VOL. 31, NO. 5 MAY 1976

Food Drug Cosmetic Law JOURNAL

Special Problems in Advertising

ELAINE S. REISS

Regulatory Aspects of Food Additives—Yesterday, Today and Tomorrow

GARY A. SUNSHINE

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, $30; single copies, $3. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

May, 1976
Volume 31 • Number 5

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Illinois and at additional mailing offices.

FOOD DRUG COSMETIC LAW JOURNAL

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TO THE READER

"Special Problems in Advertising" is *Elaine S. Reiss'* analysis of the legal climate surrounding advertisements, especially in light of recent consumerist action concerning the effect of advertising on children. Ms. Reiss, Vice-President and Manager of the Legal Department of Ogilvy and Mather Inc., discusses the Federal Trade Commission's proposed trade regulation rule on food advertising, in addition to reviewing recent Commission cases regarding alleged deception in nutrition advertisements. The article, which begins on page 252, was presented at the 31st Annual Meeting of the Food, Drug and Cosmetic Law Section of the New York State Bar Association, which was held on January 29, 1976 in New York.

In an article beginning on page 264, *Gary A. Sunshine* presents a historical overview of the regulation of food additives. Starting with the Pure Food and Drug Act of 1906, he traces the development and the refinement of the term "food additive" and describes the resultant licensing-type regulatory scheme. Mr. Sunshine also touches on areas of interest and importance in the determination of methods to assure the safety of the food supply. "Regulatory Aspects of Food Additives—Yesterday, Today and Tomorrow" was written by the Director of the Regulatory Law Department of ICI United States, Inc. It was delivered at the Chemical Marketing Research Association meeting in Hamilton, Bermuda on February 17, 1976.

Martin I. Blake, head of the Department of Pharmacy at the University of Illinois, examines the methods and the necessity of establishing and maintaining specifications and standards for drugs used in the United States. Dr. Blake explains current compendial specifications and the structure involved in establishing those standards. Based on his lecture presented at Ayerst Laboratories on February 12, 1976, the article is titled "The Role of the Compendia in Establishing Drug Standards" and begins on page 276.

In a paper first presented at the FAO/DANIDA workshop on Fish Handling, Plant Sanitation, Quality Control and Fish Inspection, which was held in Bangkok, Thailand beginning on October 20, 1975, *J. R. Brooker* explains the labeling, sanitary and additive requirements of the United States for fish and fishery products imported into the country. Appended to the article are an import procedure flow chart and a bibliography of pertinent regulatory sources. Mr. Brooker is Senior Staff Specialist of the Fishery Products Inspection and Safety Division of the National Marine Fisheries Service in the United States Department of Commerce. "How to Export Fishery Products to the United States" begins on page 289.

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Food·Drug·Cosmetic Law
Journal

Special Problems in Advertising

By ELAINE S. REISS

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MY DISCUSSION WILL FOCUS on the legal climate, in terms of marketing food products to a particular segment of our society—children. The children's issue, as raised by consumerists and the government, is divided into two main concerns: (1) a child's nutrition, health and safety; and (2) a concern about dealing with children in an unfair manner.

In 1970, headlines appeared in national newspapers when Robert Choate criticized the nutritional content of dry breakfast cereals. In 1972, he testified before the Senate Committee on Nutrition of Human Needs on the consumerists' concern about breakfast nutrition. The link between nutrition and children was, and still is, magic in what I call the consumerist years.

Choate was one of many of the consumerists to find a way to gain headlines, to use that pressure—the pressure of the public press—to exert their will through government to alter those business practices which they abhor. Industry is very much aware of their success in the food and drug area. The same pressures that were being exerted on the Food and Drug Administration (FDA) were exerted on the Federal Trade Commission (FTC).

In April of 1972, in response to some of that pressure, the FTC issued its so-called cereal complaint. The complaint alleged, in part, that cereal companies engaged in unfair methods of competition by representing in their advertisements that ready-to-eat cereals, without

other foods, enable children to perform the physical activities represented or implied in their advertisements.

The FTC alleged that these cereals do not enable children to perform the physical activity represented or implied in these advertisements. This allegation, in an anti-competitive complaint based on advertising implications, was novel and continues to be novel. These allegations were concerned with the protection of a particular class of consumers—children. The matter of the cereal complaint is still in the early stages of litigation.

Ready-to-Eat Cereals

The attack on the ready-to-eat cereals was coupled, by consumerists, with an attack on the highly sugared cereal. Mr. Choate's Council on Children's Media and Marketing used the public forum to argue that the frequent use of the sugared cereals caused tooth decay and many other health problems that children have. More recently, the Center for Science in the Public Interest petitioned the FDA to set standards for the amount of sugar permissible in packaged breakfast cereals. Action for Children's Television (ACT), the Boston-based consumerist group, raised the concern about the amount of sugar in food advertised to children. In April of 1972, ACT petitioned the FTC to eliminate the advertising of all edibles to children. ACT stated,

"A child watching a television program for children sees ads for sugared cereals, snack foods, candies and other sugared drinks in an unceasing number and learns nothing of the essentials of a balanced diet. On a typical Saturday morning a child will see no ad for fruit, vegetables, cheese, eggs or other valuable nutritional foods, but instead will be cajoled into buying new sugar cereal with a toy premium or to put syrup in his milk to make it fun."

The pressure was on the FTC to take some action. These same pressures were felt by the self-regulatory bodies, the National Association of Broadcasters (NAB) and the National Advertising Review Board (NARB).

Self-regulation of advertising by these bodies must be coped with in the development of a marketing plan for a food product, both a food product directed to children and a food product directed to the general consumer.

The FTC began proceeding on several different fronts to deal with the pressures that the consumerists were placing on them.

One, as the cereal case illustrated, was the traditional case approach. There were other cases that were based on concerns about the nutrition of children. One of these was the HI-C case. The Commission,

in its complaint, had alleged that the advertisement for HI-C compared HI-C with citrus juices, particularly with orange juice, and implied HI-C's superiority. The advertising was deceptive, the Commission said, because HI-C was not of a more nutritious value than orange juice.

Advertising Representations

The administrative law judge did not support the complaint counsel's findings and found, indeed, that consumers would not be likely to understand the advertisement to imply the drink was made from fresh fruit juice and was equal to, or better than, fresh fruit juice. On appeal, the Commission agreed and found that the advertising representations that were made were not reasonably likely to communicate that HI-C was more nutritious than fruit juices.

In another juice drink case, RJR foods entered into a consent order with the FTC for its product, Hawaiian Punch. Hawaiian Punch agreed to disclose in all of its future advertising the percentage of fruit juices contained in the product. RJR not only agreed to make the corrective advertising disclosure, which it is presently doing, but agreed that it would continue to make that disclosure until it had a market survey which found that consumers understood the disclosure. The survey had to indicate that at least 95 percent or more of the current purchasers of Hawaiian Punch product think that Hawaiian Punch contains no more than 20 percent natural fruit juice.

Consumerists were concerned about children drinking sweetened juice-type drinks that were not juice. Hence, the FTC's concern in these cases was with the products that were marketed to children. Given the juice drink cases, one would assume that a claim like "milk has something for everybody" or "everybody needs milk" would be applauded by the consumerists and the FTC. While this is not really a child-directed case, the FTC this year attacked the California Milk Advisory Board Celebrity Campaign, which used these slogans. This further illustrates the problem of advertising nutrition. Because the Board is a state entity, the FTC was precluded from interfering.

Alleged Deceptive Advertising

Another case of particular interest to this discussion is ITT Continental Baking Company. The alleged deceptive advertising was for two products, Wonder Bread and Hostess Snack Cakes. In the Hostess

Snack Cakes' advertisement, the company announced that it had fortified the product with nutrients. Yet, the FTC complained. The complaint alleged that the advertisements were deceptive because they indicated that Hostess Snack Cakes offered good nutrition for children as food. The FTC, on appeal, did not accept complaint counsel's argument that the advertising constituted either an expressed or implied deception, saying that children could eat Hostess Snack Cakes to the exclusion of other foods and still get good nutrition. Nor did the Commission accept the argument that the claim for good nutrition is misleading because the advertisements failed to disclose the fact that Hostess Snack Cakes contained large amounts of sugar. The villain sugar reappears.

The Commission found that the "good nutrition" saying was qualified in the advertisements themselves. Additionally, the Commission held that it was common knowledge that snack cakes, whether homemade or commercially manufactured, contain large amounts of sugar. The Commission mentioned, as an additional fact in dismissing the complaint against ITT and Ted Bates, that the advertisements were used as part of a short market introduction and announcing fortification where none had existed before. It remains to be seen whether or not that element of announcing a product improvement will be a controlling factor in the snack category as the only circumstance under which that type of product can claim good nutrition.

Nutritional Value

The Wonder Bread portion of the action was not dismissed. The decision issued by the FTC, which is now being appealed to the federal court, deals with the elements I set forth earlier: (1) deceptiveness as to the nutritional value of the product; and (2) unfairness. The Commission held that the advertisements represented Wonder Bread as having extraordinary properties to produce growth in children. It also held that the bread is not an extraordinary food for producing growth in children and the ad was thus false representation. The Commission relied on both its expertise and also on several market research studies that indicated consumer perception of the product and its advertising. It utilized marketing surveys, in which consumers had rated the product as being a good source of nutrition, as evidence of the intent of Wonder Bread to continue to market this product on a nutritional platform. The staff alleged that false

portrayal of Wonder Bread as an extraordinary and necessary growth food unfairly exploited children's aspirations and parental concerns about children's health, growth and development. The Commission found that, in this particular case, the unfairness issue appeared to be inseparable from the falseness of the claim. Therefore, it did not find that the deceptive claim also constituted unfair acts under Section 5.

However, the Commission did recognize that unfairness might, indeed, be a separate cause of action. The Chairman of the FTC, Lewis Engman, dissented. He stated:

"The record confirms what our accumulated knowledge and experience tells us. Mainly, children of tender years, especially children under six years of age, are highly vulnerable to the type of subtle psychological claims promising rapid growth contained in the Wonder Bread advertisement. Recent empirical studies appear to confirm the conclusion that children under six years of age may tend toward a confused perception about whether something they see on television is absolutely true or not. In these circumstances, I am persuaded that the challenged advertisement, in addition to being deceptive, also constitutes an unfair practice within the meaning of Section 5 because it capitalizes on children's anxiety about growth and exploits their difficulty or inability to differentiate between reality and fantasy.

"In my opinion, the unfairness doctrine endorsed by the court in *FTC v. S&H* is peculiarly appropriate in the circumstances of this case. I am not suggesting here either that Section 5 condemned every psychological advertisement directed to children as inherently suspect, but the advertiser who chooses a child audience as a target group for a selling message is subject not only to the standards of truthful advertising, but is also bound to deal in complete fairness with his young viewers. Advertising directed to or seen by children, which is calculated to or, in effect, does exploit their known anxieties or capitalize upon their propensity to confuse reality and fantasy, is unfair within the meaning of Section 5 of the Federal Trade Commission Act."

Capacity to Influence Children

More recently, General Foods Corporation signed a consent order that settled a proposed Commission complaint challenging four television commercials of Grape Nuts as unfairly deceptive because of their capacity to influence children to engage in harmful activity. The harmful activity objected to by the FTC is eating wild plants. The commercials in question showed natural foods advocate, Euell Gibbons, picking and eating, or pointing to, a certain wild plant and stating that the particular plant, or parts of it, are edible or good tasting.

Specific allegations in the FTC's proposed complaint concluded that the advertisements have the capacity to influence children to eat plants or plant parts which they find growing or in natural surroundings. I include this because, while Engman's opinion on Wonder Bread was a dissent, I think that this statement may well become a statement of the position of the FTC. I believe that the General Foods case is the first consent order to enter this area of unfairness.

Additionally, the proposed complaint included a statement that these ads have the capacity to undercut a commonly recognized safety principle, namely, that children should not eat any plant found growing or in natural surroundings except under adult supervision; that the commercials had the capacity to misrepresent to children that they can eat plants they find growing in natural surroundings without risk or harm.

The consent order applicable to all General Foods products prohibits representations that a plant is edible in its raw state where the visual impression is conveyed that the plant was not grown for human consumption, or where raw plants being consumed are specifically described as wild plants.

Reasonable Inquiry

Also, General Foods is barred from sponsoring advertising that has the capacity to influence the consumption of any non-commonly recognized product where it is reasonably foreseeable through reasonable inquiry that such a representation has the capacity to influence behavior which can result in physical harm.

At the outset of this paper, I indicated that I was going to review how the FTC reacted to consumerist pressure in several ways. I have reviewed only a few of the FTC cases that were peculiarly child-related with a focus on both the nutrition-health-safety element and the unfairness element. The Commission, however, did not operate only in the traditional case area.

