles, from factories, from power plants, from municipal dumps and from backyard incinerators.

(2) Not counting agricultural or industrial wastes, we discard more than 165 million tons of solid waste material every year. Automobile graveyards mar our landscape; smoking, foul-smelling dumps pollute the air; cans, no-return bottles and other packaging that cannot be recycled create mountains of trash. In low-income urban areas, garbage breeds rats, disease, and filth.

(3) Accidents, many of them involving hazardous products, take the lives of 100,000 Americans each year, and injure 52 million more. Some 3,000 deaths occur annually from accidental ingestion of poisons —most of these among our children.

(4) Each year, more than 500 new chemicals and chemical compounds are introduced into industry, along with new processes and countless innovations; thousands of workers suffer from cancer, lung disease, hearing loss, dermatitis, or other preventable diseases, because industry, unions, and government at all levels have failed to give really adequate attention to occupational hazards.

(5) An estimated 2 million Americans are stricken with illness each year from microbiological contamination of food. The salmonella bacteria are usually the chief agent responsible, but other organisms such as clostridium perfringens are beginning to present problems in this area. The new technology in food processing and packaging, together with the increased use of "convenience" foods, requiring little or no heating in the home, help to complicate the situation.

(6) The use of food additives to impart flavor, color, or other qualities, has increased 50 percent in the past decade, and each of us now consumes about three pounds of these chemicals yearly. Pesticides leave residues on food crops, and traces of veterinary drugs occur in milk, meat and eggs. We know too little about the effects of these additives, residues and traces, especially in their combination with the rest of the chemical barrage that reaches us from other parts of the environment.

(7) The world clamors for new miracle drugs produced by pharmaceutical research to treat specific disease problems. Yet in spite of our best efforts at testing, labeling, and other controls, they often produce unforeseen side effects, and may even offer sinister genetic threats. What these new formulations mean in terms of the total chemical assault on man is an area we have not begun to explore.

(8) Radiation is increasingly a threat to our and future generations. Radiation sources are now found throughout our environment. They range from the large-scale applications of nuclear energy, particularly in electric poser generation, through laser and microwave technology in industry, to the use of radionuclides and X-rays in the healing arts and the use of microwave ovens and other electronic equipment in the home. And our scientific protection against radiation is only at a beginning stage of development.

That list of environmental hazards is a mere sampling, and by no means a complete catalog. I have not even mentioned, for instance, the psychic effects upon our citizens produced by automation, regimentation, crowding, noise, and other stresses and frustrations of life today. We are barely beginning to recognize these effects.

Obviously, all these matters concern you and me in our special roles in industry and government, and just as obviously, they concern each one of us intimately in our roles as citizens, consumers and parents. We must all recognize the need for prompt and sustained action unless we are willing for the environment to deteriorate further instead of improving. We will have something like 25 million more people in this country by 1980, and urban areas will absorb most of the increase. Environmental problems of the cities will intensify. New food technology may be expected to increase the risk of food-borne disease and chemical contamination. In short, unless we increase our capacity for recognizing, averting and controlling hazards, the future can only be accompanied by more biological and psychological hazards and difficulties for all Americans.

Those, then, are some of the reasons for speaking of a "crisis" in the environment, a crisis that must be recognized for what it is, and that must be dealt with on an urgent basis.

The Role of the Federal Government

And what have we done about it so far? Let me examine briefly for you what the federal government role has been up to now:

You are aware that for some years the Department of Health, Education and Welfare (HEW) has had programs to assure safe food, drugs, and drinking water; and to control air pollution, occupational disease, radiation hazards, and other environmental threats. Moreover, in recent years we have tried to adopt a broader, more comprehensive approach to environmental problems. We have established a national laboratory for basic biological research on environmental pollutants. We have tried several organizational realignments, and have recognized that many of our activities—in food protection, sanitation, safe drugs, clean air and the like—were all related to the same overwhelming problem: the problem of man's

ability or inability to adapt to an environment which he himself is subjecting to constant change.

Nonetheless, we still limited ourselves to too narrow and rigid a definition of environmental health. We thought that before we could prove health hazards in the environment we had to be able to count the corpses, and to establish a direct, incontrovertible causal relationship, based on immutable scientific data, in strict accordance with Koch's Postulates. Unfortunately, in an environment of multiple impacts, direct causal relationships between health and individual insults are difficult to define even when the evidence is abundantly clear. Furthermore, science is never immutable; what we know today is always modified by what we learn tomorrow.

Unless our nation learns, and learns quickly, to apply the scientific knowledge we have—and it will always be incomplete—to the problems of the environment, we are courting inevitable disaster.

I believe HEW has now fully recognized the truth of this. And in our organizational structure, we have at last taken account of the interdependence and interrelatedness of all environmental factors as they affect man. We have now brought together, in a situation in which they can be mutually supportive, the FDA, the National Air Pollution Control Administration, and the diverse activities of the Environmental Control Administration, under the overall direction of the CPEHS.

As a direct result of the creation of the CPEHS, the FDA has assumed still more responsibilities—in shellfish certification, training, and product safety. Grouped under the new Office of Product Safety are five divisions: the Division of Poison Control; the Division of Hazardous Substances; the Division of Community Studies; the Division of Pesticides Registration; and the Division of Safety Services.

The new Office of Product Safety, to be located in FDA's Bureau of Medicine, will be perfectly at home because of course FDA has long experience with product hazards and their control. The Office of Product Safety over the next few years will inspect the labeling of some 4,200 marketed products containing components which could cause injury or death; it will also determine the toxicity of the approximately 200 products associated with the most serious injuries. We will participate in educational and promotional campaigns to give consumers information on safe use of products.

