A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT

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October 11, 1973

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INTRODUCTION

The Federal Food, Drug, and Cosmetic Act provides authority for the broad and varied regulation of food, drugs, cosmetics, and medical devices. The Act prohibits the adulteration or misbranding of all such products. In the case of certain drugs, food additives, and color additives, specific pre-marketing requirements are set forth in the Act. Cosmetics are subject to pre-market requirements with regard to color additives. The regulation of medical devices is limited largely to labeling and directions for use. This multilith reviews, in historical sequence, the legislative development of the Federal Food, Drug, and Cosmetic Act.

A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

I. The Food and Drugs Act of 1906 (The Wiley or Heyburn Act)

The first Federal food and drug law, the Food and Drugs Act of 1906, was signed into law by President Theodore Roosevelt on June 30, 1906.[1/] The law banned from interstate commerce any traffic in adulterated or misbranded food or drugs. The statute also made it unlawful to manufacture adulterated or misbranded foods or drugs within any Territory of the United States and the District of Columbia.

The Act defined "drug" to include all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention, of disease in either man or other animals. The term "food" included all articles used for food, drink, confectionery, or condiment by man or other animals, whether simple, mixed, or compounded.

Definitions for adulteration and misbranding were set forth in the Act for both foods and drugs:

Adulteration

Drugs were to be deemed adulterated if they were sold under or by a name recognized in the official compendia, but failed to meet the standards set forth therein. An exception was provided -- that a drug using a recognized name not meeting the official standard would not be deemed adulterated if it met its own standard of strength, quality, and purity plainly stated on the bottle, box, or other container. Any drug which failed to meet the professed standard under which it was sold would, however, be deemed adulterated.

1/ 34 Stat. 768, 59th Congress, 1st session; June 30, 1906.

Confectionery was to be deemed adulterated if it contained any ingredient deleterious or detrimental to health or any poisonous color or flavor. It was also deemed unlawful for confectionery to contain any vinous, malt, or spirituous liquor or compound or narcotic drug.

The Act set forth several conditions under which food would be deemed to be misbranded: (1) if any substance was mixed and packed with it so as to reduce or lower or injuriously affect its quality or strength; (2) if any substance was substituted wholly or in part for the article; (3) if any valuable constituent of the article was wholly or in part abstracted; (4) if the food was colored, powdered, coated, or stained in such a manner as to conceal damage or inferiority; (5) if it contained any added poisonous or other added deleterious ingredient which might render it injurious to health; (6) if it consisted in whole or in part of a filthy, decomposed, or putrid animal or vegetable substance, or any portion of an animal unfit for food, or if the food was the product of a diseased animal, or one that had died otherwise than by slaughter.

Misbranding

A drug was deemed "misbranded" where the label bore any statement, design, or device regarding the contents which was false or misleading, or where the drug was falsely branded as to the State, Territory, or country in which it was manufactured. Drugs would be misbranded if they were an imitation of, or offered for sale under the name of another article (false name) or where the original contents had been removed in whole, or in part, and other contents added (false contents). Drugs would also be misbranded, if their labels failed to indicate any quantities of alcohol, narcotics, and certain other specified substances, which might be present in the product.

Food was to be considered misbranded if it was an imitation of or offered for sale under the name of another article. Labeling or branding so as to

deceive or mislead the purchaser; purporting to be a foreign product when not so; partial or total replacement of the contents of the package as originally put up; or failure to state certain ingredients on the label all constituted mislabeling. If the food were in package form and the contents were stated in terms of weight or measure, they had to be plainly and correctly stated on the outside of the package. Any packaging or labeling bearing a statement, design, or device which was misleading in any particular rendered a food misbranded.

The Secretary of the Treasury, the Secretary of Agriculture, and the Secretary of Commerce and Labor were to promulgate rules and regulations for carrying out the provisions of the Act, including the collection and examination of foods and drugs. The Bureau of Chemistry of the Department of Agriculture was to examine specimens of food and drugs for adulteration or misbranding. Any product which was adulterated or misbranded within the meaning of the Act was subject to seizure and libel for condemnation.

II. The Sherley Amendment of 1912

Limitations in the scope of public protection provided by the 1906 Act soon became readily apparent. A 1911 Supreme Court ruling pointed up large weaknesses in the law regarding drug labeling requirements of the Act. The high court ruled that the labeling provisions related only to the identity of the drug product and not to claims about the product's curative properties. Hence labels could and did contain false, sometimes dangerous claims about the effects of using a particular product.

In response to the ruling by the Supreme Court, Congress passed in 1912 what is called the "Sherley Amendment" which prohibited false and fraudulent curative or therapeutic claims on the label.[2/] But this action appeared to have

2/ 37 Stat. 416, 62nd Congress, 2nd session; August 23, 1912.

little effect on the deficiency noted in the Court's decision, since the law required statements to be shown as both false and fraudulent, a matter extremely difficult to prove, since fraud involves proving an intent to deceive.

The 1906 Act had serious weaknesses in several other areas of food and drug regulation. In an attempt to substantially strengthen the Federal authority legislation was introduced by Senator Royal S. Copeland of New York in 1933. Congress took no action toward enacting any new law until the disaster surrounding the "Elixir of Sulfanilamide" in 1937 brought out one of the inherent weaknesses in the Act and provided an impetus for the passage of new legislation. The drug, a sulfanilamide, was marketed in a solution of diethylene glycol, a deadly poison which eventually caused the deaths of 107 persons.