In a speech delivered by FTC Chairman Engman to young lawyers several months before his published dissent in the Wonder Bread case, the Chairman called for action on the voluntary code in the children's advertising area. He called for cooperation by both industry and the consumers or consumer advocates. In announcing the Commission's involvement in this project to develop a voluntary code, he specifically mentioned eight points which should be addressed. Several of particular interest to us are:

(1) advertisements which encourage the purchase of food items, especially those involving soft drinks, candies and snacks, without, at the same time, explaining how the product fits into a well balanced nutritional program;

(2) the use of premiums and contests to create an artificial demand for a specific product;

(3) the exposure of children to advertisements for products which promise to affect the user's mood or well-being;

(4) the use of program characters, either alive or animated, to sell products to children;

(5) the use of material which can reasonably be expected to frighten children or to promote anxiety, or which portrays or appeals to violent or dangerous behavior, or which portrays children in unsafe acts.

What relevance do these points have to our discussion? During the ten months that the project continued, the consumerist participants submitted their code. Industry representatives did not accept it. Industry, in answer to the FTC's pressure, did evolve an expanded role in the area of child-directed advertising for its self-regulatory body, the NARB. It established the NAD panel of experts. The hot issues throughout the entire project were nutrition—more specifically, sugar—and premium advertising. These are issues that are not resolved yet.

Trade Regulation Rule

During this project, the FTC continued the preparation of a trade regulation rule on food advertising which was finally published in November of 1974. The FTC staff eliminated the discussion of nutrition from the children's project because of the impending trade regulation rule on food advertising.

However, there were certain provisions in the consumer's code that were of interest. The consumer's code provided that commercials directing themselves to children: (1) could not advertise any edible product or beverage containing sugar over 15 percent by wet weight or 35 percent by dry weight; (2) could not identify or imply food or other characterizing ingredients or flavor without disclosing its natural or artificial nature as proposed in 21 CFR 1.12 under the Federal Food, Drug and Cosmetic Act; and (3) could not, directly or by

implication, represent that any edible product or nutrient by itself produces, hastens or enhances vigor, stamina, strength or energy, etc.

Of greater interest was a proposal that no family commercial could advertise any edible product or beverage containing sugar over 15 percent by wet weight or 35 percent by dry weight without an audio or video warning that eating the product between meals may be harmful to a child's teeth. I have mentioned these because, although nobody has adopted them, this is where government is being pressured by constituents to do something.

Sugar Problem

The FTC, in issuing the trade regulation rule on food advertising, did not touch on the sugar problem but shifted the concern back to the FDA for its findings on sugar. The consumerists were publicly disappointed. Sugar remained an issue and remains, they contend, a concern for the consumer. One must assume that continued research in the area, such as the study that was published in the Journal of the American Dental Association in April of 1974 which indicated that there is no association that can be found between dental caries incidence and the consumption of ready-to-eat cereals, is the only way to satisfy this concern by the consumerists.

Briefly stated, the food rule, as presently proposed by the FTC, requires a firmer disclosure of nutrient content when the advertising makes a nutritional claim either directly or by implication. Other elements of what was contained in Chairman Engman's speech and what was contained in the consumer's code have been adopted by the self-regulatory bodies, the NAB and the NARB and, therefore, govern the advertising of food products as if they had been adopted by the FTC.

However, the NAB voluntary compliance with many of these provisions by the consumer's and the industry's new self-regulatory mechanism was not enough for the FTC. Having hosted these meetings and having gone out publicly and stated that it was hosting the meetings for a voluntary children's code, the FTC wanted to have some part of the consumer's code adopted.

In July of 1974, the Commission issued for public comment a guide on the advertising of premiums. This guide required that all premium advertising directed to children be eliminated. The guide was based on a concern that the technique was unfair to children. Elimination of the technique would have an effect on advertising cer-

tain food products that are now directed to children. The definition, as contained in the proposed guide as originally published, would even proscribe colorful packaging as well as the premiums contained within the package. The premium device is used commonly in cereals, snack products and in some food products from the fast food chains. A research study published early this year conducted by researchers at George Washington and Kent Universities, indicated that the concerns of the FTC over a child's ability to cope with this type of advertising technique was misplaced. The FTC issued this research for comment, and industry was again given the opportunity to comment on the proposed guide on premium advertising.

Premium Advertising

At this point in time, there is no indication whether or not the Commission will continue to proceed with its ban on premium advertising as a tool in food advertising directed to children. The consumerists still want its elimination as a marketing tool, but the research would appear to have slowed FTC action. Objective facts can modify regulations based on false assumptions.

The proposed trade regulation rule on food advertising has, of course, a greater impact on advertising than just those ads directed to children. Children are one of the special classes that the FTC is concerned about protecting, and has used as a basis for issuing this proposed trade regulation rule. The potential threat to marketing of a new food product that wants to talk about nutrition is apparent on its face. Additionally, while the Commission indicates that, at this point, the rule will only apply when a nutritional claim is made, the food rule as a precedent could apply to all future food claims that are made.

The FTC, in issuing the food rule, did not issue the staff statement. The staff statement contains a proposal for at least requiring disclosure that the food does not contain any nutrient in excess of ten percent, or does not contain any nutrient that is valuable. The FTC has indicated that the staff statement is not issued, nor has the Commission endorsed it.

You are all aware of the impossibility of bringing to market a new food product without an effective advertising program to support it. As presently proposed, the rule requires nutrient disclosure. The rule assumes that the consumer knows what nutrients are, how they function and the daily amount necessary. There is

a requirement of affirmative disclosure of the percentage of United States recommended daily allowance (U. S. RDA), delivered by a stated serving of the food.

FDA Labeling Rule

Nutrients that can be disclosed are limited to those that are contained in the FDA labeling rule. As I understand it, these are not all the nutrients that are necessary for a healthy diet.

These required disclosures would make food advertising that is attempting to give the consumer nutrient information monotonous and full of dreary repetition, an endless reading of lists of serving amounts, calorie amounts and nutrient amounts. The repetition of essentially dull material cannot be expected to enlighten, or even to be remembered by, a consumer. Commercials which are mostly dry factual talk, accompanied by a television picture of the same words in print, are notoriously low in memorability. Reciting the information in a television commercial might well be counterproductive. The advertising might create the impression that there is no longer any need to read the label, since the consumer vaguely recalls something about nutrient information from the advertising.

In all fairness, some of the FTC proposed food rules do not require disclosure. The food being advertised has to qualify in order to use certain descriptive words about the food, such as the claim "this is nourishing." While this seems reasonable, it appears that certain foods which you and I view as nourishing do not qualify under the rule. For example, most fruit juices (including orange juice), whole wheat bread and vegetables such as asparagus, broccoli, cauliflower, corn, green beans, lima beans, peas and carrots can no longer be called nutritious, nourishing or wholesome. Why not? Because the rule requires that, in order to use these words in advertising, the food must contain at least four nutrients including protein, present in an amount at least ten percent of the U. S. RDA per 100 calories.

I am bewildered since, as an attorney, I have not seen any basis for the contention that these words are presently being used in a misleading manner to consumers. As a consumer, I find this new regulation equally misleading. Why aren't green beans wholesome and nutritious? Doesn't a well balanced diet need vegetables? How is the consumer going to benefit from this restriction? On what basis was this limitation determined? Is it a scientifically correct basis?

I do not know the answers, nor has the FTC provided any answers. However, it has provided a hearing for the future wherein, I assume, these are going to be some of the many issues that will be raised.

So-Called Emphatic Claim

The proposed rule governing the so-called emphatic claim requires that a nutrient be present in at least 35 percent of the U. S. RDA in order to qualify to be called an "excellent source of," "high in" or "rich in" that nutrient. Again, this rule is reasonable enough on its face—until it is applied. This regulation would prohibit referring to milk as high in protein or an excellent source of calcium. I suggest that this is equally misleading and of no benefit to the consumer.

What is the nutritional basis of the 35 percent limitation? The FTC has provided us with a rule with no explanation. The listing of nutrients is based on the needs of a 22 year old white male. Many adults need only two-thirds to three-fourths of the suggested amounts. Children may need one-half. Yet, consumers will believe that the goal of 100 percent or more of the U. S. RDA should secure adequate, if not good, nutrient habits. As an example, women and children should get 100 percent of the iron allowance, although older boys and men require about 55 percent. Similarly, children and teenagers need more calcium than adults because their bones are still developing.

Some experts say they should aim for 120 percent of the U. S. RDA, although 80 percent suffices for adults. How will the disclosures, as presently contemplated, lead to a better understanding of the consumer's dietary needs? For these reasons, I therefore believe that this rule, which is concerned about our nutrition and particularly about the nutrition of our children, does not, in its present form, really aid children.

Extensive Hearing Process

Since the trade regulation rule will undergo an extensive hearing process, this is another area where knowledge can aid the regulatory process. The Commission itself has said in the ITT Continental case,

"The instant case, the Wonder Bread case, involved the nutritional claim with respect to a food product. An absolute claim for good nutrition may well be objectionable for the reason that the advertisement missed things that should be said. On the other hand, it would be unrealistic to impose upon the advertiser the heavy burden of nutritional education, especially with respect to radio and TV commercials which, in many cases, are shorter than 30 seconds and seldom as long as 60 seconds."

We should not attempt to establish an overly restricted standard of general application in this regard. To do so would be tantamount to a *de facto* ban on all nutritional advertising through the radio and TV media. In the final anaylsis, the question of whether an advertisement requires affirmative disclosure would depend on the nature and the extent of nutritional claims made in the advertisement. Why, therefore, is the Commission now proposing affirmative nutrient disclosure in all commercials?

The bulk of my presentation has been spent discussing children. I have not discussed the socially disadvantaged or the elderly. Why? My personal view is that what has occurred in the last five years in terms of what I view as a child protection regulation is merely a precedent as to what we may expect in the future for other segments of society. Concern for children cannot really be separated from the concern for the socially deprived child, the poor child. Once we have protected the child, then we can be concerned about protecting other segments of our society who need care, such as the elderly. I cannot now point to any specific legislation in the food area, other than the trade regulation rule on food advertising which is concerned also about the nutrition of the elderly and the poor, to support my thesis. But it is there in the trade regulation rule on food advertising.

All of our methods of selling are regulated more closely today by the various bodies and changes in marketing which have obviously occurred in reaction to this regulation. Advertising continues and, short of banning it, which none of the regulatory bodies have done in the food area, will continue. While it may be more difficult in the future to produce advertising under these rules, it is my belief, as an advertising person, that advertising will continue to remain a major factor in the marketing of food products. **[The End]**

Regulatory Aspects of Food Additives— Yesterday, Today and Tomorrow

By GARY A. SUNSHINE

Mr. Sunshine Is Director of the Regulatory Law Department of ICI United States Inc.

IT WOULD BE PRESUMPTUOUS OF ME to attempt to present a thorough and scholarly dissertation of this subject. Moreover, it would probably be impossible. What I will attempt to do is to mention a few of the key aspects of food additive regulations past and present. Then I will venture a few thoughts about the future. The opinions that I share with you are my own and should not be taken as representative of industry or even of my company.

Yesterday

Most discussions of regulation that include any historical perspective at all usually begin with a recitation of examples of codes of food laws observed by one or another obscure ancient civilization. The discussion generally moves forward to the neo-ancients and eventually cites English laws of the middle ages regarding such things as the seizure of harmful foods. While examining such perspectives is interesting, it is not particularly helpful in understanding the United States regulatory system of yesterday or today. Therefore, I have chosen to define "yesterday" as the period between 1906 and 1957, and "today" as 1958 through this day. By default, "tomorrow" begins on the day after today and goes forward.

1906 Act: The year 1906 was chosen as the dawn of yesterday because it was in that year that the first major food legislation at the federal level was enacted in this country. The new law concentrated on safety, wholesomeness and labeling of foods in order to

permit consumers to make intelligent choices. It did not attempt to mandate what people would eat.

"Added": Under the Pure Food and Drug Acts,[1] as the 1906 Act was called, the doing of various acts was considered to result in the adulteration or the misbranding of food. Among the prohibitions that would result in adulteration was one against the addition to foods of poisonous or deleterious substances which might render the food injurious to health.[2] This provision was strictly construed. In a 1916 case,[3] the government alleged that Coca-Cola was adulterated on the ground that it contained an added poisonous or deleterious ingredient—caffeine—which might render the product injurious to health. The Supreme Court ruled that any constituent of a fabricated product is an "added" ingredient even though that constituent may be part of a set formula. This case said that "added" meant just that.

