

FDA

March 1977

CONSUMER



Keeping An Eye On Imports



This Month

Many an adult has marveled at the seemingly inexhaustible energy of children. And many an adult has despaired at the seeming inability of some children to harness their energy long enough to sit still for any task, especially their schoolwork. Such children are called hyperactive or hyperkinetic. No one knows for sure why certain children are uncontrollable bundles of nervous energy, but a doctor who specializes in allergies thinks the problem is caused by artificial food colors and flavors. His theory is of more than passing interest to FDA so this month we explore the question of *Food Additives and Hyperactive Children* and what is being done to find answers.

Youthful energy and minor cuts and bruises go together like peanut butter and jelly. The treatment for a minor skin wound—regardless of the age of the victim—often is one of a number of antibiotic preparations that are available without a prescription. An FDA advisory committee has reviewed these over-the-counter medicines for safety and effectiveness. There's a report on the panel's findings beginning on page 10.

Sound is a form of energy. Some sound waves can't be heard by the human ear, but that doesn't mean they are of no interest or consequence to people. High frequency sound waves—ultrasound—can produce pictures of the body in much the same way that x rays do. And there is growing interest in the potential of sound for the treatment of disease. These developments are examined in *The Medical Uses of Sound*.

In recent years FDA has devoted more of its energies to inspecting and analyzing products that aren't made in America but are sold here. Import inspections have almost doubled since 1972. The ground rules for these inspections are simple: foreign-made products must meet the same safety, labeling, and other requirements as their American-made counterparts. For a look at how FDA is *Keeping an Eye on Imports*, see page 5.

FDA also is stepping up its surveillance of laboratories that test new drugs or food additives in animals. Regular inspection of these laboratories is part of a program that includes proposed standards covering the essential elements of their day-to-day operations. *New Standards for Test Laboratories* tells what FDA is doing and why.

Inside Front Cover Photo: "X rays" made with sound? It's done every day using high frequency sound waves. Sound pictures are called sonograms and they are produced by rubbing the transducer of the ultrasound machine across the part of the patient's body being examined. The technician making the sonogram can see the results projected on a screen on the ultrasound machine. An article on ultrasound and its current and projected uses in medicine begins on page 12.

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Section 705 [375] of the Food, Drug, and Cosmetic Act:

(a) The Secretary shall cause to be published from time to time reports summarizing all judgments, decrees, and court orders which have been rendered under this Act, including the nature of charge and the disposition thereof.

(b) The Secretary may also cause to be disseminated information regarding food, drugs, devices, or cosmetics in situations involving, in the opinion of the Secretary, imminent danger to health, or gross deception of the consumer. Nothing in this section shall be construed to prohibit the Secretary from collecting, reporting, and illustrating the results of the investigations of the Department.

Cover Design: Zeb Rogerson

Update

Rules Issued on Hearing Aid Sales

Of the estimated 15 million Americans who suffer from impaired hearing, many can be helped by hearing aids. But many others have hearing defects that cannot be corrected by any such device. An article entitled Making Sure Hearing Aids Help in the June 1976 issue of FDA CONSUMER describes what hearing aids can and can't do and tells of proposed FDA regulations aimed at protecting consumers who think a hearing aid may benefit them. Here's an update.

In an effort to assure that the people who buy hearing aids will benefit from them, the Food and Drug Administration has ordered new conditions on how hearing aids must be labeled and sold.

Under the regulation, effective August 15, 1977, hearing aids may be sold only to people who have had a medical evaluation of their hearing loss. Unless the examination is specifically waived by the purchaser, a statement from a physician that a hearing aid may help will be necessary for purchase. Waiver is not permissible for persons under 18 years of age.

The regulation also requires manufacturers to provide a detailed brochure which tells consumers what hearing aids can do, how they work and how to use them.