III. The Federal Food, Drug and Cosmetic Act of 1938 (The Copeland Bill)

Shortly after the sulfanilamide disaster, Congress adopted portions of the Copeland bill. Five years of legislative hearings and four major revisions were required before Congress adopted the 1938 Food, Drug and Cosmetic Act.[3/] The Act substantially revised the authority of the Federal government to protect the public against adulterated and misbranded food and drug products. In addition, cosmetics, which prior to this time were unregulated, were placed under Federal supervision.

The major provisions of the 1938 Act are outlined below:

Drugs and Devices

Brought under FDA control devices intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, and (2) to affect the structure or any function of the body of man or other animals.

3/ 52 Stat. 1040, 75th Congress, 3rd session; June 25, 1938.

Prohibited traffic in new drugs unless they had been adequately tested to show that they were safe for use under the conditions of use prescribed on their labels. Exemptions to these requirements were provided for drugs intended solely for investigational use by qualified scientific experts.

Required the labels of official drugs -- those recognized in official compendia -- to reveal any differences of strength, purity, or quality from the official standard (the 1906 Act merely required that the label bear a true statement of the purity, quality, and strength of the product).

Required drugs intended for use in man to bear labels warning against habit formation, as in the case of narcotic or hypnosis-forming drugs.

Required labeling of drugs and devices to bear adequate directions for use and authorized exemptions only where protection of the public health was not involved.

Required labels to bear warnings against unsafe use, where drugs or devices might be dangerous to health.

Required special precautionary labeling of drugs subject to deterioration.

Required official drugs to be packaged and labeled as prescribed by the official compendia.

Declared non-official drugs illegal if their standard of strength differed from the standard claimed.

Required the labels of non-official drugs to list the names of the active ingredients and to show the quantity or proportion of certain specified substances.

Foods

Provided for the promulgation of a reasonable definition and standard of identity, a reasonable standard of quality, and/or reasonable standards of fill of a container. With certain exceptions, no definition and standard of identity and no standard of quality could be established for fresh or dried fruits, fresh or dried vegetables, or butter.

Prohibited traffic in food which was injurious to health. (The 1906 Act permitted regulation of injurious food only in the event poison was added.)

Prohibited the addition of poisons to food. In the event the addition of a poisonous or deleterious substance was required in production or could not be avoided, the Secretary was required to promulgate regulations limiting the quantity of such substance in the food.

Prohibited the addition of any alcohol or nonnutritive article (with certain exceptions) to confectionery.

Required the label of nonstandardized food to bear: (1) the common or usual name of the food, and (2) in case it was fabricated from two or more ingredients, the common or usual name of each ingredient. Spices, flavorings and colorings could be so designated without naming each.

Required the labels of food which purported to be or was represented to be for special dietary use to bear such information concerning its vitamin, mineral and other dietary properties as the Secretary determined necessary to inform purchasers as to its value for such uses.

Required any food containing any artificial flavoring, artificial coloring, or chemical preservative to bear a label stating that fact.

Authorized emergency license control of food that might be dangerous by reason of contamination with micro-organisms. Such licensing was limited to operations in which the public health could not be otherwise protected.

Cosmetics

Prohibited traffic in cosmetics which contained any poisonous substance which might render it injurious to users under the conditions of use prescribed in the labeling or under such conditions of use as were customary or usual.

Required coal-tar hair dye to bear a warning label regarding use and preliminary testing.

Exempted from labeling requirements those cosmetics which were to be processed, labeled or repacked in substantial quantities at establishments other than those where originally processed or packed.

General

Deemed illegal any food, drug, or cosmetic whose labeling was false or misleading in any particular.

Required any food, drug, or cosmetic in packaged form to bear: (1) the name and place of business of the manufacturer, packer, or distributor, and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

Prohibited traffic in food, drugs, or cosmetics which might have been prepared or handled under unsanitary conditions.

Deemed illegal any food, drug, or cosmetic whose container was made, formed, or filled so as to be misleading.

Forbade the use of uncertified and impure coal-tar colors in foods, drugs, and cosmetics.

Authorized factory inspection of establishments producing food, drugs, or cosmetics, subject to certain conditions. (See Part VIII.)

Authorized the procurement of transportation records and other documents necessary to establish Federal jurisdiction.

Provided increased penalties for violations.

Authorized the Federal courts to restrain violations by injunction.

With the exception of new drugs and coal tar dyes, the 1938 Act did not provide for automatic pre-market testing or approval of products. A manufacturer was not required to submit foods or cosmetics to the FDA to assess the safety of the chemical additives therein prior to their introduction into commerce. If the Federal government had reason to believe that a particular substance posed a hazard to the consuming public, it had to enter proceedings to establish these hazards and the burden of proof of such fact rested with the Government, not with the manufacturer or user of the chemicals.

In an effort to prevent another disaster such as the sulfanilamide poisonings, the Act did provide for pre-market clearance of new drugs to assure safety. Prior to marketing, manufacturers had to submit to the Food and Drug Administration full reports of investigations which had been undertaken to establish safety. Unless the FDA, within a specified period of time, issued an order finding that such safety had not been established, the manufacturers could proceed to market the drug. The FDA was also authorized to act beyond the initial stages of drug development and was permitted to remove from the market any drug which it subsequently could prove unsafe. Old drugs, already on the market, were not subject to these requirements. They were allowed to remain on the market unless the FDA could prove they were dangerous.