"Injurious to Health": Another significant case under the 1906 Act involved sacks of flour that were alleged to be adulterated because they were allowed to come in contact with nitrogen peroxide gas during processing, thus adding poisonous nitrogen compounds which might render the flour injurious to health.[4] In this case, the Supreme Court held that the language of the statute does not flatly prohibit the presence of added poisonous or deleterious substances. The prohibition is not based on the nature of the poison alone but relates to the toxicity of the food. There must be enough of the substance present so that it may render the product injurious to health.

These two cases illustrate how substances that we today call food additives were regulated under the 1906 law. The ingredient had to be *added* rather than one that was naturally occurring in the food and, secondly, it had to have the potential for being poisonous in the quantity present in the food.

1938 Act: In 1938, a new food and drug law was enacted.[5] This one was known as the Federal Food, Drug and Cosmetic Act and remains as the basic law today. The new Act said that a food shall be deemed to be adulterated "if it bears or contains any added poisonous or added deleterious substance . . . which is *unsafe* within the meaning"[6] of the statute. The statute also provides that the added

[1] Food and Drug Act, Ch. 3915, 34 Stat. 768 (June 30, 1906).

[2] *Id.*, Sec. 402(a).

[3] *United States v. Coca-Cola Company of Atlanta*, 21 U. S. 265 (1916).

[4] *United States v. Lexington Mill & Elevator Co.*, 232 U. S. 399 (1914).

[5] Federal Food, Drug and Cosmetic Act (1938), 52 Stat. 1040, 21 U. S. C. Secs. 301—392.

[6] 21 U. S. C. Sec. 342(a)(2).

substance shall be deemed to be "unsafe" unless it is "required in the production"[7] of the food or "cannot be avoided by good manufacturing practice (GMP),"[8] in which case the Food and Drug Administration (FDA) shall promulgate regulations limiting the amounts that may be present in the food.[9] In comparing the new law with the old, we still have the requirement that a substance must be "added" but we now have a new standard in place of the "may render it injurious to health" test. The new test seems to make sense. If the substance is poisonous, it is poisonous and, therefore, unsafe unless, of course, the ingredient's presence is required in the food, in which case it is no longer unsafe.

Poisonous Per Se: The new test was applied in a 1945 case.[10] In this case, it was alleged that fluorine was added to beer in some unknown quantity. The government's position was that the product was adulterated because it contained an added poisonous or deleterious substance which was unsafe. The courts ruled in favor of the government on the basis that the statutory test had been met. The quantity of fluorine added was immaterial. Also, it was immaterial whether or not the finished product was harmful; only the added ingredient had to be poisonous. The test set down here came to be known as the "poisonous *per se*" test. The mere presence of a poison was enough. The test did appear to be reasonable and Congress provided an exception for those cases where the ingredients were required or could not be avoided by GMP. However, the fact of the matter is that no regulation was ever issued exempting an added substance as being required by GMP or unavoidable. The net effect of this form of regulation was an inhibitory one on the growth of food technology. Experimentation in the development of new foods was restricted.

Policing System: Under the basic regulatory scheme, which we have been examining, the use of food additives is governed by what is commonly known as a "policing" type of system. Food fabricators were free to produce foods incorporating any ingredients that they chose. At the same time, it was the FDA's obligation to police the industry to identify violators that were using ingredients which were poisonous or deleterious. To illustrate this type of statute with another

[7] 21 U. S. C. Sec. 346.
[8] *Id.*
[9] *Id.*
[10] *United States v. Commonwealth Brewing Corporation and Leo Kaufman,* (DC Mass., May 22, 1945). See Kleinfeld and Dunn, "Federal Food, Drug and Cosmetic Act, 1938-1949," pages 310—315 (1949).

example a little closer to home—a prohibition against reckless driving relies upon compliance by most members of the public and the policing of violators. This is a classic policing type of statute.

This summarizes yesterday's scheme for the regulation of food additives. It was a fairly simple system offering industry the opportunity of self-determination regarding the addition of additives but, as in the case of any policing type of system, action was at the manufacturer's peril. The use of new additives was governed by the poisonous *per se* doctrine. An additive that produced adverse effects in laboratory animals in any amount could be deemed to be poisonous regardless of the lack of any evidence of potential for harm in man.

Food Additives Amendment (Today)

In 1958, the Food Additives Amendment[11] was enacted. It made two major changes in the regulatory scheme. The first was to convert the policing-type of approach to a licensing-type approach. In the latter type of law, the act (adding an additive to food) cannot be performed unless government permission is obtained first. An example of a licensing-type law is the prohibition against operating a motor vehicle without a driver's license. The mere act of driving the car is a violation regardless of the abilities of the violator.

The second major change was the recognition of the concept well known in science that, for every chemical, there is some finite level at or below which it can be present in food without prejudicing safety. In other words, everything is safe at some level. The Food Additives Amendment provided that, with certain exceptions, the proposed use of an additive would be permitted as long as it could be shown to be safe.

Food Additive Definition: Now that we understand the philosophical basis of the regulatory approach, let us turn to the question of what are food additives. The Act defines them as:

"any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . ., if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use. . . ."[12]

The definition goes on to exempt certain classes of ingredients and "any substance used in accordance with a sanction or approval granted prior to the enactment" of the law.

[11] P. L. 85-929, 72 Stat. 1784 (Sept. 6, 1958).

[12] 21 U. S. C. Sec. 321(s).

Scope of Definition: To restate the first half of the definition, a substance is a food additive if "the intended use . . . results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. . . ."[13] Any substance intentionally added to food is a direct food additive. However, the first half of the definition makes it clear that a food additive does not have to actually become a component of the food. There merely has to be a reasonable expectation that it could become a component of the food. If this test is followed, food packaging materials are food additives. Items such as cellophane, food wrap, PVC duct work, linings used in drums, beer spigots—in short, just about anything that contacts food in manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food—may be food additives. These types of additives are called indirect food additives. In the normal course of events, they are intended to come in contact with food but are not intended to become components of food. Nevertheless, there often is a possibility that there may be some migration of materials from food contact surfaces into the food itself.

Generally Recognized as Safe (GRAS) Defined: Now let us turn to the second half of the definition. The first part related to associating the substance to food, directly or indirectly. This part relates to safety. It provides that a substance meeting the first half of the definition will be deemed to be a food additive if it "is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use."[14] That is a lot of words to say a substance will be a food additive unless it is generally recognized as safe for its intended use. This definition has been further shortened to generally recognized as safe or GRAS. In the rest of this discussion, whenever I use the term "GRAS," I mean that 34-word phrase in the statute.

Prior Sanctions: One of the important exemptions from the definition is the one that exempts substances used in accordance with sanctions granted prior to the enactment of the Food Additives Amendment. This relates to informal approvals granted by the FDA or by the United States Department of Agriculture under the Meat Inspection Act before the Food Additives Amendment was enacted. You will recall from our earlier discussion that, under the old law,

[13] *Id.* [14] *Id.*

manufacturers were free to use food additives without FDA approval but at their own peril. Obviously, responsible members of the industry did not want to take a chance on using any questionable ingredients. Accordingly, standard practice was to obtain a letter from the FDA agreeing that the food would not be rendered injurious to health by the addition of the additive. These letters became known as "prior sanctions." They were informal and private. Since they were written over a period of about 20 years, the FDA lost track of many of them and was generally dissatisfied with the situation. To limit the application of the sanctions, the FDA construed them narrowly. Because of this, as the years passed and manufacturers' processes moved stepwise away from where they had been at the time that the prior sanctions were granted, few of the sanctions were actually relied upon by food fabricators. Several years ago, in an effort to get a handle on this situation, the FDA published a notice in the *Federal Register*[15] revoking all prior sanction letters that had been issued. The FDA tried to distinguish between the letters and the sanctions, stating that the letters were out of date and needed to be updated and that the revocation of the letter did not *per se* mean that the sanction was revoked. The FDA wanted people to send in the letters and let the Agency review them and issue new letters. This is a rather subtle distinction on the part of the FDA. It would seem logical that, if Congress said a substance was not a food additive if a particular act had occurred prior to the enactment of the Food Additives Amendment, nothing could be done 15 years later to change the previously occurring exempting act.

GRAS Status: When we considered the definition of GRAS, we said that any substance that was considered GRAS in a particular application was legally not a food additive. The Statute does not provide any mechanism for formal determinations. In fact, even though the FDA now says it will make that determination,[16] industry may still be free to reach its own determination. But, again, industry makes this determination at its peril and if the FDA disagrees with the conclusions reached, it may prosecute to obtain a judicial determination. Furthermore, from a practical point of view, it is difficult, if not impossible, for the manufacturer of a food additive to convince a food fabricator to use its additive in foods on the basis that the additive manufacturer has independently decided that the product is GRAS. The food fabricator wants some assurance that its finished food, including the additive, will not be illegal. The

[15] 35 *F. R.* 5810.

[16] 21 CFR 121.3.

best assurance is a regulation or a letter from the FDA saying that the product is safe for such use.

GRAS List: At the time of the enactment of the Food Additives Amendment, there were many food additives that had been reviewed by the FDA and used over a period of years. The FDA recognized that it was important to get through the transition period and put the Food Additives Amendment into operation with as little disruption as possible. Accordingly, the Agency, in consultation with various scientific groups, published a list of several hundred substances that it felt were GRAS in certain circumstances. These included direct and indirect additives, some for general use and some for very specific uses. The FDA then turned its attention to other problems with regard to the implementation of the new law. As a result, the GRAS-listed products were left alone for the next ten years. In the late 1960s, as the consumer movement began to gain impetus and all of the other known food additives had more or less been dealt with, attention again focused on the GRAS list. Careful examination of products included on that list revealed that, although the products had been judged to be safe in 1960 based on experience and available data, long-term feeding tests in animals and other more sophisticated types of tests that had come into vogue never had been conducted on many of these products. In the President's Consumer Protection Message of 1969,[17] the President directed the FDA to re-evaluate for safety all items included on the GRAS list. This was appropriate since the concept of GRAS is a dynamic one. It is a determination that the product is generally recognized as safe at a particular point in time. At another time, new information or other considerations may be raised that would result in reaching a conclusion different from that reached on an earlier occasion. The review process is moving along and the end may be in sight. The FDA has predicted that the evaluation of the 439 substances which appeared on the published GRAS list will be completed by October of this year.[18] Then, it will be up to the Agency to take the evaluations and publish appropriate proposals for comment.

Unsafe Food Additives: We have now formed a definition for the term food additive. Those substances to be included and those to be

[17] *Weekly Compilation of Presidential Documents*, Vol. 5, No. 44, pages 1516-1524 (Nov. 3, 1969).

[18] Statement by Richard J. Ronk, Director of the Division of Food and Color Additives in the Bureau of Foods of the FDA at the Food and Drug Law Institute—the FDA Conference, Washington, D. C. (Dec. 2—3, 1976). (See *Food Chemical News*, page 6 (Dec. 15, 1976).)

excluded have been identified. Where do we go from here? The Act says that a food additive shall be deemed to be unsafe unless it is used in conformity with a regulation which provides for its safe use.[19] Another section provides that a food shall be deemed to be adulterated if it bears or contains a food additive which is unsafe.[20] What this means in ordinary English is that if the substance comes within the definition of a food additive, its use must be sanctioned by a specific regulation or the food will be deemed to be adulterated, which is a violation of the law.

Food Additive Petitions: If a manufacturer were to develop a new food additive or a new use for an old food additive, in all likelihood, it would have to petition the FDA to issue a regulation sanctioning the proposed use of the food additive. The petition would have to include information that describes the additive, proves that it will accomplish its intended technical effect, and prove that it is safe. Additionally, an analytical method must be supplied for policing the use of the additive.

As you can imagine, it takes a substantial amount of work and an appreciable period of time to develop all of the information required for the filing of a petition. An additional time period is spent by the FDA in reviewing the petition.

In the processing of the petition, the FDA may not issue a regulation if a fair evaluation of the data shows any one or more of the following[21]:

(1) that the data fail to establish that the proposed use will be safe;

(2) that the proposed use would promote deception of the consumer;

(3) that the additive does not accomplish the intended technological effect;

(4) that the cumulative effect of the additive in all food uses for which it may be approved is beyond a safe limit;

(5) that the additive induces cancer when ingested by man or animal.

Delaney Clause: No discussion of the Food Additives Amendment would be complete without some reference to the cancer clause proviso usually referred to as the Delaney Clause.[22] The clause provides "that no additive shall be deemed to be safe if it is found to

[19] 21 U. S. C. Sec. 348(a)(i).
[20] 21 U. S. C. Sec. 342(a).
[21] 21 U. S. C. Sec. 348(c).
[22] 21 U. S. C. Sec. 348(c)(3)(A).

induce cancer when ingested by man or animals, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals. . . . " While the Food Additives Amendment sought to change the regulatory scheme and move away from one based on proof of absolute safety, cancer, because of its emotional nature, was reserved as an area where absolute safety would still be demanded.