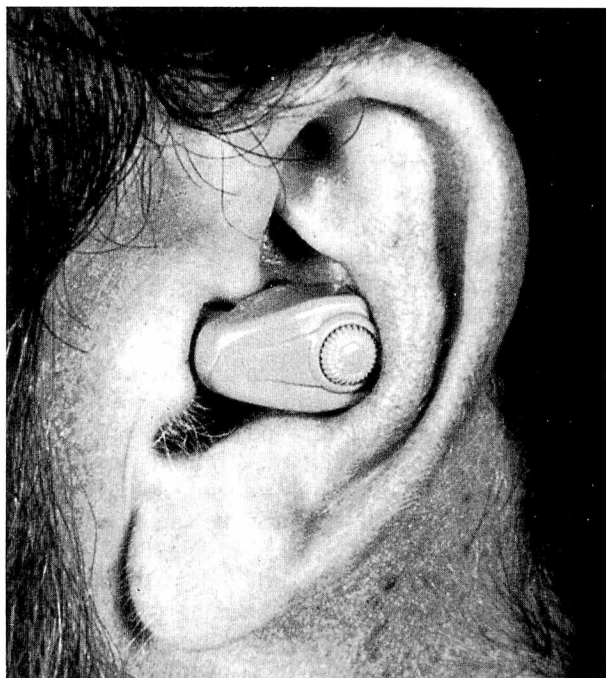
"This regulation is designed to protect consumers from being sold hearing aids that won't help them and to assure that people see a doctor if there is a medical reason for their hearing loss," said Sherwin Gardner, Acting Commissioner of Food and Drugs.

"The regulation is based in part on an FDA review of current information being given to consumers about hearing aids. The survey found this information to be inadequate and in some cases misleading. The mandatory brochure provided to prospective buyers will help avoid inaccurate information as well as misunderstandings," said Gardner.

Of the approximately 15 million Americans who suffer from hearing impairment, more than 10 million never have had medical evaluation. About 3 million Americans use hearing aids. About 1,200 different models are available.

Under the regulation, the medical evaluation must have taken place within six months before the purchase of a hearing aid.

Purchasers 18 years and older may waive the evaluation by signing a statement saying they know why a medical examination is advisable. The regulation forbids a hearing aid dispenser from encouraging prospective buyers to waive the medical evaluation.



Hearing aid dispensers must let a prospective buyer read the brochure before the sale is completed.

The brochure warns dispensers to advise prospective buyers to consult promptly with an ear specialist or other physician if any one of eight ear or hearing problems appears to exist. These problems include dizziness, ear deformity, pain or fluid drainage, rapid onset of hearing loss, or a foreign body in the ear.

The regulation also requires people who sell hearing aids to keep records for three years after the sale, including the required medical statement or waiver.

The regulation is based in part on a Department of Health, Education, and Welfare Report of Hearing Aid Health Care, issued in September 1975. The regulation was proposed on April 21, 1976, with an opportunity for the public to comment on it before a final regulation was issued.

FDA's regulation is compatible with a regulation on hearing aid purchase plans and advertising proposed by the Federal Trade Commission.

The regulation was published in the February 15, 1977, FEDERAL REGISTER.

Drug Equivalence Testing Rules Issued

The key elements in determining a drug's effect on a patient are how much of the drug is absorbed by the body, and how fast. These factors also are essential in determining whether different formula-

tions of the same drug have the same effects. An article in the November 1975 issue of FDA CONSUMER entitled Determining Drug Equality describes proposed regulations on how manufacturers should test drug products to measure the extent and rate of their absorption by the body. Here's an update.

After July 7, 1977, manufacturers seeking FDA approval to market a new drug product must submit evidence for tests conducted in human volunteers to determine how much of the active drug ingredient is absorbed by the body, how fast it is absorbed, and the length of time it circulates in the blood. The new requirements are spelled out in FDA's final regulations covering bioavailability and bioequivalence of drug products which were published in the January 7, 1977 FEDERAL REGISTER.

Bioavailability means the rate and extent to which the active ingredient in a drug product is absorbed, distributed, and excreted by the body. Bioequivalence means "equal in the body." In other words, do all drug products which have the same active ingredients and which are intended for the same purpose actually have the same effect? The intent of the new requirements is to assure that they do. This could be important in instances where the same drug is sold under a variety of brand names. For example, hydrocortisone tablets are made by 22 manufacturers and sold under as many different brand names.

Various factors could cause supposedly similar drugs to react differently in the body. For example, if an ingredient is added to a drug tablet to improve its shelf life or taste, that tablet may take longer to dissolve and do its work than a tablet of the same drug that does not include the added ingredient.