It is important to note that the 1938 Act did not require that a drug had to be proven effective, as well as safe, in order to be cleared for marketing. But in making its judgements about safety, the FDA did consider effectiveness.

The relationship between safety and efficacy is considered elsewhere. It is only significant to note that the manufacturer of a product did not have to prove that his product did the things it was reputed to do.

Because they were considered so dangerous, the law also provided certain pre-marketing requirements for coal tar dyes. Not only were the dyes required to be found safe for use by the FDA, but "batch certification" was required to assure that each individual batch of the dye was properly manufactured.

The limitations imposed by the "false and fraudulent" provisions of the Sherley Amendment were revised to become "false or fraudulent".

IV. Insulin and Antibiotic Certification Amendments

In December 1941, Congress added a section to the 1938 Act requiring the Food and Drug Administration to batch-certify drugs composed, in whole or in part, of insulin before they could be placed on the market.[4/] Each batch has to be tested for identity standards, and for the characteristics of strength, quality, and purity as specified in official compendia. These tests were designed to assure safe and efficacious use of insulin products.

In 1943, the War Production Board requested the Food and Drug Administration to assay samples of each batch of penicillin then being produced for use by the armed forces. In 1945, shortly before penicillin was to be made available for use in the civilian sector, Congress amended the 1938 Act by adding a section calling for the batch certification of penicillin products.[5/] This section of the Federal Food, Drug and Cosmetic Act has since been amended three times. In

4/ 55 Stat. 851, 77th Congress, 1st session; December 22, 1941.
5/ 59 Stat. 462, 79th Congress, 1st session; July 6, 1945.

1947, the batch certification requirements were extended to streptomycin.[6/] In 1949, Congress amended the antibiotics section of the law (Sec. 507) to include chloretracycline, bacitracin, chloramphenicol, and their derivatives.[7/] The drug Amendments of 1962 extended the batch certification requirements to all antibiotics intended for use in man.[8/]

V. Regulatory Amendments of 1948

In 1948, the Federal Food, Drug, and Cosmetic Act was amended to avoid misinterpretation of the extent of the FDA's regulatory authority. The Amendment made it clear that the 1938 provisions against adulterated or misbranded foods, drugs, devices, and cosmetics applied any time after shipment and prior to purchase by the ultimate consumer.[9/] Such legislation was made necessary by certain Federal circuit court rulings which cast doubt on the FDA's authority to move against products in instances where adulteration or misbranding had occurred after interstate shipment was completed but before the product was in the hands of the consumer.

VI. The Delaney Committee

During the 1940's there was a substantial increase in the use of commercial pesticide chemicals in the growing of raw agricultural products and in the use of chemical substances for flavoring, preserving, and packaging of standardized foods. In June of 1950, the House of Representatives adopted a Resolution creating a Select Committee to Investigate the Use of Chemicals in Foods. The Select Committee was also known as the "Delaney Committee", after its chairman,

6/ 61 Stat. 11, 80th Congress, 1st session; March 10, 1947.
7/ 63 Stat. 409, 81st Congress, 1st session; July 13, 1949.
8/ 76 Stat. 780, 87th Congress, 2nd session; October 10, 1962.
9/ 62 Stat. 582, 80th Congress, 2nd session; June 24, 1948.

Representative James J. Delaney of New York. The Committee began extensive hearings into the matter of pesticides and food additives during 1950, and as a result of a second Resolution extended its investigation through the 82nd Congress as well.[10/] Hearings were terminated a few months later in March 1952 and the Select Committee published its findings not long thereafter in four reports covering fertilizers, cosmetics, food and fluoridation. The third report of the Delaney Committee, entitled "Food", specifically recommended that chemicals used in or on foods be tested to establish their safety prior to their use in foods.[11/] Although Congress did not immediately enact legislation following publication of the Select Committee's reports, it is generally conceded that these reports and the hearings of the Committee had an important influence on the shape of the pesticide legislation in 1954 and the food additives legislation enacted in 1958.

VII. The Durham-Humphrey Amendment of 1951

In 1951, the Congress passed another amendment to the Federal Food, Drug, and Cosmetic Act, popularly known as the Durham-Humphrey Amendment after the names of its sponsors.[12/] The statute contains a legal definition of the kinds of drugs for human use which may be dispensed by the pharmacist only upon the prescription of a "practitioner licensed by law to administer such drugs." Thus it leaves to State medical practice laws and medical practice boards to determine who is qualified to prescribe drugs, just as State pharmacy laws and boards determine who is qualified to dispense drugs.

10/ "Chemicals in Food Products", Hearings before the House Select Committee to Investigate the Use of Chemicals in Food Products, 81st Congress, 2nd session; created pursuant to House Resolution 323 (1 vol.); also, "Chemicals in Food Products", 82nd Congress, 1st and 2nd sessions; pursuant to House Resolution 74 and 447 (4 vols.); 1950-52.

11/ "Foods", House Report No. 2356; 82nd Congress, 2nd session; June 30, 1952.

12/ 65 Stat. 648, 82nd Congress, 1st session; October 26, 1951.

Under the amendment, it is unlawful to dispense a drug bearing the Rx Legend without a prescription or to refill a prescription for an Rx Legend drug without an authorization from the prescriber. The amendment is grounded in the principle that the physician should control the amount of medication given to his patients. A prescription or refill may be transmitted by telephone, but such authorizations must be promptly reduced to writing and be filed by the pharmacist. Certain narcotic drugs can only be dispensed upon written order of the practitioner. The law further required that prescription-restricted drugs be labeled with the Rx Legend, and that it is illegal to place this legend on drugs not so restricted. The fundamental purpose of the legislation was to provide the pharmacist with clear guidance as to which drugs may not be sold, or refilled, without a prescriber's authorization, as distinguished from those products which may be sold to the layman for self-medication (known as over-the-counter, or OTC drugs).