As interpreted by the FDA, this provision permits no latitude for scientific judgment as to the safety of any substance which has been found to induce cancer in any animal, at any dose, ingested for any period of time, and regardless of how extensive human experience may be in support of the safety of the use of the additive. Great controversy preceded the enactment of this proviso and continues even today. From time to time, modification is proposed by one group or another. These movements seldom make significant progress. As long as there are some scientists who believe that no one has data which can serve as a basis for deciding a safe level for a carcinogen, the law will not be changed. Only on the day when the scientific community can agree that no hazard is presented to man by the use in food of an additive which when fed to some test animals in large amounts has produced cancer, will the law be changed.

Tomorrow

I believe that we have now established a brief overview of the regulatory scheme presently being followed in the area of food additives. What of tomorrow?

Consumerists: When considering the future of food additive regulation, the first aspect that comes to mind is the consumer movement.

It is only in recent years that loud voices claiming to represent the consumer are finally being heard. Many people question whether or not the professional consumerists speak with the true voice of the consumer. If an additive producer makes a representation to the FDA, it is demanded that the representation be based on data which are made available to the government and which are subjected to close scrutiny. No such demands are made on professional consumerists. I believe that, in time to come, the government will make such demands. Today, professional consumerism is still in its infancy. Nevertheless, what it lacks in sophistication, it more than makes up in emotionalism and sensationalism. It is difficult to argue with someone who demands the ultimate in protection and refuses to

assume any risk. The government as the regulator must weigh the demand for perfection against the consumers' willingness to sacrifice the particular benefit in question. Reasonable assurances of safety can be given by the scientists without achieving perfection.

In years to come, I expect that we will see vast improvements in the professional consumerists' sector of our society. The same techniques that are currently being used by Madison Avenue to further the interests of producers must surely be adaptable to the determination of basic questions with regard to consumer attitudes to support the position of the consumerists. I only hope that this development occurs in the private sector of our economy and not as another agency of the federal establishment. It seems pointless to me for the same government to fund a regulatory agency that attempts to go forward with affirmative regulatory programs and also fund a second agency whose objective is to take the regulatory agency to court whenever it believes that the interests of the consumer are not being served appropriately. Is not the regulatory agency responsible for the protection of the consumer's interests?

I hope also that the voice of the consumerist will be kept in perspective. But, at the same time, the voice of the scientist should not be permitted to reign supreme.

The Citizens Commission on Science, Law and the Food Supply, in considering the determination of acceptable risk with regard to food and food additives, concluded that, on the subject of government regulation: "Formation of policy decisions should rest upon the assumption that questions of policy are not solely scientific questions but are matters which also must involve societies value judgment."[23] This is important to bear in mind because the scientists obviously do not have all of the answers. And, even if the scientists did have all of the answers, that does not mean that a future society might not elect to assume certain risks for the benefits to be derived. As the report points out, policy decisions must reflect a weighing of the concerns of consumers, producers, scientists and the general public. No one voice must be allowed to get undue consideration.

Another area for future concern is the regulation of GRAS substances. While the law still makes a distinction between those products that are food additives and those that are GRAS, the distinction is becoming more and more illusory as time goes by. The

[23] Citizens Commission on Science, Law and the Food Supply, "A Report On Current Ethical Considerations In The Determination of Acceptable Risk With Regard to Food Additives" (March 25, 1974).

statute contemplated that food additives would be permitted for use under specific regulations whereas GRAS substances would not require any regulations. We have moved to the point where GRAS substances are now being covered in regulations frequently more detailed than had previously existed for food additive uses. When one considers the pattern being followed with regard to GRAS substances, coupled with the FDA's attempt to revoke the old prior sanction letters, it is apparent that, at least in the view of the Agency, the concept of GRAS and the concept of prior sanction both have outlived their usefulness. Philosophically, it is difficult not to agree that there should be one single system for the regulation of food additives. Nevertheless, it is the job of the Congress, not the FDA, to change that system.

New Regulations: Peter Barton Hutt, the FDA's General Counsel in 1972, set forth an extremely liberal philosophy of regulation.[24] He also stated that, "I am not at all certain that the Food and Drug Administration has yet begun to explore the full reaches of existing statutory authority."[25] While Mr. Hutt has since left the Agency, what we can learn from his pronouncements is that the regulation of tomorrow will depend only on the limits of the imagination of tomorrow's regulators. There will be changes in the statute which will add new requirements and grant the Agency additional authority. But, in spite of that, the greatest changes will occur through the implementation of new programs. Regulatory schemes will be devised to accomplish goals believed by the regulators to be worthwhile.

Some of these new regulatory programs will focus on the physical and chemical aspects of food additives. In the past 18 years, we have focused on the safety testing of additives, much of it retrospective. We are getting reasonably well caught up in that task. Tomorrow, we will have to be able to assure not only ourselves and the FDA, but the consumer as well, that the additive we are using is identical in every way to the additive that was subjected to safety testing. Changes in manufacturing procedures can bring about subtle differences in the finished products. Comprehensive and meaningful specifications will be established in order to ensure that minor changes anywhere in the production process do not result in significant changes in the finished product, whether or not such changes are relevant to safety. Increased record keeping by producers and

[24] Hutt, Peter Barton, "Philosophy of Regulation Under the Food, Drug and Cosmetic Act," 28 FOOD DRUG COSMETIC LAW JOURNAL 177 (March 1973).

[25] *Id.*

surveillance by the FDA will be required in order to effect some of these changes.

Conclusion

Throughout this entire discussion, I have attempted to avoid the issue of economics. We started in 1906 with an uncomplicated regulatory scheme and have progressed from there to today's cumbersome regulatory requirements. Certainly the testing and control requirements have multiplied the dollar costs of food additives beyond the wildest dreams of the early regulators. Yes, we have bought increased consumer protection for our dollars and some of us are demanding even more protection. But how much protection have we actually bought? Are we getting our dollar's worth? Because it is our dollar that pays for all the work done. I do not have an answer. Perhaps a retrospective study should be done comparing the incidence of injuries due to the ingestion of food additives over the years to the cost of testing additives at various points in time. It might be interesting to know the extent to which conducting studies on animals, the results of which are not translatable to man, protects the American consumer's well-being. I commend that task to this audience.

[The End]

CITRIC ACID PROPOSED AS INGREDIENT OF CANNED MUSHROOMS

A proposal to allow the use of organic citric acid as an aid in the processing of canned mushrooms when the inside of the container is fully enamel-lined has been issued by the Food and Drug Administration. In 1952, the standard of identity for mushrooms was amended to delete the use of citric acid in canned mushrooms on the ground that the citric acid makes mushrooms appear lighter than normal because of a reaction between the acid and the tinplate present in the mushroom cans. With enamel-lined cans there is no such reaction, so that the mushrooms appear darker than those packed with citric acid in tin cans. Mushrooms packed in enamel-lined cans with the addition of citric acid appear similar in color to mushrooms packed in plain tin cans without the use of citric acid. Comments on the proposal, based on a petition submitted by the Mushroom Processors Association, may be filed until July 2, 1976.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,363

The Role of the Compendia in Establishing Drug Standards

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I. Introduction

FOR THE PAST 150 YEARS in the United States, drug compendia have been compiled for the purpose of assuring drug product standardization and providing specifications limits for identity, quality, purity and potency of drug entities and dosage forms. More recently, the compendia have shown a concern for the development of protocols for assuring the bioequivalency of drug products. It is the intent of this paper to review the historical perspectives of drug standardization in this country and to consider the current state of the art regarding the establishment of specifications and standards to which the drug industry, the Food and Drug Administration (FDA), and the compendia can accommodate. Finally, several major problem areas are referred to, which are receiving the attention of those who are involved in developing drug standards.

II. Historical Perspectives

A. *Prior to 1800.* In the early days of medicine—prior to the 19th century—standardization of drugs was not of major concern. Physicians would give their patients a bark to chew on, leaves from which to make a tea or a mixture or concoction of generally harmless and frequently ineffectual natural products. The patient usually became well, not because of, but rather in spite of, the drugs he was receiving. Very often, however, the drug treatment did relieve the patient of his complaint because of some active component present in the natural product being administered. Since the treatment did not involve a potent active ingredient or a "dangerous" drug, there was little potential for harm from the drug, and the possibility

of an iatrogenic effect was generally remote. Drug standardization prior to 1800 was not at all a pressing problem.

B. *1800—1875.* The first attempt at drug standardization came in 1820 when a group of physicians met in Philadelphia to develop the first book of standards, the USP. The purpose was *not* to develop assays, or limits for impurities or contaminants but rather to establish formulas or recipes for the preparation of dosage forms. These did not include tablets and capsules. In those days, the common dosage forms were the elixir, mixture, tincture and the like—oral liquid medications primarily. The purpose of the compendium was to provide formulas in order to assure standardization of products in terms of taste, appearance and approximate concentration of components so that a particular product prepared in New York would be the same or similar to the product made in Philadelphia or Baltimore. Likewise, a patient taking a particular potion would be assured of receiving the same product every time it was prepared for him. Such formularies and recipe books sprung up throughout the nation during this time period. The USP was nevertheless referred to as the "official" compendium. In 1888, the American Pharmaceutical Association (APhA) published the first National Formulary (NF) which was a collection of recipes and formulas for "unofficial" products or concoctions. Thus we have USP I prepared in 1820 and NF 1 published in 1888—the origins of the current drug compendia.

C. In the latter part of the nineteenth century (1875–1900), we have the inception of the patent medicine market where aniline dyes, natural products, alcohol and opiates were incorporated into nostrums that were touted to be panaceas for virtually every malady from hypertension to urinary infections to impotency. There were no government regulations at that time and complete labeling was not a requirement. Medicines were advertised as all-purpose treatments and contained colored water and one or more of the following components: alcohol; cocaine; opiates; etc. These did produce symptomatic relief from the condition and the patient really did not care about his ailment because of a euphoria and feeling of well-being produced by the concoction he was consuming. At this time, the churchwomen and prohibitionists of the day became concerned because their husbands and relatives were becoming "high" and addicted to the patent medicines they were taking.

D. *Since 1900.* As a result of this situation, a serious, unintentional and widespread addiction problem developed in this country which was even more severe than our persent day drug problem.

In addition, the poor quality and extensive adulteration of drug products at this time moved the United States Congress to pass the Pure Food and Drug Act of 1906 which recognized the USP and the NF as *"official compendia"* and as legal standards for identity, strength, quality and purity of drugs. Also at this time, there was the emergence of the pharmaceutical industry which actually had its birth in Germany in the late 1890's. New dosage forms such as *tablets* and *capsules* appeared on the market for the first time and, in general, standardized dosage forms of all types began to make their appearance on the national and international market. It was thus an appropriate time for legislation to be enacted in order to impose controls and legal standards on all types of medicines made available to the American public. The Pure Food and Drug Act in essence required all drugs and drug products listed in the USP and the NF to conform to the specifications and standards set forth in these texts.

Proof of Safety

As a result of the notorious "sulfanilamide elixir" incident which occurred in October of 1937, it became necessary to revise the Act. In this catastrophe, some 120 infants died as a result of the injudicious use of ethylene glycol (anti-freeze, Prestone) as a vehicle for the water-insoluble sulfa drugs. The 1938 Federal Food, Drug and Cosmetic Act reaffirmed the role of the compendia as legal standards for drugs and drug products and, more importantly, required for the first time *proof of safety* before a drug product could be placed on the market. In addition, it required the disclosure of all active ingredients on the container label.

In 1962, both as a result of the Kefauver investigations into drug industry profits and the thalidomide incident which occurred in Europe, the United States Congress passed the Kefauver-Harris Amendments to the Federal Food, Drug and Cosmetic Act which required that both *safety* and *efficacy* be established before a drug product could become marketable. This has caused the expenditure of huge sums of money in order for a drug product to be marketed. The cost is perhaps over five million dollars and requires five or more years before the product eventually finds its way to the commercial market. The safety of the drug (proof of non-hazard) must be established in three species of animals, one being a primate. Toxic effects are noted after the administration of increasing doses of the drug. This study requires roughly two years. The excretion and metabolism of the drug must be examined. Teratogenicity must be

studied in at least two species of animals over two generations. Again, one must be a primate. After such studies have been successfully completed, the company may then apply for an investigational new drug (IND), which involves three phases of clinical investigations. Then, a new drug application (NDA) may be applied for. The question now being raised is whether or not we have gone too far by imposition of such extensive and rigid regulations by the FDA and whether we are now actually experiencing a "'drug lag." A case in point is that of rifampin, the drug of choice for treating tuberculosis (TB), which was developed in Europe about ten years ago but which was denied access to American practitioners because it had not undergone the extensive clinical testing required for the marketing of drugs in this country. It is presumably an extraordinarily effective drug against resistant TB. Have we properly balanced the benefit-to-risk ratio in the case of other drugs which are available in other countries, but which are not made available here because of overly strict FDA regulations?