The fact that the FDA is now a part of the CPEHS will in no way diminish its effectiveness in carrying out its several complex responsibilities. Indeed as time goes on and as we succeed in defining more precisely the adverse effects on man of contaminants, whatever their source, the FDA should be able to perform its mission even better than it can today.

You will note that I referred to the FDA's responsibilities as complex.

They are complex and those who insist on contending that the FDA must be totally in favor of regulatory compliance or totally committed to voluntary compliance are calling for a degree of simplification that I cannot accept. The FDA must be free to employ, as necessary, all the authorities it has earned in its long struggle to protect the interests of the American people.

To carry out its complex responsibilities, the FDA needs the support of consumer protection programs at state and local levels of government. There is a lack of such programs now, mainly because of a shortage of funds and manpower. We need, and I hope can obtain, authority for HEW to fill the void, by providing financial and technical assistance for that purpose. Meanwhile, FDA has been strengthening its ties with state and local government. During 1967 and 1968, FDA Regional Assistant Commissioners were appointed by the secretary in seven of the nine HEW Regional Offices. These Commissioners are establishing cooperative relationships with the executive branches of the states within their respective regions. The FDA also has entered into agreements to provide professional assistance to states under the Comprehensive Health Planning and Public Health Amendments. For example, a former FDA District Director was assigned upon request from the Illinois State Health Department to assist in implementing a new food, drug and cosmetic law in Illinois, and a request from the Wisconsin State Health Department brought an FDA expert on loan to help develop legislative proposals for updating Wisconsin's food and drug laws and regulations.

The lack of strong programs at the state and local level is just one deficiency that must be met as soon as possible. Here are some others:

1. We in HEW continue to believe that we should publish and disseminate a catalog of prescription drugs, with each drug listed by its generic name. This compendium would include a brief description of the drug, its important uses, dosage, side effects, contraindications, precautions, and other pertinent information. The compendium should be *widely* distributed, so that all medical facilities, pharmaceutical dispensaries, and the medical fraternity, can avail themselves of its contents.

2. It would be advantageous to the work of the FDA if a means could be found whereby industry made available more of its records and reports which pertain to the investigation and research surrounding its products. This would enable FDA to render its decisions on a broader spectrum of knowledge and experience when it examines petitions for clearance of new products.

It certainly is recognized that after a product is marketed, the wider experience under an infinite number of varying conditions often

gives rise to information about the product safety and effectiveness which was *not* previously known.

3. The revoluntionary advances in the development of medical devices expose the public to a vast array of medical technology not formerly encountered. The patient as well as the physician should have assurances that a particular device has been adequately tested and proven to be safe, reliable and effective. The authority of the FDA should be extended so that it can provide such assurances.

4. In order to provide for prompt medical treatment in cases of accidental ingestion of drugs, we need a method of ready identification of medications. To help meet this need, the FDA is currently involved in stimulating the drug industry to take voluntary steps in the establishment of an identification code which would be imprinted on each tablet and capsule. Eventually these informal arrangements will need to be formalized.

In all of these areas, we will welcome your cooperation and support.

Conclusion

In my remarks today, I hope I have made clear that there is a tremendous interdependency among your interests and concerns, those of FDA, and the interests and concerns of man as he contends with the hazards of the environment. I have tried to describe for you how our new organization, the CPEHS, plans to carry out its mission; how the FDA fits in, and some of the details of how the activities in the FDA impact upon the broad package of insults man has to face. I will conclude by saying that we in the CPEHS, including the FDA, the National Air Pollution Control Administration, and the Environmental Control Administration, intend to move ahead as quickly as possible with a program whose impact will be felt in every facet of our national life. We must not fail; we dare not forget that man does not have an unlimited capacity for accommodation to environmental change, and insult piled upon insult—particularly when such forced accommodation comes not over a period of many centuries, as has been typical in man's history, but in a few short years and at an increasing pace.

I solicit most earnestly your strong and enthusiastic support in meeting the challenge that confronts all of us: to restore and improve man's living environment—to make life worth living in the ghetto and the suburbs, the town house and the cottage, the city and the country—and to prove that ugliness, danger and misery do not have to be a part of the birthright of *any* American, wherever he may live in this land.

[The End]

FDA Today and Tomorrow

By HERBERT L. LEY, JR., M.D.

Dr. Ley Is Commissioner of the Food and Drug Administration.

THE CONFERENCE THIS YEAR is my first as Commissioner of Food and Drugs. But since joining the Food and Drug Administration (FDA) in 1966—two Conferences ago—I have had ample opportunity to recognize the value of this annual meeting and I hope we will be coming together for this same purpose next year, and for many years to come. This kind of dialogue is essential—essential for the Government, essential for industry, and, most important of all, essential for consumers. It is the consumer, after all, who has the most to lose if we fail to do our respective jobs well.

I decided when I assumed the responsibilities of this office nearly six months ago that the personnel and the various organizations within FDA deserved first priority of my time. As Director of FDA's Bureau of Medicine for nearly two years, I was familiar, of course, with the overall operation of the Agency. But, as most of you know, the activities of FDA are both broad in scope and complex in detail. I felt it was essential to become intimately acquainted with every phase of the Agency's operations before assuming the time and travel commitments necessary to meet with and speak to industry and professional associations—though I must quickly add that I also appreciate the importance of this kind of communication and I'm looking forward to the meetings on my schedule for the months ahead.

I don't want to gve you the misleading impression that I have been completely isolated in my office over the past few months. There have been frequent meetings with industry representatives. For the most part, these have been congenial sessions, and I have welcomed these opportunities to discuss my views, and to listen to industry's views, on the many matters in which we must take a mutual interest. There have been other meetings in less cordial settings, but these, too, are necessary when it happens that private interests collide with the public interest.