The Durham-Humphrey Amendment defined three categories of prescription drugs:

--hypnotic or habit-forming drugs that are specifically named in the law, and their derivatives, unless specifically exempted by regulation;

--a drug which is not safe for self-medication "because of its toxicity or other potentiality for harmful effect, or the method of use, or collateral measures necessary to its use";

--and a "new drug" which has not been shown safe for use in self-medication, and which, under the terms of an effective new-drug application, is limited to prescription dispensing.

Many drugs which are considered "safe," insofar as their inherent toxicity is concerned, must be restricted to prescription sale because of the conditions for which they are intended to be used, because of diagnostic techniques, or because of collateral therapeutic techniques which are required in connection with their use. In brief, the Rx Legend drugs are not safe enough for a layman to use in self-medication. The labels on such drugs do not, therefore, contain

detailed directions for use, precautions, and so forth, which would be needed by the layman to use the drugs safely and effectively. The physician and the pharmacist, however, must be provided with such information and the Amendment requires that the manufacturer provide them with such data.

Drugs which are not restricted to prescription sale (over-the-counter-drugs) must bear adequate directions for safe and effective use and warnings against misuse which the layman needs to know. The distributor of OTC drugs is required by law to label the product with such information. Drugs which may legally be sold over-the-counter must bear a "7-point label:"

1. the name of the product.
2. the name and address of the manufacturer, packer, or distributor.
3. the net contents of the package.
4. the established name of all active ingredients, and the quantity of certain other ingredients whether active or not.
5. the name of any habit-forming drug contained in the preparation.
6. cautions and warnings needed for the protection of the user.
7. adequate directions for safe and effective use.

Typical warnings tell how to use the medication safely -- "Do not apply to broken skin;" when not to use the medication -- "Do not drive or operate machinery;" and when to stop taking the drug -- "Discontinue use if rapid pulse, dizziness, or blurring of vision occurs." Other warning statements answer questions for the layman, such as whether he should see a physician -- "If pain persists for more than 10 days or redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately."

Any drug which does not bear the Rx Legend can be sold without a prescription, and the consumer has the responsibility for reading and heeding the directions and warnings.

VIII. Factory Inspection Amendments of 1953

In 1952, the U.S. Supreme Court, in the case of U.S. v. Cardiff,[13] held that the 1938 Act did not clearly permit mandatory factory inspections. One section of the Act provided that a factory could be inspected only with permission of the owner or operator. However, another section required that permission be granted. The Court found these two sections to be "fatally inconsistent".

As a result, Congress passed an amendment in 1953 to permit the FDA inspections, after written notice to the owner, without a warrant and without permission of the owner.[14] Subsequent litigation holding that a business proprietor can refuse to admit a government inspector unless he has a search warrant prompted the FDA to issue guidelines for its inspectors to follow in obtaining a search warrant.

IX. Food Standard Amendments of 1954

In 1954, the Food, Drug, and Cosmetic Act was amended to simplify the procedure for establishing standards of identity, quality and fill of containers for foods. The existing law required a formal hearing upon any proposal to issue, amend, or repeal regulations regarding several sections of the Act, including definitions and standards for foods. The amendment eliminated the requirement for a formal hearing when there was no controversy over the proposed rule.[15]

X. The Pesticide Chemical Amendment of 1954

In 1954, Congress passed the Pesticide Chemical Amendment to the Federal, Food Drug and Cosmetic Act, sometimes known as the "Miller Amendment", after its principal sponsor, A. I. Miller, Representative from Nebraska.[16] The amendment was designed to provide a new, more effective procedure for controlling the residues of pesticide chemicals used in connection with the growing of raw agricultural commodities. Under the provisions of the 1938 Act, food which

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13/ 344 U.S. 174.
14/ 67 Stat. 476, 83rd Congress, 1st Session; August 7, 1953.
15/ 68 Stat. 54, 83rd Congress, 2nd Session; April 15, 1954.
16/ 68 Stat. 511, 83rd Congress, 2nd Session; July 22, 1954.

contained chemical residues could be deemed adulterated and prohibited in interstate commerce. However, it was generally acknowledged that the method was slow and inadequate due to the large number of pesticides in use.

The Miller Amendment incorporated a pre-market testing principle advocated by the Delaney Committee in 1952. The procedure used for the pre-market testing made use of the 1947 Insecticide, Fungicide and Rodenticide Act which required a manufacturer to register the label of a pesticide with the Department of Agriculture.[17/] Under the new amendment to the Food, Drug, and Cosmetic Act, the manufacturer had to obtain from the FDA, prior to registering the label, a "tolerance" for a pesticide to determine how much pesticide chemical might remain on or in the raw agricultural product. The burden for proving that the residue levels were safe was made the responsibility of the manufacturer. If the FDA, on the basis of the scientific data presented, decided that any amount of residue would be dangerous to health, they could refuse to establish a tolerance level. Consequently, the manufacturer could not register the pesticide with the Department of Agriculture. Any raw agricultural product which had a residue exceeding that set by the FDA was subject to seizure and condemnation by the FDA. The 1954 Amendment also provided procedures for determining tolerance levels for pesticides registered prior to enactment of the legislation. The FDA was given the authority to exempt any pesticide chemical from the tolerance requirement when the safety of the consumer was not affected.