III. Current Status of Drug Standardization

A. *Tripartite Structure of Activities.* A drug may be defined as an agent employed in the diagnosis, mitigation, treatment or prevention of disease in man and in other animals. Also included are articles (other than food) intended to affect the structure or any function of the body of man or other animals, articles recognized in the official USP, NF, and Homeopathic Pharmacopeia (HP) or any supplement to any of them, and articles intended for use as a component in any of the articles referred to above. Generally speaking, drugs are chemical compounds and are referred to as *drug entities.* They are not administered to patients as such, but rather are combined as part of a formulation with one or more nontherapeutic agents called excipients, pharmaceutic aids, additives or adjuncts. The final product is a *dosage form* or *drug product.* Typical dosage forms are tablets, capsules, ointments, suppositories, etc. The purpose of the nontherapeutic agent is to provide the active therapeutic agent in a form suitable for administration to a patient with the assurance that the optimum therapeutic effects will result. The specific role of the added agent or agents may be to emulsify, stabilize, suspend, preserve, dilute, solubilize or flavor. If it were not necessary to incorporate the active component in some type of formulation, there would be no problem in assessing "equivalency" or "nonequivalency" of drug products. In comparing dosage forms, one must take into consideration the nature of the other components in the formulation, the

manufacturing procedure used in preparing the formulation and the possibility of interaction between the active constituent and the other components. These factors, and others, may affect the therapeutic efficacy and bioavailability of dosage forms. It is the purpose of the compendia to devise and to evaluate tests and procedures, and to establish specification limits to assure the identity, the quality, the purity, the potency, the efficacy and the safety of drugs and drug products regarded as official.

The marketing of drugs and drug products in the United States is unique in the world in that it involves a tripartite structure of activities which constitutes an effective system of checks and balances on an important aspect of health care delivery in the United States. It is the primary responsibility of the pharmaceutical manufacturer to produce commercially drug products which comply with compendial standards and to adhere to good manufacturing practice (GMP) and quality control procedures. The FDA is administratively an agency of the Department of Health, Education and Welfare (HEW) which is part of the executive branch of government. The FDA's function is that of a regulatory and enforcement agency. Its prime role is to enforce the standards and the specifications set forth in the official compendia. It is noteworthy that the compendia are prepared by a completely private and independent organization. The United States is essentially the only country in the world in which the compendia are under the control of private groups instead of being an instrument of the government. Practically all other pharmacopeias throughout the world are published by an agency of the central government.

Role of the FDA

Unfortunately, over the years there have been several exceptions to the general principle espoused above, and it may be that, in the future, the federal government through the FDA will take an even greater role in establishing drug standards. One such threat was apparent when the APhA and the USPC moved too slowly in arriving at a merger agreement. Other incursions into the realm of the compendia could conceivably occur if the compendia are unable, for example, to develop adequate protocols for controlling bioavailability. Since the turn of the century, the USPHS has supervised production and has set purity and potency standards for all biologicals. This is now a responsibility of the FDA. The FDA, moreover, sets standards and batch certifies most antibiotic preparations. Since 1939, when

the patents on insulin expired, the FDA has batch certified insulin products, although the compendia have been establishing the specifications and the standards for most of these products. There appears to be no sound basis for this dichotomy in standards responsibility. In sum, then, the pharmaceutical and medical professions through private groups prepare and publish the official compendia which contain standards for drugs and drug products. An agency of the government, the FDA, enforces the standards adopted by the official compendia. The pharmaceutical industry produces drug products and combinations of highest quality which must comply with compendial specifications. There are about 1200 major manufacturers of prescription drug products in the United States. Of these, some 125 are members of the Pharmaceutical Manufacturers Association and they market perhaps 95 percent of all prescription drugs on the market.

As a result of the tripartite arrangement, the public and the members of the health professions are assured that only safe and efficacious drug products reach the market. It now appears that with the burgeoning of consumerist activities, a fourth group will be seeking entrance into the drug marketing process, thus expanding it from a tripartite to a fourpartite arrangement.

B. *Current Compendial Specifications.* The major portion of the compendia is devoted to monographs for drugs, dosage forms and nontherapeutic agents. The monographs for drug entities contain standards, specifications and other pertinent data concerning the particular entity. These include the generic name, structural and chemical formulas and the chemical name where applicable, definition, description, composition, tests for identity, limits tests for impurities, assay for the active constituent, potency requirement or purity rubric, special precautions for handling, pharmacologic category or use, dosage and dispensing information, and packaging and storage requirements. Of particular import are those specifications which are intended for the establishment of the *identity, purity, strength* and *quality* of the drug entity.

For *identification* of the drug, there are one or more simple tests which are not intended to characterize the compound, but rather to confirm its identity. These may include color reactions, flame tests, spot tests and precipitation reactions. More and more identification tests today are based on chromatographic techniques, infrared and ultraviolet absorption spectral comparisons. Tests in other cate-

gories within the monograph may also serve to establish and to confirm the identity of the drug entity.

Purity tests are included in the monograph to establish limits for numerous impurities which may be present from a variety of sources. These may be of a general nature (heavy metals, halide ions) or they may be for specific impurities (water, sulfate, selenium). Limits tests are generally included for contaminants which may be intermediates or by-products resulting from the synthesis of the drug such as p-chloroacetanilide in phenacetin, morphine in codeine, and trifluoroethanol in flurothyl. Tests are also included for impurities which may result from the breakdown of the molecule, for example, p-aminophenol in acetaminophen, m-aminophenol in p-aminosalicylic acid, or adrenalone in epinephrine.

Assay Procedure

Essentially every drug monograph has an *assay* procedure for the quantitative determination of the strength or the potency of the entity. It is manifestly essential that the assay procedure be specific and selective in the presence of impurities arising from the decomposition of the drug or possible contaminants occurring through its preparation or synthesis. Also imperative is that the assay procedure be stability-indicating.

Tests for controlling *quality* of the drug product may overlap with one or more of the categories referred to above. Nevertheless, these include melting range, boiling range, specific rotation, refractive index, infrared, ultraviolet and NMR spectral analyses, and other tests involving physical measurements.

Monographs for Dosage Forms

Monographs for dosage forms differ somewhat from those for the drug entity. Since, generally, all ingredients indicated for each dosage form are listed in separate monographs and since adequate standards and specifications are included there, only those tests and specifications are included in the dosage form monograph which pertain to the performance of the dosage form and are not otherwise included in the individual drug monograph. Usually, one or two identification tests for the active constituent are required, appropriately modified to take into account possible interference from excipients or other constituents which may be present in the dosage form. An assay is required more as a quality control check on the manu-

facturing procedure than for assessing the purity of the active constituent. For example, in the monograph for epinephrine, there are limits tests and specifications for adrenalone and levarterenol in addition to the assay. But, in the monographs for Epinephrine Inhalation, Epinephrine Injection, Epinephrine Nasal Solution, etc., only the assay procedure is given. The active constituent epinephrine must of course meet all of the specifications indicated under its monograph. Otherwise, it is considered adulterated.

A tablet dosage form may assay acceptably between 90 and 100 percent recovery of active constituent, while the purity rubric for the drug substance may require a purity of better than 99 percent recovery.

The assay procedure for the dosage form must be specific and stability-indicating for the drug entity in the presence of contaminants, decomposition products and excipients and additives used in the formulation of the dosage form. As a rule, the compendia specify a preliminary isolation or extraction procedure for separation of the active constituent from the other components of the dosage form.

Weight Variation

For certain classes of dosage forms—for example, tablets and capsules—the monographs include a weight variation or a content uniformity test which controls dosage form homogeneity. A variety of other tests are designed to control the suitability of the dosage form for administration to patients. These may include sterility testing, tablet disintegration time and dissolution rate test, pH, particulate matter (ophthalmic ointments), acid-consuming capacity (antacid preparations) and others. Forms and sizes of dosage forms commonly available from commercial sources are generally included in these monographs.

Standards pertaining to packaging, storage and labeling are provided. These are particularly important to the community and hospital pharmacist.

IV. Several Problem Areas in the Development of Dosage Form Specifications

A. *Bioavailability Standards and Dissolution Testing.* Perhaps the most important problem facing the compendia today is the development of protocols and standards for controlling the bioavailability of dosage forms. As noted earlier, the current editions of the official compendia provide standards and specifications pertaining to the

identity, the purity, the quality and the potency of drugs and their dosage forms, thus assuring the assessment of *chemical equivalency* of drug products. The Second Interim Report of the HEW Task Force on Prescription Drugs[1] has attempted to resolve the confusion resulting from the term *"generic equivalent"* and the report has redefined the designation in terms of chemical equivalents, biological equivalents and clinical equivalents. These definitions are summarized here:

(1) *Chemical equivalents* are identical dosage forms which contain identical active ingredients in essentially identical amounts and which meet the physical and chemical standards in the official compendia.

(2) *Biological equivalents* are chemical equivalents which produce the same biological or physiological availability when administered in the same amounts as measured by blood, serum or plasma levels, or from urinary excretion data.

(3) *Clinical equivalents* are chemical equivalents which provide essentially the same therapeutic effect when administered in the same quantities to patients suffering from the condition or disease for which the drug is intended.

It is generally accepted by pharmaceutical and medical scientists that compliance with compendial standards assures chemical equivalency and not necessarily biological equivalency and clinical or therapeutic equivalency. While it has been stated by some that the establishment of chemical equivalency is presumptive evidence of biological and clinical equivalency, this is by no means a generally accepted thesis. Others will argue that just because products ***do*** meet the chemical and physical standards of the compendia, this does not mean that the products are necessarily therapeutically equivalent. This question has not as yet been resolved.

As many as two dozen factors have been implicated as having an effect on the physiological or biological availability of the active constituent in drug products, thereby influencing the therapeutic activity of the dosage form and rendering unpredictable the course of treatment of a disease and possibly constituting an incidence of therapeutic nonequivalency. Many, if not most, of these factors are presently controlled by appropriate standards and specifications already established by the compendia. Several are rapidly reaching the state

[1] Second Interim Report and Recommendation, Task Force on Prescription Drugs, HEW, Washington, D. C. (Aug. 30, 1968).

where adequate specifications are being developed and will be under effective control. Examples are particle size and polymorphism, both of which are important factors in controlling bioavailability.

Such factors as isomeric form, disintegration time, chemical form and degree of hydration, to mention but several, are controlled adequately to the point where meaningful and enforceable specifications have been developed for those products where a problem may possibly exist.

Manufacturing and Formulation Factors

Manufacturing and formulation factors represent a more complicated problem since the details concerning these factors are in the realm of "trade secrets." Whether specifications for controlling formulation factors and manufacturing processes should come under the purview of the compendia is a subject for debate and beyond the scope of this paper. Of major concern are compressed tablets which are the most widely used of all dosage forms, and which offer the most problems with respect to bioavailability of the active component. This is particularly true where the drug has a high dose, low solubility, low dissolution rate, is unstable in the gastrointestinal media and is poorly absorbed. Other classes of dosage forms, including solutions, suspensions, emulsions, and capsules, may also demonstrate manufacturing and formulation factors which possibly could alter the bioavailability of the active therapeutic agent and contribute to the nonequivalency of drug products. It should be emphasized that the compendia provide standards and tests primarily for finished drug products and for the ingredients used in their preparation. Protocols and specifications for manufacturing and formulation procedures, as well as quality control assurance, come under the aegis of the FDA and, to an extent, are left to the integrity of the manufacturer. The FDA feels that most, if not all, of the problems related to drug quality can be solved by compliance with the minimum requirements of the current GMP regulations which were first promulgated in 1963 as one of the important provisions of the Kefauver-Harris Drug Amendments of 1962. Proposed revisions by the FDA to the current GMP regulations are expected to become effective in mid-1977. In summary, at the present time the official compendia do not include specifications and standards for controlling factors related to formulation and manufacturing procedures.

Drugs Taken Orally

The therapeutic activity of most drugs which are taken orally depends on the drug first dissolving in the gastrointestinal fluid to a sufficient extent. Once in solution, the drug must then be absorbed into the blood stream before its intended therapeutic effect can be realized. It is generally agreed that the tablet disintegration test is not suitable as a meaningful procedure for evaluating bioavailability of active constituents from solid dosage forms. The official dissolution rate specification is an alternative *in vitro* procedure to the tablet disintegration test for assessing bioavailability. Although *in vitro* testing may not always correlate with *in vivo* bioavailability results, dissolution testing is a useful technique for controlling formulation variables involved in the manufacturing process. The dissolution test was included in 12 tablet dosage forms and one capsule dosage form in USP XVIII and NF XIII. The current compendia include an additional four tablet dosage forms and two capsule dosage forms, among them being Digoxin Tablets, Ergotamine Tartrate and Caffeine Tablets, Digitoxin Tablets, and Methaqualone Capsules. The USP Executive Committee of Revision recently approved a "Policy Statement on Dissolution Requirements" whereby the Committee favors the inclusion of a dissolution test in all official oral solid dosage forms except where such a test may be considered inappropriate. It is emphasized in the Statement, however, that the test requirements are established primarily to assure control of manufacturing and formulation factors; and as more data become available, ultimately bioavailability will be assured. But, at this time, it is being advocated more as a quality control measure than for providing specifications for bioavailability assessment. The latter will follow as correlative data between *in vivo* and *in vitro* behavior become available.