Since assuming this office, I have also tried to give time to members of the press for I recognize and appreciate their obligation to report to the public on what those of us in Government are thinking and doing. This kind of contact is not without its perils, of course. I received a phone call some days ago from an irate Washington attorney who demanded to know why I was attacking the legal profession. It seems that I had been quoted as saying that FDA and industry could settle disputes much easier if lawyers were kept out of the picture. Let me assure the attorneys here today that even if I held such a view—and I do not—I would not be so rash as to announce it. What I did say, in answering a question about the need for legal representation, is that a businessman or any other citizen doesn't have to engage an attorney to take up a matter with FDA. That's a matter of individual choice, not a matter of FDA policy. We have gone to great pains on many occasions to point out that the Agency does not regulate the practice of medicine; I assure you we have no designs on the practice of law either.

No, our regulatory responsibilities are sufficiently demanding as it is; we are busy enough without venturing into alien fields. The program for this Conference gives some indication of the wide range of our consumer concerns—sanitation, self-regulation and self-certification, intensified drug inspections, fair packaging—and these are merely a sampling of FDA activities that are of particular interest at this point in time.

I do not plan to intrude into the subject matter that will be explored in detail by other speakers and panelists, but I do want to share with you my own views on some of the specific problem areas with which FDA is now concerned. Some of these also have implications for the future—and I know you are interested in what lies ahead—for it seems to be in the nature of things that the problems with which FDA must grapple are not of the kind that lend themselves to quick, overnight solutions.

Food Additives

First, however, let me take a few moments, if I may, to describe the broader context of FDA's program, for this, too, offers some outline of the shape of things to come. Mr. Johnson has already introduced you to some of the goals of the Consumer Protection and Environmental Health Service, of which FDA is now a part. The challenge is an awesome one. For example, the topic of food additives, whether intentional or accidental, is today a matter of vigorous dialogue between the FDA and industry. The range of such additives is enormous—from colorings and flavorings on one hand to pesticide and antibiotic residues on the other. The FDA has

adopted a posture that such additives are acceptable only after evidence or expert scientific opinion is available to confirm that no injury or harm to the consumer will result from ingestion of foods containing the additives. It is not satisfactory, as some would have us believe, to use the additive and wait for ill effects to be reported. If human experiments are necessary they must be on a controlled, small-scale basis, rather than market-scale experiments. Our approach is conservative, but designed to reduce risks to the consumer to a minimum.

I am not going to tell you that FDA has devised the perfect system for keeping hazardous chemicals out of our foods, and you'll simply have to live with it. I must also point out that our scientific knowledge in this particular field is still extremely superficial. We know too little of potential secondary and long-range effects of man's chemical diet. And we must remember that we cannot consider each new food additive as a single, isolated factor in the environment. The consumer is confronted with combinations of chemicals in his foods, his medicines, even in the air he breathes.

Industry scientists, as well as government and academic scientists, can contribute, and should contribute, to our understanding of additives and their effects. This is cooperation in a meaningful form. As our knowledge advances, I suspect that testing procedures will change as well. But unless we do learn more, debating whether animal studies should be of two months' or two years' duration is a sterile exercise.

Intensified Drug Inspection Program

As you know, FDA has given greater emphasis in recent years to preventive programs. We are still committed to effective enforcement action when unsafe or misrepresented products reach the marketplace. But consumer protection is even more effective when there is positive action to insure the consistent production of consumer commodities that meet the highest quality standards.

Preventive programs can be carried out at the research level, as I indicated a moment ago in discussing food additives. They must also be carried out at the production level. And at this level, too, FDA-industry cooperation is an essential to make this approach work successfully for the consumer. I believe the Intensified Drug Inspection Program, begun last July 1, will provide one good measure of how fruitful such cooperative efforts can be.

Plant inspections, of course, have long been an important part of FDA's regulatory program. Since 1962, the Food, Drug and Cosmetic

Act has required inspection of prescription drug firms at least once every two years. FDA's inspectors, over the years, have done a thorough, efficient job of checking plants for violative practices and products. Frequently, their inspections led to enforcement actions against a firm or one of its products. But this, admittedly, was a spot check program, with no consistent follow-through to assure that corrective action was taken.

The Intensified Drug Inspection, on the other hand, is just what the name implies. Mr. Barnard will be telling you more about how the program works in the plant. Let me simply say that the primary purpose of the Intensified Drug Inspection is bringing about whatever corrections are necessary to put a plant in full compliance with the laws.

This program does not foreclose legal action when violations are uncovered during the course of the inspection. There may be, and frequently are, recalls or seizure actions to take off the market substandard drugs detected by inspectors. And an Intensified Drug Inspection doesn't go on forever; if a firm is unwilling, or unable, to correct poor manufacturing practices or other deficiencies, we have no alternative but to go into court to put that firm out of the drug business.

Up to now, however, we have found drug companies both receptive and cooperative. Before the Intensified Drug Inspection actually begins, the FDA district director meets with top management of the company involved to explain the purpose of the program and to outline what is expected of the manufacturer. We want no confusion about what FDA expects to achieve as a result of the Intensified Drug Inspection.

As I have mentioned, the program began last July 1. Since the inspections are exhaustive and time must be allowed for corrective action, it is still too soon for any real measure of the success of the program. As of the end of last week, 118 inspections of this kind were in progress. Eleven had been concluded. We had hoped at the outset of this program to complete 250 Intensified Drug Inspections during the current fiscal year, and to cover the other 250 prescription drug manufacturers in fiscal 1970. It now appears that this schedule may have been overly ambitious, but we will move ahead as rapidly as possible. Obviously, this program will not eliminate the need for inspections in subsequent years. But I strongly believe it will achieve significantly higher standards of drug manufacturing on an industry-wide basis.