The FDA no longer has the responsibility for setting tolerance levels for pesticide residues. The President's Reorganization Plan of July 9, 1970, established the Environmental Protection Agency and transferred the function of establishing tolerances from FDA to the new agency. Authority was also transferred

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17/ 61 Stat. 163, 80th Congress, 2nd Session; June 25, 1947.

for (1) monitoring compliance with the tolerances and the effectiveness of surveillance and enforcement, and (2) providing technical assistance to the States and conducting research under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act.

XI. Orange Coloring Amendment of 1956

The 1938 Act placed two restrictions on the use of coal-tar dyes: (1) the dye must be found harmless by the FDA, and (2) it must be from a batch certified by the FDA. In 1956, Congress legislated an exception to the requirement of safety.

The exception was a dye, FD&C Red No. 32, which was the only coloring suitable for giving ripe oranges the color expected by consumers. This dye was found to be toxic and was subsequently removed from the list of coal-tar dyes approved by the FDA. Without the use of this dye, the orange growers in Florida and Texas expected to suffer great financial loss due to a decrease in the attractiveness of the fresh fruit. Since there was no evidence that the use of the dye in coloring orange peels was harmful, Congress passed a bill to allow such limited use.[18/] The Committee report on the bill stated that the legislation was to provide time to develop an alternative coloring which would meet the requirements of the 1938 Act regarding coal-tar dyes.

XII. Food Standard Amendments of 1956

In 1956, legislation was passed to further simplify the rule-making process for food standards.[19/] Amendments in 1954 had eliminated the requirement for formal hearings prior to issuance of standards on identity, quality and fill of container when there was no controversy over the proposal. The new amendment applied this

18/ 70 Stat. 512, 84th Congress, 2nd Session; July 9, 1956.
19/ 70 Stat. 919, 84th Congress, 2nd Session; August 1, 1956.

simplified procedure to the regulations on foods for special dietary uses, tolerances for poisonous ingredients, use of emergency permits, and certain other areas requiring rule-making.

XIII. The Food Additives Amendment of 1958

A number of bills had been introduced into the 83rd, 84th, and 85th Sessions of Congress to implement the recommendations of the Delaney Committee on the use of chemical substances added to foods. In 1958, the House Committee on Interstate and Foreign Commerce, after 11 days of hearings on a variety of food additive proposals, reported out the Food Additives Amendment of 1958. The bill contained, among other things, a specific requirement for pre-clearing certain chemical additives for safety before such substances could be used in foods. The legislation provided that no additive could be used unless the formula and a description of the proposed conditions for use had been submitted to and approved by the Food and Drug Administration. If the agency approved the application for use of the additive, it could also establish the maximum amount of the substances, or tolerances, which would be permitted for use in foods. The provisions of the bill did not pertain to fresh fruits and vegetables as these were already subject to pre-market testing under the 1954 Pesticide Chemicals amendments.

The Food, Drug, and Cosmetic Act of 1938 already prohibited poisonous or deleterious substances in foods except in certain instances where such substances were allowed in small amounts. However, the lack of a pre-market clearing requirement made this provision relatively ineffective. In order to bar the use of a dangerous additive, the FDA had to assume the burden of proof and show the additive was poisonous or deleterious. This process was extremely time-consuming and while it continued, the additive remained on the market. The House bill applied the principle of pre-market testing to food additives for the first time.

Two important areas of disagreement arose in connection with the proposed Food Additives Amendment. The first of the controversies concerned what is now known as the "Delaney anti-cancer clause". Representative Delaney who had favored strong additive control legislation had sponsored legislation to forbid the approval of using additives which were found to be cancer-inducing in man or in animals. The bill reported by the House Committee on Interstate and Foreign Commerce did not contain such a provision, although the Committee had considered the proposal. There was opposition to the clause by the Food and Drug Administration, and by a number of scientists who opposed the clause on the grounds that it interfered with the exercise of scientific judgement. Why, they argued, should an additive at safe levels in foods used by man be barred simply because the same substance at higher levels induced cancer in animals? Some also thought it unnecessary to single out one specific disease category within the legislation. In any event, the bill was amended when it reached the House floor on August 13, 1958, to contain the Delaney clause: 19/

> Provided, that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, 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 animal.

A second problem area in the bill related to the question of how to deal with additives already in use on the market. Industry spokesmen originally proposed that additives already in use be exempted from the provisions of the bill, while a number of Members objected on the ground that such an exemption would leave many

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19/ Congressman Delaney, a member of the House Rules Committee, convinced the Administration of the wisdom of accepting his amendment.

untested additives still in use. As a result, the bill provided for the following scheme: new additives not in use before January 1, 1958 would be automatically subject to the pre-clearance requirements set out in the bill; substances generally recognized as safe (GRAS substances) after years of repeated use were to be exempted from the procedures of the bill; additives approved under the old procedures contained in the Food, Drug, and Cosmetic Act or under the meat and poultry inspection laws were also exempted, although they could be removed from the market if later discovered to be hazardous; and, additives previously untested and unapproved already on the market as of January 1, 1958 would be subject to the procedure in the bill, except that they were allowed a grace period, ranging from **18 to 30 months. During this time they could apply for or otherwise receive a tolerence standard and could remain on the market during this period of time.**

It is important to note that the bill (and the law, after the bill was passed) did not apply the pre-clearance safety procedures to substances generally recognized as safe (GRAS) among experts qualified by training and experience to evaluate such safety considerations. The Department officials noted in 1958, that while GRAS substances would be exempt from the pre-clearance procedure, such substances could immediately become controlled if evidence appeared to warrant the conclusion that their safety was not generally recognized safe by experts.