A manufacturer will be required to supply evidence that his drug product is absorbed at the same rate as similar products in all cases where lack of equality would pose a significant hazard to patients. Testing to prove equality (bioequivalence) will have to be done by the manufacturer, but FDA will continue to survey and test samples of marketed drugs to assure that they are bioequivalent.

The requirement that manufacturers submit data from bioavailability tests will not affect drugs already approved by FDA unless new information suggests that the dosage information on a drug is no longer appropriate or that significant variations in the absorption rate of any particular product have been found to occur from one batch to another. Bioavailability testing will not be required for injectable drugs, drugs that are applied to the skin, medical gases or vapors, or drugs whose chemical properties do not cause variations in the absorption rate.

Those drugs that have shown inconsistencies between various products in the absorption rate already have been identified and a list has been published by FDA for use by doctors and pharmacists to aid them

in deciding the appropriate medications to give their patients.

Timetable Set on Additive Decisions

A law passed in 1960 requires that anyone wishing to use a color additive in food, drugs, or cosmetics must first prove to FDA that the color is safe for its intended use. But many color additives already were in use when the law was enacted. The 1960 law authorized FDA to permit color additives in use at the time the legislation was passed to continue to be used on a provisional basis pending settlement of safety questions. A major effort to clear up the backlog of colors that have received only provisional approval was described in the November 1976 issue of FDA CONSUMER in an article entitled Countdown on Color Additives. Here's an update.

FDA has issued regulations setting a timetable for making final decisions on the safety of the 52 colors still provisionally approved for use in foods, drugs, and cosmetics.

Three of the provisionally listed colors are for use in foods, the remaining 49 are for use only in drugs or cosmetics or both.

The timetable for making final decisions on the colors is as follows:

- A deadline of July 1, 1977, has been established for 12 colors requiring studies on the safety of their use near the eyes.
- A deadline of October 31, 1977, has been set for 8 colors requiring additional chemistry or short term toxicity data.
- A deadline for 32 other colors requiring lifetime rat or mouse feeding or other studies (these studies usually take about two years to complete) has been set for January 31, 1981. These colors include the three food additives Green No. 3, Blue No. 2, and Yellow No. 6.

FDA also established specific dates by which industry must submit data needed to make the final safety decisions. These dates vary with the type of information required.

FDA's regulations setting these timetables fulfill an Agency commitment made in January 1976 to resolve the status of all provisionally listed color additives. FDA first proposed the regulations requiring a timetable for deciding the status of the 52 remaining colors on September 23, 1976. At the same time, FDA began taking steps to remove color additives from the provisional list by terminating the provisional listing for 12 color additives, including FD&C Red No. 4 and carbon black. In addition, FDA recently permanently approved 20 colors for use in drugs or cosmetics or both.

The final timetable regulations were published in the February 4 FEDERAL REGISTER.

Keeping An Eye On Imports



Whether it's "health sandals," television sets, or shrimp, FDA inspectors check imported products to make sure they meet U.S. standards. Some 8,000 products—more than one-half of them food—were detained at U.S. ports of entry last year because they violated or were suspected of violating U.S. laws and regulations.

by James Greene

They looked like ordinary sandals. But there was nothing ordinary about the literature accompanying them. It claimed that the sandals, which were imported from Hong Kong, would strengthen the liver, lungs, and large intestine and even enhance the wearer's sexual abilities.

These sandals were one of almost 8,000 products detained at U.S. ports of entry last year by FDA inspectors because they violated or were suspected of violating U.S. laws or regulations. Many of the products were allowed entry after the importer did whatever was necessary to bring them into compliance with FDA regulations. The sandals, for example, were permitted to enter the country after the withdrawal of all health claims, which FDA considered to be false

and misleading labeling.

Food accounted for more than 4,500 of the products detained last year by FDA; another 1,700 detentions involved medicines for human use and more than 900 medical device products were detained. Other imported products detained by FDA included cosmetics, television sets, microwave ovens, and veterinary drugs and medicated animal feeds.