B. *Stability-Indicating Assays.* Assay procedures are an important aspect of every monograph whether it is for a drug entity or one of its dosage forms. Several characteristics of a useful assay procedure are noted here. First, the assay must be *accurate*. Accuracy is defined simply as the extent of deviation of a particular measurement from the true value. Secondly, the assay must be *precise*. Precision is a measure of the reproducibility or reliability of a measurement. Methods of analysis applied in drug assay must assure that reproducible results will be obtained in any laboratory by competent analysts and must be equally applicable to all manufacturers' samples of the drug product. The assay procedure must be precise and

capable of maximum accuracy reflective of each step invoved in the assay procedure. Thirdly, Banes[2] uses the term "ruggedness" which he defines as the effect of slight variations in experimental conditions (temperature, humidity, etc.) on the results of an assay. Methods which are not rugged are usually imprecise and inaccurate. Accuracy, precision and ruggedness of an analytical procedure are best evaluated by means of interlaboratory collaborative studies. Fourthly, a *stability-indicating* assay is a procedure which is specific and is capable of determining exclusively the quantity of a desired active constituent or intact drug molecule in the presence of predictable contaminants which may include synthetic by-products and intermediates, process contaminants, decomposition products and, in the case of dosage forms, excipients and additives which may be present as a result of the manufacturing process. Preliminary treatment of the sample for analysis utilizing conventional isolation and extraction techniques is generally applied in order to eliminate the presence of these potentially interfering substances. The ability to isolate quantitatively the active component in pure form is a significant factor in evaluating the specificity of an analytical procedure. In rare instances, an analytical procedure may be sufficiently specific to permit analysis for a constituent without requiring the pretreatment of the sample. Chafetz[3] recently presented a comprehensive review on the subject of stability-indicating assay procedures for drugs and drug products. He defines such an assay as one which permits the selective determination of a drug substance in the presence of its decomposition and reaction products. Several approaches are presented for devising stability-indicating assay methods. These include:

(1) the estimation of the intact drug molecule by a highly selective procedure;

(2) the measurement nonselectively of the total drug content and estimation of the degradation products; or

(3) the selective measurement of both the intact drug and its decomposition products.

While the third alternative may appear to be the most desirable, Chafetz suggests that it may be neither possible nor practical.

[2] Banes, D., "A Chemist's Guide to Regulatory Drug Analysis," Association of Official Analytical Chemists, Washington, D. C. (1974).

[3] Chafetz, L., *J. Pharm. Sci.* 60, 335 (1971).

C. *Assays for Combination Drug Dosage Forms.* In previously official compendia, combination drug dosage forms were restricted to such combinations as vitamin mixtures, electrolyte solutions, a triple sulfonamide combination, combinations of local anesthetics with epinephrine, several oral contraceptive combinations and possibly one or two other combination drug dosage forms. In the present USP and NF, the number of such combinations has increased substantially and will undoubtedly expand further in subsequent revisions and supplements to the compendia. Many dosage forms containing complex mixtures are on the market both as prescription items and as over-the-counter products. Although the mixture may not be official *per se,* the individual components generally are recognized by an official monograph. The task of designing suitable assay procedures for such complex dosage forms may represent a monumental undertaking since not only are multiple active constituents involved, but they may be present in widely divergent concentrations depending on their relative potency as well as other factors. In addition, the presence of additives, excipients, etc. further complicates the analytical procedure. Nevertheless, the therapeutic advantage of such combinations takes precedence over any potential analytical complications and becomes the concern of the analyst. The first step in such an assay is generally a separation procedure for quantitatively isolating the active constituents of the mixtures. This is followed by the estimation of each individual component. Chromatographic procedures are ideally suited for the separation step, and usual analytical techniques can be applied for estimating the isolated constituents. Occasionally, a differentiating technique can be developed for determining the individual components without a preliminary extraction procedure. An example of this would be nonaqueous differentiating potentiometry. The development of simple, yet sensitive methods for analyzing complex dosage forms is a true challenge of the skill and ingenuity of the analyst. **[The End]**

How to Export Fishery Products to the United States

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Introduction

THE ROLE OF IMPORTED FISH AND FISHERY PRODUCTS as they contribute to the United States supply of edible products for human consumption is a very important one. To illustrate the level of importance, in 1974, approximately 4.1 billion pounds of edible fishery products (round weight basis) were imported. This constituted 63.2 percent of the total United States supply of edible fishery products.

Imports of fish and fishery products to the United States come from 110 to 120 different countries. The variety of imported fishery products are many. They range from extremely large amounts of raw materials such as fish blocks, frozen tuna and shrimp for further processing into end products, to other finished packaged products of all types, such as canned, smoked, cured, fresh, frozen, dried or otherwise processed. The United States is extremely interested in maintaining a continuing supply of these important products to its consumers.

Need for Import Surveillance

All governments today accept the principle that measures designed to protect public health and safety and consumer welfare, applying to both domestic products and imports, are both necessary and desirable, although international trade is almost certain to be affected by any regulation of imports.

In order to facilitate the growing volume of international trade in food, including seafoods, it is important that health and sanitary requirements be drawn up and administered in such a way that they do not impose unnecessary burdens on imports. The United States has taken the lead in opposing arbitrary or discriminatory import regulations by any country. The United States fully subscribes to and supports in practice the General Agreement on Tariffs and Trade (GATT) principle that health and sanitary requirements not be used to restrict international trade. The United States has played a leading role in international forums, such as Codex Alimentarius, to foster uniform international practices to facilitate increased trade.

The intent of United States inspection, sanitary and health requirements is to ensure that products from abroad are free from dangerous diseases and pests, and that they conform to the same standards of wholesomeness, sanitation and labeling as are required of domestic products. These standards are often revised to ensure maximum protection to the ultimate consumer.

Cost of Import Rejections and Health and Sanitary Measures

Losses resulting from rejected imports of all types of fish and fishery products amount to millions of dollars annually to exporters. Further, detentions and rejections greatly increase the cost of surveillance by the United States Government. For example, during a 31-month period from January 1972 through July 1974, United States import detentions of various fish and fishery products from countries of Southeast Asia amounted to several million pounds of product valued at over 21 million dollars.

These detentions were due primarily to product decomposition, contamination with microorganisms, insects or filth, and other miscellaneous reasons. A breakdown of the principle reasons for retention and the related value of the products follows:

	1972	1973	1974 (7 months only)	Grand Totals
Decomposition	$1,026,900	$1,398,500	$2,655,400	$5,080,000
Contamination (Hygienic reasons)	424,400	3,456,600	7,043,400	10,924,400
Others	577,800	3,480,700	1,017,500	5,076,000

These examples are illustrative. Comparable losses often occur on imports from other areas. A substantial portion of the Southeast Asian product detentions mentioned above could have been avoided if adequate inspection procedures had been available at plant and

governmental levels in the countries of origin. Detentions and rejections of this type can be reduced or eliminated by better understanding and cooperation between the United States and the exporting country involved.

Procedures for reprocessing and/or sterilization available at United States ports of entry can help to reduce some losses. Illustrated in the Appendix[1] is a flow diagram of the procedural steps through which imports may proceed at U. S. ports of entry.

Current Laws and Regulations

The primary mandatory requirements applicable to fish and fishery products imported into the United States are those contained in the Federal Food, Drug and Cosmetic Act, as amended. All fish and fishery products imported into the United States are subject to compliance with the requirements of the Act in the same manner as are the domestically produced fish and fishery products. Under the Act, there are regulations pertaining to a variety of subject matter topics, as follows:

(1) adulteration;
(2) misbranding;
(3) labeling requirements;
(4) definitions and standards of identity;
(5) tolerances for poisonous and deleterious substances;
(6) pesticides residues on agricultural commodities;
(7) food additives;
(8) good manufacturing practices (GMPs);
(9) defect action levels.

The significant aspects of the regulations relating to these topics as they apply to fish and fishery products are the same as those applied to other imported food products except meat and poultry products which are covered by other somewhat similar regulations set forth by the United States Department of Agriculture.

Regulatory requirements relating to several topic areas, such as labeling, pesticides, food additives, GMPs and defect action levels, merit further detailed explanation.

Required label information must not only be conspicuously displayed but it must also be in terms that the ordinary consumer is

[1] Appendix is on page 304.

likely to read and understand under ordinary conditions of purchase and use.

Details concerning type sizes, location, etc., for required label information are contained in the Food and Drug Administration (FDA) regulations, which cover the requirements of both the Federal Food, Drug and Cosmetic Act and the Fair Packaging and Labeling Act. Food labeling requirements of the regulations are summarized below.

If the label of a food bears representations in a foreign language, the label must bear all the required statements in the foreign language, as well as in English. (Note: The Tariff Act of 1930 requires all imported articles to be marked with the English name of the country of origin.)

The following statements must appear on the label in the English language:

(1) If the food is packed, the name, street address, city, state and zip code of either the manufacturer, packer or distributor, and an accurate statement of the net amount of food in the package must be listed. The street address may be omitted by a firm listed in a current city or telephone directory. A firm whose address is outside the United States may omit the zip code. The basic units of measure are the avoirdupois pound and the United States gallon.

(A) If the food is not manufactured by the person or company whose name appears on the label, the name must be qualified by "manufactured for," "distributed by" or a similar expression.

(B) The quantity of contents declaration must appear on the principal display panel of the label in lines generally parallel to the base of the package when displayed for sale. If the area of the principal display panel of the package is larger than five square inches, the quantity of contents must appear within the lower 30 percent of the label. The declaration must be in a type size based upon the area of the principal display panel of the package and must be separated from other printed information on the package.

Net Weight Statement

The net weight on packages containing one pound (avoirdupois) or more but less than four pounds must be declared first in total avoirdupois ounces, followed by a second statement in parenthesis in terms of pounds and ounces, or pounds and common or decimal fractions of the pound. (Example: net weight 24 ounces (1½ pounds)

or net weight 24 ounces (1.5 pounds).) The contents of packages containing less than one pound must be expressed as total ounces. For example, three-fourths pound must be expressed as net weight 12 ounces.

Net volume on packages containing one pint or more and less than one United States gallon must be declared first in total fluid ounces or fractions of the pint or quart. (Example: 40 fluid ounces (1.25 quarts) or 40 fluid ounces (1¼ quarts).) Volume of packages containing less than one pint must be declared in fluid ounces.

Packages four pounds or larger or one gallon or larger need not have their contents expressed in terms of total ounces. However, for such packages, the contents must be stated in the largest unit of weight or measure, with any remainder in ounces or common or decimal fractions of the pound. In the case of gallons, the remainder must be in quarts, pints and fluid ounces, or decimal fractions of the gallon. The metric system of weight or measure may also be used to declare the quantity, in addition to the English system. If the label of any food package also represents the contents of the number of servings, the size of each serving must be indicated.

Common or Usual Name

(2) The common or usual name of nonstandardized food or, in the case of standardized foods, the complete name as designated in the Standard of Identity, must appear on the principal display panel, in bold type and in lines generally parallel to the base of the package as it is displayed. The form of presentation of the product also must be included unless depicted by vignette or unless the product is visible through the container.

To prevent substitution of one kind of seafood for another, it is essential that labels bear names which accurately identify the products designated. Labels of seafoods must bear the common or usual name of the food, if there is one. Words like "fish," "shellfish" or "mollusc" are not sufficient. The name of the specific seafood must be used. Many fish, crustaceans and molluscs have well-established common or usual names throughout the United States (for example, "pollock," "cod," "shrimp" and "oysters"). These may not be replaced with other names even though the other names may have limited local usage in some areas. Neither may they be replaced with coined names, even though the coined name may be considered more attractive or to have greater sales appeal.

The fact that a proposed designation is used in a foreign country, or is the translation of such a name, does not justify its use if it conflicts with the common or usual name in the United States or some other species, or it otherwise is misleading.

(3) The ingredients in a food must be listed by their common names in order of their predominance by weight unless the food is standardized. In that case, the label must include only those ingredients which the regulation requires to be declared. The word "ingredients" does not refer to the chemical composition but means the individual food components of a mixed food. Spices, flavors and colors may be listed as such, without naming the specific material. If the presence of a specific expensive ingredient is promoted, additional information such as the percent of the expensive ingredient may be required.