The bill passed the House by voice vote on August 13, 1958 and by voice vote, with minor amendments, in the Senate on August 23, 1958. The amendment was signed into law by President Eisenhower on September 6, 1958.[20/] Congress passed legislation in 1961[21/] and 1964[22/] to extend the grace period through December 31, 1965.

20/ 72 Stat. 1784, 85th Congress, 2nd Session; September 6, 1958.
21/ 75 Stat. 42, 87th Congress, 1st Session; April 7, 1961.
22/ 78 Stat. 1002, 88th Congress, 1st Session; October 3, 1964.

XIV. Orange Coloring

In 1959, Congress passed legislation to allow a new coal-tar dye, FD&C Red No. 2, to be used to color oranges until September 6, 1961.[23/] The legislation was necessary because the dye was found toxic at certain levels and therefore its use was prohibited under the Food, Drug, and Cosmetic Act of 1938. Similar legislation had been passed in 1956 to permit the use of FD&C Red No. 32, a slightly more toxic coloring. In both instances, the FDA held that it did not have the authority to establish tolerance levels for coal-tar dyes even at levels which presented no danger to health.

On December 15, 1958, the Supreme Court in Flemming v. Florida Citrus Exchange[24/] upheld the position of the FDA which forbade the use of coal-tar dyes found to be harmful in any amount. The Court ruled that Red 32 could not be used after March 1, 1959. This ruling had a much greater impact than the use of the one dye; it affected the use of all coal-tar dyes not only in foods but in drugs and cosmetics. As a result of the ruling, the food, drug and cosmetic industry called for a revision of the Act to allow tolerances to be set for safe use of dyes. The FDA was in favor of such a change and had sent a letter proposing such to the House Committee on Interstate and Foreign Commerce on June 27, 1958 and again on February 19, 1959. However, although legislation regarding the use of all color additives would not be passed until 1960, this emergency legislation was passed in 1959 to allow the orange growers to continue use of FD&C Red No. 32.

23/ 73 Stat. 3, 86th Congress, 1st Session; March 17, 1959.
24/ 358 U.S. 153; Rehearing Denied 358 U.S. 948.

XV. Insecticide Amendments of 1959

The Pesticide Chemical Amendments of 1954 established controls on residues of pesticides left on fresh fruits and vegetables. Subsequent to its enactment, new forms of chemical insecticides were developed for use in agriculture which were not covered by the existing provisions. These new insecticides were nematocides, defoliants, dessicants, and plant regulators. In 1959, Congress passed legislation which brought these chemicals under the 1954 Pesticide Chemical Amendments.[25/]

XVI. Color Additive Amendments of 1960

In 1960, Congress revised the provisions of the 1938 Food, Drug, and Cosmetic Act regarding the use of color additives. One of the major provisions of the Amendment was the requirement that the conditions for safe use of a color additive be established by regulation. The new law placed the burden of proof for showing the additive was safe for the intended use on the manufacturer whereas before it had been up to the Government to prove an additive was unsafe. The regulations regarding use of an additive could set forth tolerance limitations which specified the maximum amount of the additive permitted to remain on or in the product. In addition, the amendment also required all color additives to be batch - certified unless exempted by the Secretary of HEW. Those color additives already on the market were allowed up to two-and-a-half years to obtain FDA approval. Pre-market testing and batch certification had previously been required only for coal tar dyes.

A change was also made in the existing requirement that a coal-tar dye could be used only if found to be harmless in any amount. The new legislation allowed the use of any coal-tar dye or any other color additive if it could be established that the substance was safe for the intended use, a change in the Food, Drug, and Cosmetic Act which was supported by both spokesmen from industry and HEW. The cosmetic industry had a particular interest in the provision as the FDA had recently

25/ 73 Stat. 286, 86th Congress, 1st Session; August 7, 1959.

removed 14 dyes used for coloring lipstick from the list of approved coal-tar dyes even though many of the dyes were considered safe as they were being used.

The controversial Delaney Clause which prohibited use of any food additives known to produce cancer in man or animals was applied to color additives. Many industry spokesmen who opposed the Delaney Clause in 1958 also opposed its inclusion in the Color Additives Amendments. However, the Secretary of HEW testified strongly supporting use of the Delaney Clause in regard to color additives.[26/]

> The preponderance of scientific evidence clearly dictates our position: Our advocacy of the anti-cancer proviso in the proposed color additives amendment is based on the simple fact that no one knows how to set a safe tolerance for substances in human foods when those substances are known to cause cancer when added to the diet of animals.

XVII. The Drug Amendments of 1962 (the Kefauver-Harris Amendments)

The Drug Amendments of 1962 were, like the 1938 Act, enacted into law following a serious drug incident, the "thalidomide disaster".[27/] Use of thalidomide, a sedative, by pregnant women can cause severe deformity of the child. Although the drug was never approved by the FDA for commercial marketing, it was distributed to doctors for experimental purposes. A 1962 survey by the FDA showed the drug was given to 3,879 women of child-bearing age, nine of whom gave birth to a malformed child.