These products enter the United States at some 370 locations, including airports, seaports, border crossings, and post offices. Over 75 percent of the products arrive by ship at coastal ports, where they are subject to examination by FDA inspectors. If a product appears defective, dangerous, or in any other way in violation of FDA regulations, samples may be collected for laboratory examination or detention action. Products such as television sets and medical devices may be tested to see if they meet FDA performance and safety standards. Food and drugs are subject to chemical and microbiological analysis. FDA inspectors also assure that imported products conform to labeling regulations.

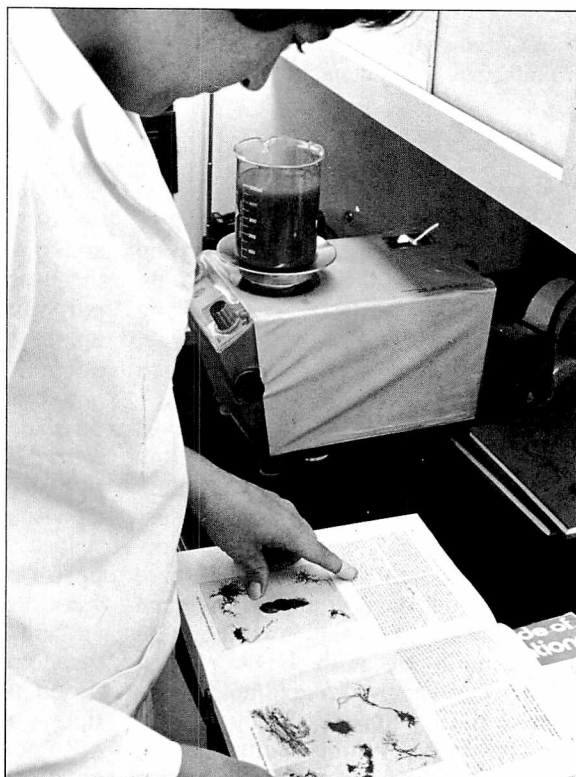
Importers are responsible for the condition of the goods they import but

Over 75 percent of the imported products regulated by FDA arrive by ship at coastal ports of entry such as this one in Miami. Last year FDA conducted about 135,000 import inspections, almost double the number that were carried out in 1972.

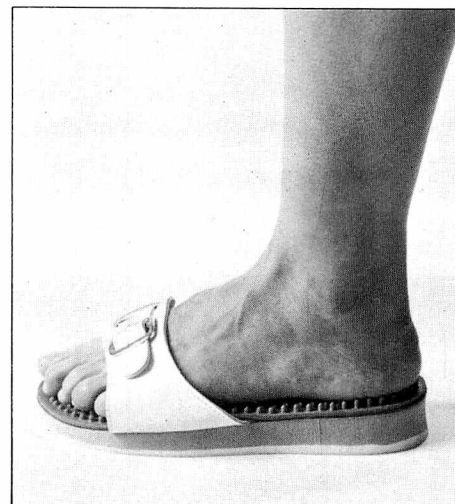
they usually bear little financial risk when the products consigned to them are detained. This is because importers often do not take possession, nor do they pay for the products, until after the goods are cleared by U.S. Customs and FDA. FDA favors a change in the law which would place a legal obligation on importers to register with FDA all the products they receive as imports. Such a law would require importers to assure FDA that the products were manufactured in accordance with FDA regulations and that they comply with appropriate safety standards.

The number of import inspections conducted by FDA has almost doubled over the past 5 years, rising from 74,000 in 1972 to about 135,000 in 1976. FDA inspectors now examine about one of every five lots of imported products that fall under the Agency's jurisdiction. This marked increase was the result of a new strat-

Scales, flasks, rulers, and even a reference book on plant contaminants are among the "tools" used by FDA Chemist-Technician Jeanne Bush in checking a sample of canned tomatoes from Israel to make sure they meet U.S. standards.



FDA refused to permit these sandals to enter the country until all claims that they could improve the wearer's health were dropped. A diagram on the box in which the sandals originally were offered for import showed what parts of the foot the sandals massaged to benefit specific organs of the body.



egy initiated in 1972 to improve the techniques used in examining, sampling, and analyzing imported products. Key elements of the program to increase and improve import inspections include:

- More visual examination of imported products. FDA inspectors examine imported products while they are being unloaded from the ship, or at warehouses near the port of entry. This is done primarily to determine what shipments ought to be tested or analyzed. In the past, products were selected for testing or analysis mainly on the basis of entry documents accompanying the product rather than visual examination of the product itself. Visual examination gives FDA inspectors an opportunity to detect any damage that might have occurred during loading or shipping of the product.