Consumer Problems and Administrative Programs

No single program, of course, can insure the American public of safe drugs that will do what they are intended to do. In addition to other en-

forcement and compliance activities, we plan to further expand the capabilities of our National Center for Drug Analysis at St. Louis. We are also moving ahead with the implementation of the recommendations of the National Academy of Sciences-National Research Council concerning the efficacy of pre-1962 new drugs. This will provide the prescriber, and the purchaser of over-the-counter products, a more precise picture of what these medications will do. And we are continuing biologic availability studies to determine whether there are therapeutically significant differences between chemically equivalent drugs.

In this connection, I'm sure most of you will recall the performance differences among chloramphenicol capsules that required FDA action just about a year ago. That situation, unfortunately, became part of the so-called "generic-brand name" controversy. I say "unfortunately" because it seems to me that drug equivalency problems aren't necessarily related to the name by which a drug is sold. Just a few weeks ago, for example, Merck Sharp & Dohme recalled from the market 15 lots of its hypertensive preparation, Aldomet tablets (or, generically speaking, methyldopa tablets). The recall was undertaken because disintegration rates were below the company's specifications. The cause, apparently, was related to the particle size of a so-called inert ingredient. This is not dissimilar to the earliest problem with chloramphenicol capsules. The Merck management acted with commendable responsibility in catching the problem, confirming the deficiency through human blood level studies, and promptly initiating the recall. But it does illustrate that an equivalency problem can occur anywhere within the drug industry. We have to get at the basic causes of these problems; they can't be solved by comparing the names that appear on product labels.

There is another problem area concerning drugs which also requires, I believe, renewed concentration on causes. During the last fiscal year, the FDA received 406 New Drug Applications (NDAs). During the same 12 months, 59 NDAs were approved. These figures are not directly related, of course, since an application may not be acted upon in the same fiscal year that it is submitted. Nevertheless, I think it is significant that, for the year, the number of applications found incomplete, or returned as not approvable, outnumbered those approved by better than 5-to-1. More than 80 percent of the applications that were found not approvable lacked adequate information about manufacturing processes. More than half of these applications also suffered from deficiencies in clinical studies and inadequacies in efficacy data. The message, it seems to me, is clear: there is still a need for better data in industry's submissions to the Agency.

We are interested as industry in getting to the market as swiftly as possible new drugs that can mean better health care for American citizens. But we cannot disregard our responsibility to determine that such drugs are safe and effective for their intended uses before they reach the market. By the same token, the manufacturer cannot disregard his responsibility to submit sound data that demonstrate safety and efficacy. I must tell you frankly that we have not seen the degree of improvement in the quality of clinical data from drug investigations that we would like. I intend to give this matter renewed attention in the weeks ahead, and possibly call upon experts outside the Agency as well to see if we cannot find the means to correct existing shortcomings.

As far as other priorities are concerned, the Agency as a whole will continue to give its most urgent attention to potential health hazards in every area of our responsibilities. Our concern with microbiological contamination of consumer commodities is, of course, part of this overall health-protection program.

Last September, as some of you know, a National Center for Microbiological Analysis went into operation on a pilot basis at our Minneapolis District laboratory. Samples of food products from around the nation, starting with those classes of foods most susceptible to contamination by harmful bacteria, are being sent to the Minneapolis Center for analysis. This pilot operation should begin to give us a better grasp of the extent of the problem, and, more important, pinpoint the product classes where the hazard is greatest. The necessary next step, of course, is to track down the sources of contamination and develop effective preventive measures. In addition to food products, we also plan to have our Districts submit samples of drugs and cosmetics to the National Center.

This pilot program in Minneapolis represents a new approach to further enlarge FDA's capabilities to monitor and control bacterial contamination. As you know, we had previously assigned bacteriologists to each of our District Offices to carry out this essential analytical work. The frequent recalls of products because of Salmonella contamination gave major impetus to the expansion of this program within FDA. And, I must add, industry has also responded to this growing awareness of the health hazard posed by microbiological contamination.

In dealing with a problem such as bacterial contamination. I think it is clear that FDA and industry are not adversaries. We have had to act together to begin to combat this threat to the public health, and I am happy to say that there has been a high degree of cooperation in this effort. I would hope that this same attitude—this mutual appreciation of the

importance of the consumer interest—can prevail in other areas as well. Certainly, we will have ample opportunity to test this premise in the weeks ahead.

Very soon now, we will publish a new proposal outlining Good Manufacturing Practices (GMPs) in the food industry. Also ahead are proposed revisions of the GMP regulations for the drug industry. I do not expect unanimous support by industry for these proposals. But I do hope we don't encounter automatic opposition either. This is not an adversary contest, a kind of game in which FDA proposes all the regulations it can think of and industry defeats as many as it can. Rather, the fundamental question has to be: What rules are necessary to safeguard the consumer? If we keep that principle in mind, it is much easier to deal with and resolve the disagreements that do arise between FDA and industry.

Now, of course, the FDA has taken on new responsibilities—product safety, shellfish certification, broader pesticide research, and other activities mentioned by Mr. Johnson. In all of these, too, it is the consumer who is our first concern. With the organization of the Consumer Protection and Environmental Health Service, I believe we are in a better position than ever before to translate that concern into effective action.

Conclusion

It's clear to me that we can be most effective when we have the cooperative support of industry in coping with consumer problems. Your participation in this Conference is evidence that we have the kind of dialogue going that can encourage this cooperative effort. I am looking forward to working with you in this endeavor. **[The End]**

PROPOSALS ON LABELING EXEMPTIONS ISSUED BY FDA

In response to a petition submitted by Kraft Foods Division of National Dairy Products Corp., Chicago, Illinois, the FDA has issued the proposal that cheese and cheese products in non-random packages would be exempt from the labeling requirements that the statement of net contents appear within the bottom 30 percent of the principal display panel and that the contents appear in both ounces and pounds; these products would also be exempt from the use of the type sizes specified in regulation § 1.8b(i).