Drug legislation to achieve many of the objectives for which the 1962 Amendments were enacted had, also like the 1938 legislation, been before the Congress when the thalidomide incident occurred. Unlike the 1938 Act, however, the Drug Amendments of 1962 did not represent an entire revision of current law or the drafting of a completely new proposal. Instead, the legislation extended,

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26/ House of Representatives, Committee on Interstate and Foreign Commerce, Subcommittee on Public Health and Environment. Report on Color Additive Amendments of 1958, 86th Congress, 2nd Session; June 7, 1960.

27/ 76 Stat. 780, 87th Congress, 2nd Session; October 10, 1962.

expanded, and strengthened the regulatory authority of the Food and Drug Administration. The Food and Drug Administration had taken the position that the 1938 law was defective in the following ways: 28/

1. the producer of a new drug did not have to establish that his product would be effective, as well as safe, for its intended uses.

2. FDA had to work against deadlines of 60 and 180 days to prevent the automatic approval of new drug products.

3. there were no provisions requiring regular record keeping and reporting of clinical and other experience with new drugs.

4. the FDA could not remove a new drug from the market unless it could prove that it was an unsafe product; it was not enough just to show that new developments had drawn the question of the drug's safety into issue.

5. there were inadequate controls over the distribution and use of investigational drugs, as the thalidomide episode showed.

6. prescription drug advertising was virtually unregulated.

7. trade names for products were being used without proper reference to generic or established names, resulting in confusion for the medical profession.

8. the quality of "old" drugs was not assured, as it was with "new drugs".

9. only five classes of antibiotic drugs were subject to routine batch-testing and certification.

10. factory inspection authority was severely restrictive.

28/ Hearings before a Subcommittee of the House Committee on Government Operations on Drug Safety; statement by George P. Larrick, Commissioner, Food and Drug Administration; March 24, 1964.

The changes brought about by the 1962 Amendments included the following:

1. The Food and Drug Administration was authorized to establish, by regulation, current good manufacturing practices. Drugs which are not manufactured under conforming methods or in non-conforming facilities are considered adulterated.

2. The factory inspection authority was widely expanded to all matters bearing on violations of the Act. Included within the reach of this authority are data concerning the qualifications of technical and professional personnel employed by the manufacturer. Each establishment must be inspected at least once every two years.

3. Every manufacturer had to register annually with the Department of Health, Education, and Welfare. This provision aids in identifying and inspecting all places where drugs are manufactured, and aids in certain enforcement areas. Drugs coming from non-registered plants are deemed misbranded.

4. The Amendments provided that a new drug cannot be marketed until the FDA approves it as having met the statutory requirements for safety and effectiveness. The 1938 law permitted automatic clearance of drugs through lapse of time without FDA action. Approval was now conditioned upon the test of "substantial evidence" of efficacy, and the burden for proof rested with the manufacturer.

5. Labeling now took on a material bearing on the matter of new drug approval--it must not be false or misleading in any particular. This prohibition relates to the claimed effects of such drugs, as well as to other aspects of labeling.

6. The Secretary of HEW, on finding an imminent hazard to the public health, could immediately suspend a new drug approval, with the manufacturer afforded an expedited hearing.

7. Withdrawal from the market of a previously approved drug could be made for any one of the following reasons:

   a. if its labeling is found to be false or misleading in any particular and it is not corrected within a reasonable time after notice from FDA.

b. if, after reevaluation in the light of new evidence, its safety cannot be established or its claimed efficacy is not supported by substantial evidence.

c. if, after reevaluation in the light of new evidence it is found that manufacturing facilities, methods, or controls employed in manufacturing or packaging do not conform with standards of good manufacturing practices and are not changed after a reasonable period of time.

d. if the manufacturer fails to establish a system of maintaining adequate records, fails to make required reports, or refuses to give the FDA access to such records.

8. With respect to drugs already on the market, the manufacturer was now required to report promptly to the FDA information concerning adverse effects and other clinical experience or data relating in any way to safety and effectiveness.

9. New authority was granted to prevent the testing of investigational new drugs, including antibiotics, on humans unless specified safety conditions are met, including: submission of reports of preclinical testing, including animal studies and the obtaining of signed agreements from investigators that clinical work will only be done under personal supervision and experimental drugs will not be supplied to others.

10. Manufacturers who sought an exemption for investigational drugs had to secure from their scientific investigators assurance that they will obtain informed consent from the persons to whom the drugs or controls are to be administered or from their legal representatives (certain exceptions were provided).

11. Exemptions for experimental drugs from the new drug procedures were conditioned upon the keeping of records and the making of reports. This requirement would enable the FDA to evaluate the safety and efficacy of the drug in the event that a New Drug Application were filed at some later date.

12. **All human antibiotics became subject to batch-testing and certification. This provision added 30 additional groups to the five previously subject to this procedure.**

13. Labeling changes were made. The quantity of all active ingredients and specified inactive ingredients must be stated. Labels had to bear the established name of the drug designated under the name standardization authority provided for in the act, or certain other official or common name where an established name had not been designated.

14. Prescription-drug advertising was required to show the established name (in similar half-type size as any other name used, such as a trade name), the quantitative formula to the same extent it is required on the label, and a true and nonmisleading brief summary of adverse effects, contra-indications, effectiveness, and other information for the guidance of physicians.