Packing Medium

Failure to declare the presence of added salt or the kinds of oil used as the packing medium in canned fish has resulted in detention of fish products. If permitted artificial colors or chemical preservatives are used, their presence must be conspicuously declared in the labeling. Artificial coloring is not permitted if it conceals damage or inferiority or if it makes the product appear better or of greater value than it is.

The packing of canned fish and fish products with excessive amounts of packing medium has resulted in detentions. Where the fish are in a packing medium such as anchovies in oil, the container should be as full as possible of fish with the minimum amount of oil.

(4) The labeling of food intended for special dietary uses must bear certain prescribed additional information concerning vitamin, mineral and other dietary properties which is necessary to inform purchasers fully as to the food's value for such uses. Regulations that have been issued under this section prescribe the specific additional mandatory label information.

(5) Foods must bear labeling stating the presence of any artificial flavoring, artificial coloring or chemical preservative.

(6) Imitations must be labeled as such.

Pesticide Residues and Tolerances for Poisonous Ingredients in Food

Raw agricultural products containing pesticide residues are in violation of the Federal Food, Drug and Cosmetic Act unless:

(1) The pesticide chemical has been exempted from the requirement of a tolerance; or

(2) A tolerance has been established for the particular pesticide on the specific food and the residue does not exceed the established tolerance.

"Raw agricultural product" means any food in its raw or natural state, including fishery products and all unprocessed fruits, vegetables and grains.

Products which contain any poisonous or deleterious substance added to any food are in violation of the Federal Food, Drug and Cosmetic Act unless:

(1) Such substance is required in the production of the food or cannot be avoided by GMP;

(2) A tolerance has been established for the particular poison in a particular food and the residual amount does not exceed the established tolerance.

Tolerances for pesticidal residues and contaminants have been established under the law for various products. Tolerances are established, revoked or changed as the facts warrant such action. Firms considering offering entry into the United States of fishery products which may contain pesticidal residues or contaminants should write to the U. S. FDA for current information concerning the status of tolerances for residues and/or contaminants for the products in question.

In the regulation of pesticide residues or contaminants, the amount or level of a pesticide residue or contaminant is classified as to status, that is, tolerance, guideline or action level depending upon the details of a particular situation at any given time. Further explanation of the classifications follow.

Tolerance:

is established by law;
is published in the *Federal Register;*
potential adherents have an opportunity for comment;
compliance and burden of proof rests with the manufacturer.

Guideline:

is set where no tolerance has been established;
informal but enforceable administrative action can be taken before regulations are established;
publication in the *Federal Register* is optional;
compliance rests with the manufacturer with the burden of proof on regulatory agency.

Action level:

level at which regulatory agency would consider taking action.

For fish and fishery products the current situation relative to pesticides or contaminants follows:

Contaminant or Pesticide	Product	Level	Status
Mercury	Fish and shellfish	0.5 ppm	Guideline
PCB	Raw fish	5.0 ppm	Tolerance
PCB	Fishmeal and oil	2.0 ppm	Tolerance
DDT	Raw fish—edible portion	5.0 ppm	Tolerance
Dieldrin	Oil of fish	0.30 ppm	Action level

The question of pesticide residues and contaminants in food—both raw and processed—is related to public health measures in developing countries. It is also related to techniques of industrial production as experience during the past few years with polychlorinated biphenyls (PCB) indicates.

One of the most effective insecticides in the eradication of malaria is DDT which leaves a potentially harmful residue in meat and meat by-products and other foods. Direct application to crops increases dangers of human and plant intake and water supply pollution. Run-off water carries DDT into streams, rivers and lakes resulting in uptake by fish. However, an economical and effective substitute has not been developed as yet, and many countries still rely on DDT for insect control programs. The problem of DDT residue has assumed an international dimension since ocean fish have shown traces of the chemical.

Food Additives

"Food additives" are substances which may by their intended uses become components of food, either directly or indirectly, or which may otherwise affect the characteristics of the food. Such additives may enhance flavor, stabilize, thicken, neutralize, alter acidity or alkalinity, retain moisture or increase volume and smoothness. The term specifically includes any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding the food, and any source of radiation intended for any such use.

But the law excludes from the definition of a "food additive":

(1) substances generally recognized as safe by qualified experts;

(2) substances used in accordance with previous approval ("prior sanction") under the Federal Food, Drug and Cosmetic Act, and other laws;

(3) pesticide chemicals in or on raw agricultural products;

(4) a color additive.

Manufacturers or importers not certain whether the chemicals or other ingredients used in their foods are subject to the safety clearance requirements of the food additives amendment may seek an opinion regarding the status of the material intended for use.

Food Manufacture Practices

Processed foods for export to the United States are required to be manufactured under a system, including physical plants and controls, equal to that in the United States.

Equality involves similarity in such matters as legislation, personnel, and procedures to combat particulate and bacterial contamination over a range of activities including processing, storage, handling and distribution as well as other operating practices within the plant. The United States regulations provide for the rejection of articles of food which contain "filth." The term can be widely interpreted to embrace any substance regardless of whether such substance can be detected by laboratory procedures. This is an area of potential conflict between the inspector and the plant technician.

Many countries are now in the process of establishing systems for food manufacture. In view of this, it is advisable for them to gear their systems to international requirements through which access to several markets could be assured. Advisory international recommendations relating to food hygiene are now available in published form entitled, "Recommended International Code of Practice—General Principles of Food Hygiene."

United States regulations pertaining to GMPs (sanitation) are very similar to the international advisory recommendations.

Defect Action Levels

Food defect action levels for natural or unavoidable defects in food for human use are set in the United States on the basis of no hazard to health. Any products that might be harmful to consumers are acted against on the basis of their hazard to health, whether or not they exceed the action levels.

In addition, poor manufacturing practices by a manufacturer will result in regulatory action, whether the product is above or below the defect level.

The action levels are set because it is not now possible, and never has been possible, to harvest and process foods, including fishery products, that are totally free of natural defects.

The alternative to establishing natural defect levels in some foods is to insist on increased utilization of chemical substances to control insects, rodents and other natural contaminants. This alternative is not satisfactory because of the very real danger of exposing consumers to potential hazards from residues of these chemicals, as opposed to the aesthetically unpleasant, but harmless, natural and unavoidable defects.

Legal Action

The fact that a defect level has been established does not mean that a manufacturer need only stay below that level. The action levels do not represent an average of the defects that occur in any of the food categories. The averages are actually much lower. The levels represent the limit at or above which the FDA will take legal action against the product to remove it from the market.

Two key points regarding defect action levels merit emphasis.

(A) Compliance with defect levels will not prevent the FDA from acting against a manufacturer who does not observe current GMPs. Insanitary plant conditions, for example, are a violation of GMPs and render the food unlawful. This applies even though the defect levels may be below the FDA's action level.

(B) The mixing of a food containing any amount of defect at or above the current defect level with another lot of the same or another food is not permitted and renders the final food unlawful regardless of the defect level of the finished food.

The current defect action levels for fish and shellfish in the United States follow:

Blue fin and other fresh water herring	*Fish averaging 1 lb. or less:* 60 cysts per 100 fish provided that 20% of the fish examined are affected. *Fish averaging over 1 lb.:* 60 cysts per 100 lbs. of fish, provided that 20% of the fish examined are affected.

Rose fish (red fish and ocean perch)	3% by count of the fillets examined contain one copepod.
Fresh and frozen fish (definition of classes of decomposition)	(1) 5% by count of fish or fillets in sample (but not less than 5) show class 3 decomposition over 25% of their areas;
	or
(1) no odor of decomposition	(2) 20% of the fish or fillets in the sample (but not less than 5) show class 2 decomposition over 25% of their areas;
	or
(2) slight odor of decomposition	(3) The percentage of fish or fillets showing class 2 decomposition as above plus 4 times the percentage of those showing class 3 decomposition as above equals at least 20%, and there are 5 decomposed fish or fillets in the sample.
(3) definite odor of decomposition	
Fresh and frozen fish, as listed: tullibees, ciscoes, inconnus, chubs and white fish	50 cysts per 100 pounds (whole fish or fillets) provided that 20% of fish examined are infested.

Enforcement Procedures

In its enforcement operations in the United States, the FDA gauges the levels of practical and reasonable compliance by the principles of what are or are not GMP. Enforcement activities are carried out on a selective basis. Products which represent a safety or health hazard to the public are given first priority. Second priority is given to products which are decomposed, filthy or produced in an unsanitary environment, but which do not constitute a hazard to the health or safety of the public. The remaining effort is devoted to deceptive practices or the so-called economic class of violations.

Factory inspections and laboratory analysis of samples are the major means employed by the FDA in conducting its enforcement activities. While the requirements are the same both for products manufactured in the United States and for those imported, the enforcement procedures are different. Within the United States, enforcement is maintained through inspections of food-producing plants,

through the collection and analysis of samples collected at various stages of the production process, and by legal actions brought against foods found to be not in compliance.

Authority does not exist for the FDA to conduct food plant inspections in other countries. Therefore, imported foods must be examined when they are offered for entry into the United States. Foods that do not comply with the regulations are subject to reexportation or destruction. In many instances, an importer may be permitted to try to recondition an unacceptable shipment before a final decision is made. This is not a right, but a privilege which may be withdrawn in cases of repeated or flagrant failure to comply with the provisions of the Federal Food, Drug and Cosmetic Act.

Sanitary Control of Shellfish for Prevention and Control of Diseases

Because raw shellfish, such as oysters, clams and mussels, may transmit intestinal diseases such as typhoid fever, it is important that they be grown in unpolluted waters and produced, handled and distributed under sanitary conditions. Shellfish must conform to the general requirements of the Federal Food, Drug and Cosmetic Act but, in the importation of shellfish into the United States, consideration must be given also to the requirements of the states to which the shellfish are destined, if they are to be accepted under the respective state laws.

The Public Health Service Act of 1944 provides authorization for assistance to states and local municipalities in the development, conduct and maintenance of effective programs for the prevention and control of diseases which may be transmitted through shellfish, that is, all edible species of oysters, clams or mussels either shucked or in the shell, fresh or frozen.

Shellfish are not ordinarily accepted by the states since objective analysis in the absence of known growing water quality is not adequate to guarantee the safety of these shellfish. That is, there is no feasible analytical procedure for detecting the broad spectrum of potential chemical, bacteriological or virological contaminants common to shellfish from estuarine areas subject to pollution. Recognizing that estuarine pollution is almost universal and that shellfish analysis is neither reliable nor indicative of an unsampled portion's quality, the United States has sought to assure, for over 50 years, safe shellfish through stringent application of sanitary controls at the growing area rather than at the market level only. Growing area

control and safety are of paramount importance, all other considerations adjunctive.

Federal-State-Industry Program

Such controls have been applied through a cooperative Federal-State-Industry program to ensure safe growing waters, prevent harvesting from unsafe areas and prohibit the sale of all shellfish not produced and certified under the auspices and the standards of this program. Accordingly, shellfish from a nonparticipating country are summarily rejected by the states even though they may be passed through customs under the Federal Food, Drug and Cosmetic Act.

For an importer to gain acceptance of imported shellfish by the various states within the United States, such shellfish must not only meet the sanitary requirements of both federal and state laws, but the country-of-origin must be a participant in the national program. This requires a shellfish treaty or agreement between the United States and the country desiring to participate.

Three foreign countries—Canada, Japan and South Korea—subscribe to this program for the sanitary control of raw shellfish. These countries accept responsibilities similar to those of the individual states and carry out similar procedures for sanitary control of shellfish designated for export to the United States. Government agreements exist wherein the responsibilities of the cooperating countries are described in detail. While trade with the United States in these commodities—fresh or frozen shellfish—does not depend upon the establishment of agreements, it should be noted that many of the individual states which themselves subscribe to the program prohibit the sale of raw shellfish from noncertified sources within the United States or a foreign country.

Certain shellfish, particularly clams, may contain a toxic substance—gonyaulax catenella—derived from a plankton organism upon which the shellfish feed. Such toxic shellfish may cause illness or even death. The sources of supply of shellfish intended for shipment to the United States should be periodically tested for the presence of gonyaulax.

Disease Control of Salmon

In addition to the mandatory requirements of the Federal Food, Drug and Cosmetic Act for importation of fish and fishery products, there are also United States regulations which require that fish of the salmonidae family be certified free from viral hemorrhagic septi-

cemia and whirling disease before they are imported into the United States. The provisions of these regulations require that all live or dead fish or eggs of salmonids of the fish family salmonidae are prohibited entry into the United States for any purpose unless such inportations are by direct shipment accompanied by a certification that the importation is free of the protozoan *myxosoma cerebral* (whirling disease) and the virus-causing viral hemorrhagic septicemia (egtved disease).