The exemptions were requested on the basis that such labeling requirements are confusing to the public because these non-random cheese packages are now labeled the same as random cheese packages.

Views and comments may be filed by January 21, 1969. List of Proposed Regulations, CCH Food Drug and Cosmetic Law Reports ¶ 40,003.

The FDA Program for 1969

By WINTON B. RANKIN

Mr. Rankin Is Deputy Commissioner of the Food and Drug Administration.

IT IS A PLEASURE TO MEET WITH YOU AGAIN and discuss the Food and Drug Administration (FDA) program for fiscal year 1969 (July 1, 1968 to June 30, 1969). In the spring of 1967 the Commissioner stated the objectives of the Administration for the coming five-year period, 1969 to 1973 inclusive; the objectives for the first two years were in greater detail than those for the last three. (We had then just completed our testimony before Congressional appropriation committees in the House and Senate for fiscal year 1968—the one that ended June 30, 1968).

The Bureaus and other principal offices of FDA stated what they considered to be a reasonable and practical program for accomplishing the first year (1969) objectives. The planning and budgeting staffs reviewed these proposed programs, made adjustments where necessary and estimated the manpower and the money needed to reach the FDA goals. The Commissioner and his immediate staff then reviewed the proposals and made changes where necessary for a balanced program, and the Commissioner recommended a program with accompanying budget to the Secretary of Health, Education and Welfare for consideration and approval.

The Secretary's staff reviewed the recommendations and made suggestions for changes it considered necessary to keep the FDA effort in line with overall Departmental objectives and in line with the funds that the Bureau of the Budget believed the President would wish to seek from Congress. Following a series of discussions between FDA and the Department, our budget containing a description of program plans was incorporated with the proposals of other agencies into a Departmental budget. This went forward to the Bureau of the Budget, was reviewed there in detail, appropriate adjustments were made, the budget was revised and incorporated in the President's budget that went forward to the Congress early in calendar year 1968.

The Appropriations Committees of both houses of Congress held hearings, and made recommendations to the House and Senate which approved the appropriation for our Department (and FDA) in October, 1968.

By this process of planning in a series of steps, FDA determined what program of consumer protection in the food and drug area would best meet the recommendations of its program experts and the goals and financial guidelines of the National Administration and the Congress. The program resulting from this process is part of the total consumer protection effort of the federal government.

Last July the FDA, already a part of the Public Health Service (PHS) following a reorganization a few months earlier, became part of the Consumer Protection and Environmental Health Service of PHS. This permits a single agency to give its attention to the various pollutants and hazards that confront man because of his changing environment and the products he uses. The Service can now look at the air pollutants, the food pollutants, the drugs (which some regard as pollutants), the various industrial and household poisons, the hazardous products man uses, and so forth, and be in a position to determine the significance of any one of them or any combination of them. At least we hope to be able to do this.

Traffic Control and Evolution

There are a couple of potential problems in this arrangement that should be kept in mind: The control of traffic in food and drugs is a highly specialized activity in the United States; the system has evolved over more than two generations. Some of the other consumer protection systems now under the same supervision are relatively young. There is no doubt that some of the expertise which FDA has developed should prove useful to our companion agencies. We are anxious to help out in any proper way. But it is important for all of us—you consumers, you businessmen, and we in government—to guard against a situation in which effective and essential food and drug activities are lost or harmfully diluted. Don't misunderstand me; I am not opposed to general consumer protection—I support it. But I would view with the greatest concern, general consumer protection measures that subsist at the expense of an established effective mechanism for insuring pure food and drugs.

The second potential problem is how to foster continuing evolution of food and drug control to meet the needs of changing times without destroying worthwhile portions of that control, already developed and already serving a useful purpose. Again, lest I be misunderstood, let me assure you that I do not oppose change—I favor it, and the record of the past

several years shows that FDA has undergone dramatic change. It must continue to change if it is to be responsive to the needs of our society. But the change needs to be orderly, carefully thought out, and constructive. Some of the changes that have been considered recently do not appear to meet these criteria.

One suggestion that fortunately has received little support would have this country abandon its present system of approving new drugs for marketing and adopt another mechanism that has been likened to that employed in England. The proponents overlook a very significant fact—the English system until recently was a non-system. They did not have effective governmental control over the marketing of new drugs. And since the thalidomide disaster convinced them that a real national control is necessary in today's society, they have been developing a plan that looks more and more like the United States' system. I think it would be a serious mistake to throw our plan of control overboard in favor of a less well-developed and less effective one from another country that is only now beginning to catch up with the progress we have made over the past 30 years.

Other changes have been and will be proposed. We have to tinker with food and drug control to keep it up-to-date just as you have to tinker with a fine watch occasionally to be sure it keeps the correct time. I understand that there are many ways you can tinker with a watch. Some are good. One that would have a very small chance of success would be to place the watch on a fence post and blaze away at it with a shotgun loaded with buckshot. Perhaps it would be wise to avoid the buckshot approach as we tinker with food and drug control.

When the Congress decides how much money and how many positions it will make available for food and drug control, and when we deduct from these figures the tariffs that are levied upon FDA by those in positions of greater authority, and when we take into account the various directives that indicate how the remaining funds and people are to be used, then we know what is available for the conduct of ongoing programs and how it is to be applied.

Appropriation Allocations

The plan for this fiscal year called for the appropriated money to be used as follows: about 1/3 for food programs; about 2/5 for drug programs; about 1/5 on hazardous products programs; about 1/16 on general administration; and minor amounts—approximately 1% each—on cosmetic and therapeutic device programs.