A much cited weakness in the 1938 law was the requirement that drugs had only to be shown safe before marketing; there were no requirements for the manufacturer to prove that his product was effective as well. However, in testimony before a Committee of Congress, FDA Commissioner George Larrick noted that the FDA, since 1938, had assessed the effectiveness of certain products when making safety determinations in the case of drugs for use in life-threatening or grave diseases: 29/

> Basically we were saying that the dangerous characteristics of many drugs were such that they would automatically be outlawed unless they had some lifesaving or other very beneficial aspects that out-weighed those dangers.

Where the FDA could not establish that the product was unsafe, the manufacturer was free to proceed to market the product. In short, under the 1938 statute the manufacturer had the burden of proof that the product was safe, while the Government had the burden of proof to disprove efficacy. The 1962 Amendments now required the manufacturer to show both safety and efficacy.

Prior to 1962, the manufacturer was also under no obligation to report any adverse information on findings, after the product was introduced into the market,

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29/ Hearings on Drug Safety; House Intergovernmental Relations Subcommittee, Part 1, pages 185-86; March 24, 1964.

that would cast doubt or disprove the safety of the product. The 1962 Amendments required the manufacturer to keep the FDA advised of adverse experience and other data which would shed light on the status of the manufacturer's product.

An important feature of the 1962 Act was those provisions which enabled the Food and Drug Administration to apply tests of effectiveness to every product which was subject to the new drug provisions of the 1938 Act. In short, a review--which is still going on--could be made with respect to every new drug introduced between 1938 and 1962.

XVIII. Animal Drug Amendments of 1968

In 1968, legislation was passed to consolidate provisions of the Federal Food, Drug, and Cosmetic Act, with respect to the regulation of new animal drugs.[30/] Both the House and the Senate reports on the Amendment pointed out that, in many cases, the requirements for clearance of new drugs for administration to animals were more complicated than the clearance procedures for drugs for human beings. The reports expressed a need for simplification of the clearance procedures because the existing procedures had led to long delays in the clearance of new animal drugs.

Prior to the Amendment, a drug which was intended for use in animal feeds was regulated both as a new drug under the new drug requirements of the Act and as a food additive. This meant that the drug must be cleared under the procedures of both sections of the law. Where the product was a combination of drugs containing a certifiable antibiotic, the product was regulated under the antibiotic section of the Federal Food, Drug, and Cosmetic Act.

30/ 82 Stat. 342, 90th Congress, 2nd Session; July 13, 1968.

The Amendment added a new section to the Act, "new animal drugs" to consolidate into one place the various parts of the Act which related to drugs for administration to animals and animal feeds containing new drugs (including antibiotics). A definition for "new animal drug" and "animal drug" was also added by the Amendment.

During the Congressional consideration of the proposed legislation, an attempt was made by the House Committee on Interstate and Foreign Commerce to broaden the existing provisions of the Act regarding the export of animal drugs and feeds. The bill, as reported from that Committee, contained a provision to exempt those new animal drugs and feeds intended for export from the requirements of the Act. New, more lenient requirements were proposed for those products. The requirements were that the animal drug or feed must (1) comply with the law of that foreign country; (2) comply with the specifications of the foreign purchaser; and (3) be labeled for export.

The Senate Committee on Labor and Public Welfare was opposed to this amendment and it was omitted in Conference. Any new animal drug intended for export must comply fully with the requirements of the Federal Food, Drug, and Cosmetic Act.

XIX. The Drug Listing Act of 1972

As of 1972, the Food and Drug Administration had no ready means of determining what drugs were actually being manufactured and commercially distributed by establishments registered under the Food, Drug, and Cosmetic Act except by periodic inspection of the establishments.

In an effort to increase the FDA's regulatory tools in this area, legislation was introduced in the 92nd Congress to provide for a current listing of each drug manufactured, prepared, propagated, compounded, or processed by a registrant under the Act. During the hearings on the proposed legislation, the Commissioner of the FDA stated that availability of a current inventory of drugs would substantially

assist in the enforcement of Federal laws requiring that drugs be pure, safe, effective, and properly labeled. The legislation under consideration was passed and signed into public law on August 16, 1972.[31/]

The Drug Listing Act required manufacturers and processors of drugs to submit to the Secretary a list of all drugs manufactured or processed for commercial distribution. Any drug contained in the list which is subject to the requirements of the Act for new drugs, insulin, antibiotics, or animal drugs must be accompanied by a reference to the authority for marketing and a copy of all labeling for the drug. Those prescription drugs not subject to these specific requirements must be accompanied by a copy of the current labeling, and representative sampling of advertisements for the product. Over-the-counter drugs not subject to requirements for new drugs, insulin, antibiotics, or animal drugs must be accompanied by the label and package insert and a representative sampling of any other labeling for the drug.

In the case of those drugs (prescription or over-the-counter) not subject to special requirements of the Act, a quantitative listing of all active ingredients is to be submitted. The submission of a quantitative listing of all ingredients (including inactive ingredients) of a particular drug may be required if deemed necessary to carry out the purposes of the Act. The manufacturer or processor may also be required to state why he has determined a particular product is not subject to the requirements for new drugs, insulin, antibiotics or new animal drugs.

Supplemental filings are required every six months if there has been a material change in any information previously submitted, if a drug is introduced for commercial distribution after the previous filing, if a drug has been discontinued, or if a previously discontinued drug is reintroduced.

The Act also contains a number of other provisions designed to increase the efficiency of the FDA in regulating drugs.

31/ 86 Stat. 559, 92nd Congress, 2nd Session; August 16, 1972.