The certification must be signed in the country-of-origin by a designated official acceptable to the Secretary of the Interior as being qualified in fish pathology or in the United States by a qualified fish pathologist designated for this purpose by the Secretary of the Interior. This restriction, however, does not apply to salmonid fish or eggs that have been processed by canning, pickling, smoking or otherwise prepared in a manner whereby the spores *myxosoma cerebralis* and the virus-causing viral hemorrhagic septicemia have been killed. Fish so prepared are not required to be accompanied by a disease certificate.

Marine Mammal Protection Act

Effective December 21, 1972, the Marine Mammal Protection Act of 1972 imposed (subject to certain limited exceptions) a complete ban on the importation into the United States of marine mammals and marine mammal products. The act also prohibits the importation of fish caught with techniques which result in the incidental killing of marine mammals in excess of standards set for United States fishermen. Exceptions may be made on the basis of economic hardship and for scientific and display purposes in certain limited instances as may be specifically authorized.

Voluntary Standards Pertaining to Fish and Shellfish

Under the provisions of the Agricultural Marketing Act of 1946, the National Marine Fisheries Service of the Department of Commerce operates programs relating to the development and improvement of fishery standards of quality, quantity, condition, grade and packaging, and issues federal regulations setting forth such standards. The standards are voluntary and not mandatory in the usual sense that they world be applicable to imported fish and fishery products. These voluntary standards generally provide for quality gradations or grades that are established and are usually designated Grade A, B or C. These grade designations are not required on imported products nor are they required under the provisions of the Federal

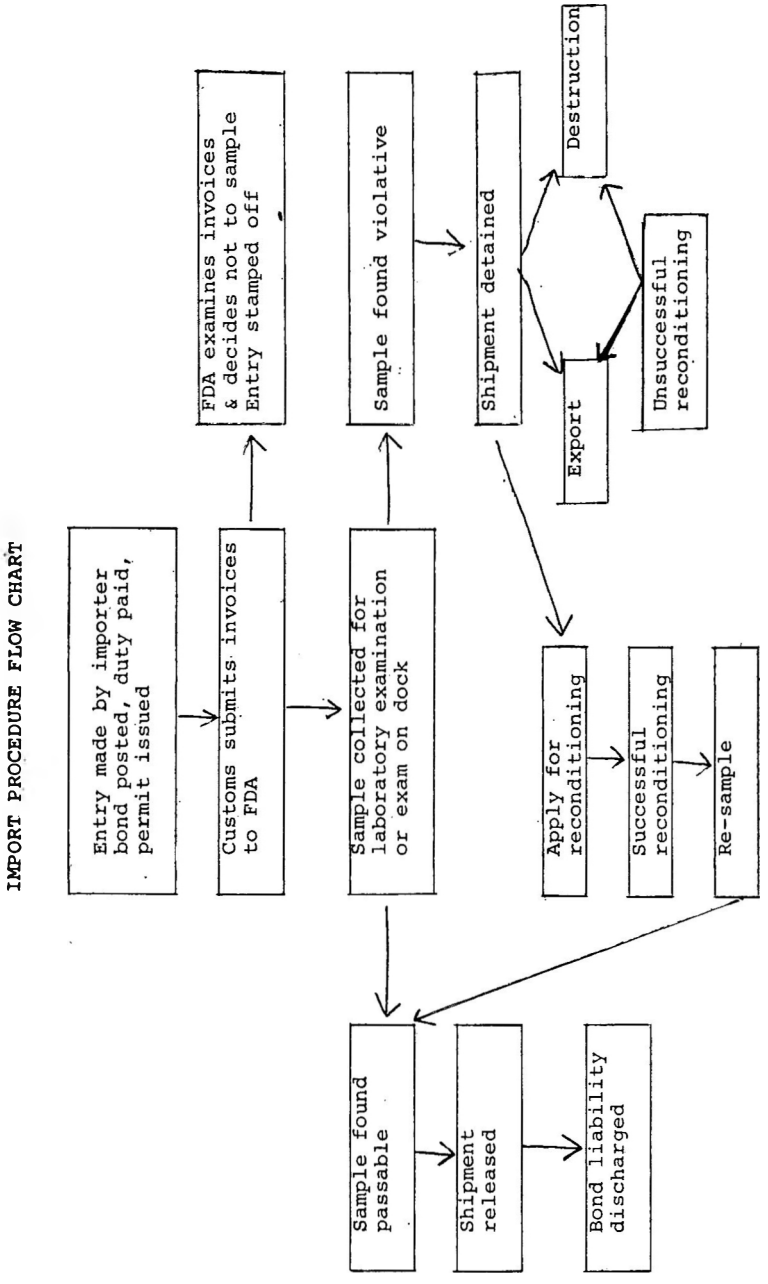
Food, Drug and Cosmetic Act to be stated on the labels. However, if stated, the imported product then must comply with the specifications for the declared grade. These quality standards may be of importance as they provide technical information for various quality levels of a product, and may promote the sale of the products to United States importers.

Voluntary Inspection Programs

The National Marine Fisheries Service of the Department of Commerce operates a voluntary inspection program for domestic fishery products on a fee-for-service basis. Under this program, the quality standards previously mentioned are applied as well as basic sanitation requirements for processing plant equipment and the general handling, processing and packaging of fishery products. Inspection services are also available in the United States on imported products. Such inspection service is available on a lot or consignment basis. If appropriate quality standards for the specific foreign product are available, the standards may be applied to the consignment and an official certificate issued indicating whether or not the consignment is in compliance with applicable standards.

These voluntary standards for grades should not be confused with standards of identity, quality or fill of container as may be established by the FDA. Under FDA requirements, a food for which a standard has been promulgated must comply with the specifications of the standard in every respect.

[Appendix is on the following page.]


IMPORT PROCEDURE FLOW CHART
Entry made by importer bond posted, duty paid, permit issued
Customs submits invoices to FDA
FDA examines invoices & decides not to sample Entry stamped off
Sample collected for laboratory examination or exam on dock
Sample found violative
Shipment detained
Destruction
Export
Unsuccessful reconditioning
Apply for reconditioning
Successful reconditioning
Re-sample
Sample found passable
Shipment released
Bond liability discharged

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(a) Part 13—Importation of Wildlife or Eggs Thereof.

(b) Part 260—Inspection and Certification—Voluntary Regulations.

(c) Part 261—U. S. Standards for Grades of Frozen Fried Fish Sticks.

(d) Part 262—U. S. Standards for Grades of Frozen Raw Breaded Shrimp.

(e) Part 263—U. S. Standards for Grades of Frozen Fish Blocks.

(f) Part 264—U. S. Standards for Grades of Frozen Haddock Fillets.

(g) Part 265—U. S. Standards for Grades of Frozen Halibut Steaks.

(h) Part 266—U. S. Standards for Grades of Frozen Raw Breaded Fish Portions.

(i) Part 267—U. S. Standards for Grades of Frozen Cod Fillets.

(j) Part 268—U. S. Standards for Grades of Frozen Salmon Steaks.

(k) Part 269—U. S. Standards for Grades of Foreign Ocean-Perch Fillets and Frozen Pacific Ocean-Perch Fillets.

(l) Part 270—U. S. Standards for Grades of Frozen Fried Scallops.

(m) Part 271—U. S. Standards for Grades of Frozen Headless Dressed Whiting.

(n) Part 272—U. S. Standards for Grades of Frozen Raw Headless Shrimp.

(o) Part 273—U. S. Standards for Grades of Frozen Raw Scallops.

(p) Part 274—U. S. Standards for Grades of Frozen Flounder and Sole Fillets.

(q) Part 276—U. S. Standards for Grades of Frozen Fried Fish Portions.

(r) Part 277—U. S. Standards for Grades of Frozen Raw Breaded Fish Sticks.

(s) Part 279—U. S. Standards for Grades of Frozen Raw Fish Portions.

(2) PHS No. 33—Revised 1965, National Shellfish Sanitation Program, Manual of Operations:

(a) Part I—Sanitation of Shellfish Growing Areas.

(b) Part II—Sanitation of the Harvesting and Processing of Shellfish.

(c) Part III—Public Health Service Appraisal of State Shellfish Sanitation Programs.

(3) Requirements of the U. S. Federal Food, Drug and Cosmetic Act, FDA Publication No. 2, Revised June 1970, gives principal requirements of that Act with emphasis on those aspects of special interest to foreign manufacturers.

(a) *Federal Food, Drug and Cosmetic Act, as amended.* The law enforced by the FDA. The Act appears in the United States Code under Title 21.

(b) *Requirements of the United States Food, Drug and Cosmetic Act*—(FDA) 72-10131/Revised February 1972. A synopsis of the principal requirements of the Food, Drug and Cosmetic Act with emphasis on those aspects of special interest to foreign manufacturers and importers.

(c) *Fair Packaging and Labeling Act.* The legal requirements contained in Public Law 89-755 enacted by Congress on November 3, 1966. **[The End]**

PUBLIC HEALTH HAZARD LEADS TO DIGOXIN LABELING PROPOSAL

After a two-year stay on its previous attempt to provide labeling for digoxin, the Food and Drug Administration (FDA) has proposed revisions of the labeling regulation for oral digoxin products. Serious, even lethal, overdosages could result if the labeling now being provided by the drug industry were followed literally. The labeling guidelines which were stayed by objections have not been followed, the FDA stated. The dosage information in the labeling now in use is suitable only for the older, less bioavailable formulation, which the Agency has removed from the market.

The FDA feels the situation presents a potential public health hazard and has proposed revising the labeling set out in the regulation to reflect the comments received in response to the publication of the regulation in January, 1974, the comments aired at a public meeting in March, 1974, and the recommendations of the FDA's Cardiovascular and Renal Advisory Committee. Other issues raised by the comments on the regulation will be the subject of a later notice.

Dosage

The majority of the labeling changes proposed relate to "Dosage and Administration" and primarily relate to lowering the recommended dosages in a variety of circumstances. Lowered dosage recommendations, in general, reflect the increased bioavailability of digoxin products. Lower loading dosages are recommended, more specific recommended dosages for children are stipulated, and several changes and additions stress smaller dosages in the case of renal insufficiency or impairment, a condition frequently found in the elderly. Two dosage regimes are proposed as the end-points of the spectrum of regimes that may be used to achieve digitalization.

Warnings

Among the other changes proposed is a revision of the "Warnings" section requiring a boxed warning on the dangers of using digoxin in the treatment of obesity. In view of the past widespread promotion and misuse in this area, the warning states that use of digoxin or other digitalis glycosides may cause potentially fatal arrhythmias or other adverse effects.

Comment Period

Interested persons have until May 28, 1976 to submit comments on the proposal. Because of the potential public health hazard, the Commission has advised that it does not expect to grant any extension of the comment period. Unless comments regarding the proposal raise substantial issues that cannot be immediately resolved, the FDA intends to issue a final regulation within 30 days following the end of the comment period. This regulation would be effective 60 days after the date of its publication in the *Federal Register,* or approximately on or about August 26, 1976.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,356

COMMENT SOUGHT ON RADIATION MISHAPS INVOLVING FOOD AND ANIMAL FEED

Interested persons have been invited to participate with the Food and Drug Administration (FDA) in the development of guidelines for emergency-response planning for radiological incidents involving human food and animal feeds by submitting relevant data, information and views. The FDA noted that, because a determination of the appropriate emergency response to a radiological incident must take into account such diverse factors as the health significance of any potential contamination, the agricultural practices of the geographical area involved, and the possible distribution and use pattern of potentially contaminated human food and animal feeds, the guidelines should be of a general nature and adaptable to a wide range of conditions.

The FDA stated it is especially concerned with the following issues: (1) the relative feasibility of alternative protective actions; (2) the rationale for establishing protection action guides; (3) the suitability of contaminated human food or animal feeds for use in food-producing animals as it affects their edible by-products; (4) the level of contamination at which resumption of normal use of human food and animal feeds should be allowed; (5) the effectiveness of various protective actions; (6) potential adverse effects and protective actions; and (7) the monetary costs of protective actions.

All submissions should be filed with the FDA by July 6, 1976.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,629

REVISIONS PROPOSED IN DRUG PRODUCT CODE REGULATIONS

In response to a January 1975 petition from the Pharmaceutical Manufacturers Association, the Food and Drug Administration has issued a proposal to amend the regulations implementing the Drug Listing Act of 1972. The proposed revision would allow the reassignment of product codes for discontinued products, permit the deletion of leading zeros from the National Drug Code (NDC) number, and change the conditions that require the use of a new NDC number for a drug product that has been altered. Interested persons may submit comments on the proposal until June 28, 1976.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,355

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