In terms of man years, food activities and drug activities take a slightly higher proportion of total resources and hazardous products a lower pro-

portion; this is true because a significant part of the hazardous products program recently transferred to FDA is handled through grants or contracts which support non-federal participation.

Another way to look at the planned use of the money is to see how it is supposed to be allocated by organizational unit:

Organizational Unit	Percentage of Allocation
Field forces (Districts)	38%
Bureau of Medicine	24%
Bureau of Science	21%
Bureau of Regulatory Compliance	3.5%
Bureau of Veterinary Medicine	2.5%
Bureau of Voluntary Compliance	¼ of 1%
All other units combined	less than 11%

There are some interesting observations that can be made on the basis of these tables:

First: The ratio of field personnel to headquarters personnel is now about 2 to 3; a few years ago it was essentially 1 to 1. This shift to greater concentration in headquarters reflects the increased emphasis on drug evaluation and availability, increased emphasis on scientific research and decreased emphasis on field programs that are not clearly associated with health hazards.

Second: The ratio of drug activities to food activities has shifted from about 1 to 2 a few years ago to about 4 to 3 now. In other words we no longer do twice as much work on foods—we plan this year to devote over 125 per cent as much attention to drugs as to foods. This reflects the increasing attention that drug problems are now receiving in our society.

Third: The cost of general administration in FDA is very reasonable. We have maintained for a long time that we run an efficient and effective operation. The figures support the claim for efficiency. Without detailing the support at this time, may I simply say that in my view, the efficacy is also present.

The *fourth* observation that flows from the data cited above is that FDA has not been very successful in getting funds to support the voluntary compliance effort. This is the result of a number of influences. One of the most important, in my view, is a belief in a number of quarters that the regulated industry is not ready to assume a significantly changed role; that the time for much more reliance on industry self-control is not here. This view is not restricted to the Executive Branch. One of the committees of the Congress, in approving our funds for this year, singled out voluntary compliance as an area that is not to receive an increased push. More on this when we come to the self-certification program.

Hazardous Substances Program

With the reorganization in July, FDA assumed the pesticide functions formerly assigned to the National Communicable Disease Center, the functions pertaining to product safety aspects of the Injury Control Program, and shellfish certification that were in the National Center for Urban and Industrial Health, and the poison control functions of the Health Services and Mental Health Administration. Several of these activities have been combined with the hazardous substances program in the Bureau of Medicine.

Protecting the American consumer from needless injury caused by hazardous products is clearly a task of serious magnitude. Each year some 18,000 Americans are killed and an additional 20 million are injured in accidents associated with consumer products. This is a major public health problem and is certainly among the most complicated of safety problems because of the incredible variety of products, environments and behavioral patterns involved.

During 1969, the various epidemiology and surveillance activities on poisons and other hazardous consumer products will be integrated. This will provide a system of identifying for corrective action products associated with a high rate of injuries and disability. Special emphasis will continue to be directed toward the investigation of injuries associated with burns, particularly those from flammable fabrics.

Product control activities will include: establishing product safety standards, developing voluntary control measures, labeling hazardous products properly, and sponsoring consumer information and education programs on special product hazards not corrected through product design.

During this year we will be operating three highly specialized laboratories equipped to handle volumes of samples on an assembly line basis. These are the National Centers for: Antibiotic and Insulin Assay in Washington, Drug Analysis in St. Louis, and Microbiological Analysis in Minneapolis.

The first of these is a continuation of the former antibiotics and insulin analytical units except that much of the administrative detail has been shifted to other offices, leaving the laboratory specialists free to devote full time to laboratory work.

The National Center for Drug Analysis assays samples from selected groups of drugs on a mass production basis, and develops improved, faster analytical methods for drugs. Using statistically reliable sampling procedures developed in Washington, we are able, with the help of this Center,

to evaluate in a short time the quality of the nation's supply of a given kind of product—reserpine-containing drugs, for example—as it occurs in the market place. By the end of this year we will have covered some 15 classes of prescription drugs. The rate of sample analysis at St. Louis will soon be about 20,000 units per year and by 1974 it is supposed to reach 300,000 samples a year. This added control will help guarantee quality drugs for all.

The third National analytical center went into operation on a pilot scale last summer to determine the feasibility of greatly expanding FDA's ability to handle microbiological samples in a specialized unit. The results are already very encouraging though the test period does not end for another week. If established on a permanent basis, the laboratory will provide the most practical and economical way of examining the large volume of samples required to deal with growing problems of bacteriological contamination of foods and of a number of drugs. We expect to examine 1,500 samples bacteriologically in Minneapolis this fiscal year, and if the Center continues, to be able to handle 6,000 samples next year.

The Microbiological Center is required now. We anticipated, in addition, that it would prove to be a worthwhile aid if the industry self-certification program gets off the ground.

Self-Certification Study

We are studying self-certification to determine whether it is possible through a new cooperative government-industry approach to identify the factors in important industries that are critical to the production of quality foods; establish acceptable standards for those factors; test the standards, revise them as necessary, and ultimately rely heavily upon individual firms to apply the standards in their own plants and report significant deviations to FDA.

Initially, the self-certification approach would take more FDA manpower than the conventional approach. I had hoped we could spend that manpower in several trials to determine answers to a number of questions that have to be answered before we can make final decisions. We need answers to such questions as:

(1) What kinds of products are best suited to self-certification?

(2) How can we arrive at proper standards with a minimum of waste motion on the part of industry and government?

(3) What kinds of firms are the most likely candidates for a self-certification approach? Thus far we are dealing with a couple of the best manufacturers.

(4) What is the role of the cooperating state or local food and drug official?

(5) Given budgetary and manpower limitations that do not permit extension of self-certification to all firms that may desire to participate, what is an equitable basis for choosing participants?

(6) When, if ever, should we consider extension of this control mechanism to drug manufacturers?

(7) Would the same manpower be more effective if it were devoted to conventional control measures aimed at the part of the industry that is having the most difficulty?

I had hoped that this new approach could be given a thorough trial, that it would prove useful for application to food firms that need it more than those who are helping us on the initial experiment, and that it, or some workable variant, could be employed in a few years with the drug industry. Whether we will ever learn the answers remains to be seen. We don't have the funds or manpower to run a test today on the scale needed to get good answers, and if the current de-emphasis on FDA's voluntary compliance activities continues, then the self-certification is headed down the drain.

Conclusion

This is a very quick overview of FDA's programs for this year. We do not exercise the full control over our programs or the fate of the regulated industries that some might imagine. Our activities must be responsive to many controlling factors:

(1) The wishes of the public as expressed through substantive legislation and appropriations that do or do not allow for effective administration.

(2) The willingness of the regulated industries themselves to participate in worthwhile control measures rather than fighting us at every turn.

(3) The directives of our supervisors in the Executive Branch and the support they give.

(4) The organizational structure within which we operate.

(5) Other factors.

If you consumers and you industries are satisfied with things as they are now going, then you can relax and cheer at whatever success or failure we achieve. If you are not satisfied, we need help. **[The End]**

The Regulator and the Regulated

By ALFRED BARNARD

Mr. Barnard Is the Director of the Bureau of Regulatory Compliance of the Food and Drug Administration.

MUCH HAS BEEN SAID IN THE LAST COUPLE OF YEARS about the impact of Dr. James L. Goddard on the philosophies and policies of the Food and Drug Administration (FDA). Much emphasis has been laid on the shift which is said to have occurred from a law enforcement orientation to a broader compliance orientation in the Agency.

I am not so sure that as great a basic change has been wrought as seems to have been perceived by some. Our basic training manual for beginning inspectors contained, at least as long ago as 1960, a statement of FDA basic enforcement policy which may interest you.

> To the greatest extent possible with the facilities at our disposal we will further the objectives of the laws we enforce. These objectives are to protect the health and welfare of the consumer and to protect the honest manufacturer from his unscrupulous competitor. This policy embraces the philosophy, first of all, that the consumer and the regulated industries are entitled to know what the laws mean and, secondly, that they are entitled to expect fair, equitable, and efficient enforcement of these laws. This contemplates that since we do not have the facilities to deal with all violations simultaneously we have an obligation to make a work selection in order of its importance to the consumer and the regulated industries; namely, health, hygienic and economic.

This statement of basic enforcement philosophy does not seem to me to differ in any significant way from that which guides the Agency today.

It *is* true that there is a freer exchange of information between industry and FDA in many areas, but I cannot help but note that this seems to be not only current FDA policy, but the tenor of the times as well.

It *is* true that we have developed more ways of working with regulated industries to further the objectives of the laws we enforce—that is, achieve compliance. This, it seems to me, more reflects a higher degree of

sophistication of the administrative process than some major shift in basic policy.

It is also true that our current emphasis is on broader use of sound scientific educational approaches. This is consonant with the views of the Second Citizens Advisory Committee and again reflects a higher degree of sophistication, as well as an ever more scientific orientation, in our total compliance approach.

Intensified Drug Inspection Program

Our Intensified Drug Inspection Program (IDIP) is a good example of these more sophisticated compliance-seeking techniques. It involves the application of education based on sound scientific background. For the benefit of those of you who may not know what the IDIP involves, let me explain briefly.

The IDIP contemplates placing a highly qualified inspector in a plant on essentially a full-time basis until he is there long enough to really learn what goes on in the plant and identify the plant's weaknesses and problems, if any, or assure himself that the operation is one which will consistently result in the production of legal products.

Problems are called immediately to the attention of management and such advice and assistance as is appropriate is offered by the inspector, and, if necessary, by other members of the FDA District Office staff. The broad aim is to either bring about the production of legal drugs or a cessation of drug production.

While in many ways this is a voluntary compliance effort, the fact remains that the consumer is still protected by FDA's big stick which is available for use, if needed. In other words, refusal, whether willful or negligent, to bring about compliance will, and, in fact, in at least one instance, already has resulted in the termination of the Intensified Drug Inspection, and an appeal to the Courts for injunctive relief. This program, in our view, constitutes just one more effort to develop an effective blend of so-called voluntary and regulatory compliance.

Federal-State Cooperation

Another evidence of the increased sophistication of our approach to compliance can be found in our present attitude toward federal-state relations. There exists today a far greater and more effective exchange of information between FDA and its state and local counterparts than has existed at any time in the past of which I am aware.

Today, our district directors sit down with their state counterparts to openly and frankly discuss problems within the particular state, to make considered decisions as to which agency can most effectively deal with which problems, and to reach agreement on the deployment of resources. This obviously results in a substantially higher level of consumer protection per tax dollar spent, since duplicated coverage, overlapping actions, repeated inspections, and similar wasteful practices can be largely eliminated.

There are pluses in this for the regulated industry, since individual plants will be bothered by fewer inspectors and can deal to a greater extent with single rather than multiple points of contact. On the other hand, some members of industry have expressed concern to me about the desirability of the delegation of authority to enforce federal laws to the various state agencies because, it has been said, there are great differences in the resources, qualifications of personnel, philosophies, political atmosphere, administrative competence, technological skill and the like, between the several states.

The fact is that our programs in this area are designed, not to attempt to shift the responsibility for the enforcement of federal statutes to state agencies, but to develop better consumer protection through joint planning. To advance this effort, we have several important programs under way designed to assist and support states in carrying out their compliance programs and to provide a sound scientific basis for a greater degree of uniformity in the application of compliance efforts at the state level.

Specific examples include detailed training programs where state people receive training in sound inspection and analytical techniques, as well as familiarization with federal regulations and current interpretations of them.

Another example is to be found in the development and dissemination of Good Manufacturing Practices (GMP) regulations, inspectional guidelines, and plant evaluators. All of these have been developed with input from many of our state counterparts, all are made freely available to them for their guidance, and all, we believe, contribute to greater uniformity among the state activities.

To summarize this part, FDA, as the regulator is concerned with bringing about compliance. As problems become more complex, industries larger, more far-flung, and more conglomerate, we are forced to seek ever more effective ways of achieving the goal with the total resources at the public disposal.

Regulator's Responsibilities

I cannot close a discussion of this kind without taking just a moment to outline my concept of the responsibilities of the regulator. There is, of course, the obvious: that paramount responsibility to assure that the public is protected from harm and abuse. I have already briefly referred to the responsibility to provide the honest manufacturer with protection from his unscrupulous competitor. Of equal importance is the necessity to maintain public confidence in the regulated industries *and* in the agencies charged with regulating them. This is, in my opinion, especially a federal responsibility. My friend, Jim Cope, in a report to the Proprietary Association a year and a half ago, emphasized this responsibility when he suggested that, in the absence of this confidence, it is reasonable to anticipate a virtual plethora of disruptive, if not destructive, state regulation. In his words, and I quote, "Imagine, if you will, a situation where public confidence in the Food and Drug Administration is shaken to the extent that each state demands and expects its own new drug application, its own labeling, its own packaging."

Thus, it seems to me, another important responsibility of the regulator is to maintain to the extent possible, an atmosphere in which compliance is encouraged. We are fond of saying in this country that you can't trust anybody anymore. However, I have been advised by both financiers and sociologists that, if it were in fact true that as many as 15 per cent of the people in this country really could not be trusted, it would be totally impossible to carry on the business of our society.

I think it is equally obvious, and perhaps we see some evidence of it in the world around us today, that, if the vast majority are not motivated to comply, the job of the regulator or enforcer becomes totally impossible. Resources are not available to our society to even begin to cope with a situation where there is anything other than a willingness to try to comply on the part of the vast majority of the regulated industry.

Conclusion

In conclusion then, I think it is fair to say that the regulator has the responsibility to try to assure fair, even-handed enforcement, to strive to achieve compliance through all available approaches, to exercise imagination and effective innovation to find better approaches, and to create an atmosphere in which compliance can breed compliance. In addition to the obvious, I think the regulated can also fairly be held to have the responsibility to respond favorably to these efforts and to accept a degree of responsibility for supporting and promoting them. **[The End]**

BOOK REVIEW

Fundamental Principles and Objectives of a Comparative Food Law: Volume 2, Elements of Motivation and Elements of Qualification. By E. J. Bigwood, Director of the Food Law Research Centre of the Institute of European Studies of Brussels University, and A. Gérard, a Belgian Lawyer and a Member of the Food Law Research Centre. 234 Pages. S. Karger, Basel, Switzerland, or c/o Albert J. Phiebig, Inc., P. O. Box 352, White Plains, New York 10602. 49 Swiss Francs—$11.90 U. S. Currency, plus postage. Reviewed by Franklin M. Depew.

This excellent volume by Messrs. Bigwood and Gérard compares various provisions of the food laws of a number of European countries with each other and with those of the United States and Canada. These are discussed under two basic categories: Elements of Motivation (objectives of food laws) and Elements of Qualification (terminology and basic concepts).

Under the first category the socio-economic factors which brought about the enactment and development of the food laws in the various countries are identified and discussed. These include new methods of production, marketing and distribution, changes in standards of living and the conditioning of the consumer by publicity. It is pointed out that these economic and social factors surveyed cannot fail to influence the way in which authority, legal or administrative, will act in the sphere of regulating and controlling foods. The objectives of the national food laws are then described in some detail. For instance, that of France is entirely directed at the prevention and repression of frauds with care for the protection of health playing an accessory role. However, it is stated that administrative power and the judiciary have made the protection of health predominant. Fraud, in France, appears to mean, in its broad sense, all conduct or acts tending toward an illegal or false result. The descriptions of the various methods used by the respective countries to achieve commercial honesty and to protect the public health make interesting reading.

Under the second category, the various methods of dealing with the important topics of vitamination of foods and of dietary food generally are reviewed. It is stated that the opposition to food vitamination in certain countries is due, in large part, to the prevailing traditional view that one must in principle oppose the tendency to add chemicals to foodstuffs. In addition, legal texts are frequently influenced by such misleading old-fashioned and out-of-date concepts as that there is a difference between natural and synthetic vitamins. The authors also discuss the concept of "necessity" including technological, economic, psycho-sociological and commercial "necessity" and the criteria of "necessity" of a food additive in opposition to its "usefulness", or to "advisability" of its acceptance. The methods whereby the various national food legislations have dealt with these matters are then examined.

Of especial interest are the very fine appendices to the volume which include the topics: "The G.R.A.S. Status in the U. S. Food Law," "What is the Exact Meaning of the Word 'Ingredient'" and "Admissible Daily Intake of Food Additives and Food Additive Tolerances in Foodstuffs".

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VOLUME 23 — 1968

FOOD DRUG COSMETIC
LAW JOURNAL

PUBLISHED BY
COMMERCE CLEARING HOUSE, INC.
PUBLISHERS of TOPICAL LAW REPORTS
4025 W. PETERSON AVE., CHICAGO, ILL. 60646
RETURN REQUESTED

SECOND CLASS POSTAGE PAID
AT CHICAGO, ILLINOIS AND
AT ADDITIONAL MAILING OFFICES

A COMMERCE CLEARING HOUSE PUBLICATION