- Use of mobile laboratories. A fleet of 27 mobile laboratories is used for on-the-spot analysis of some imported products. Doing analyses at dockside rather than at the nearest FDA field laboratory cuts the time required to determine if a product is in violation of FDA regulations.

- Saturation sampling of troublesome products. An effort is made to examine and take samples from every lot of those products that are known

to pose major problems or those which come from a foreign manufacturer or shipper with a history of violations.

- Automatic detention of certain products. FDA establishes "block lists" of foreign firms, importers, or specific commodities that have repeatedly figured in violation of FDA regulations. Any specific product that is block listed and all products of block-listed firms are automatically detained at the port of entry without any sample or analysis of the products. It is then the responsibility of the importer to demonstrate that the product is in compliance before it may be released. In recent years block lists have been used for such products as frog legs and low-acid canned foods.

- Alert bulletins on hazardous products. FDA issues an Import Alert Bulletin when information is received about a potentially hazardous or otherwise serious import violation. Such a bulletin would be issued, for example, if FDA inspectors discovered that a lot of imported shrimp was contaminated by *Salmonella* bacteria. Since this represents a serious health hazard, a bulletin would be distributed to all FDA field offices instructing them to examine every lot of shrimp from the same shipper. If the shrimp simply contained a non-serious labeling prob-

lem, however, a bulletin would not necessarily be issued because this type of violation normally does not pose a serious health hazard. A total of 21 bulletins were issued in 1976, most involving food products.

In addition to checking imported products when they arrive in this country, FDA also conducts on-site inspections of certain foreign firms with the permission of their governments to assure that their manufacturing practices meet U.S. standards. Inspection of foreign firms has increased substantially in recent years. In 1970, FDA inspected 30 firms in a few foreign countries. In 1976, over 190 firms located in about 25 foreign countries were inspected. Most of the firms are in Italy, England, France, Germany, Denmark, Mexico, and Japan, and FDA anticipates more activity in this area as more and more foreign countries seek to sell their products in the United States.

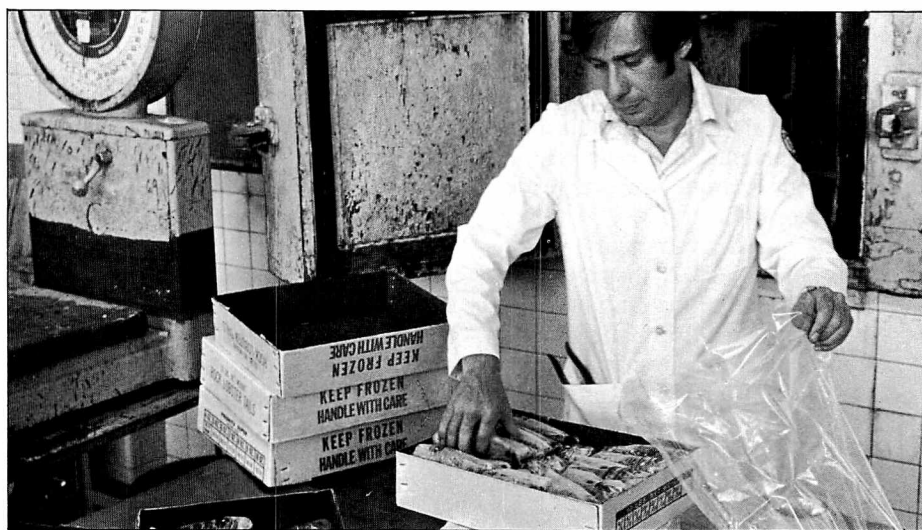
The overwhelming majority of the foreign firms inspected manufacture drugs. Of the 192 foreign plants inspected in 1976, 153 manufacture drugs or biological products for medical purposes, 30 produce television sets or other electronic products, 5 make food, and 4 manufacture medical devices.

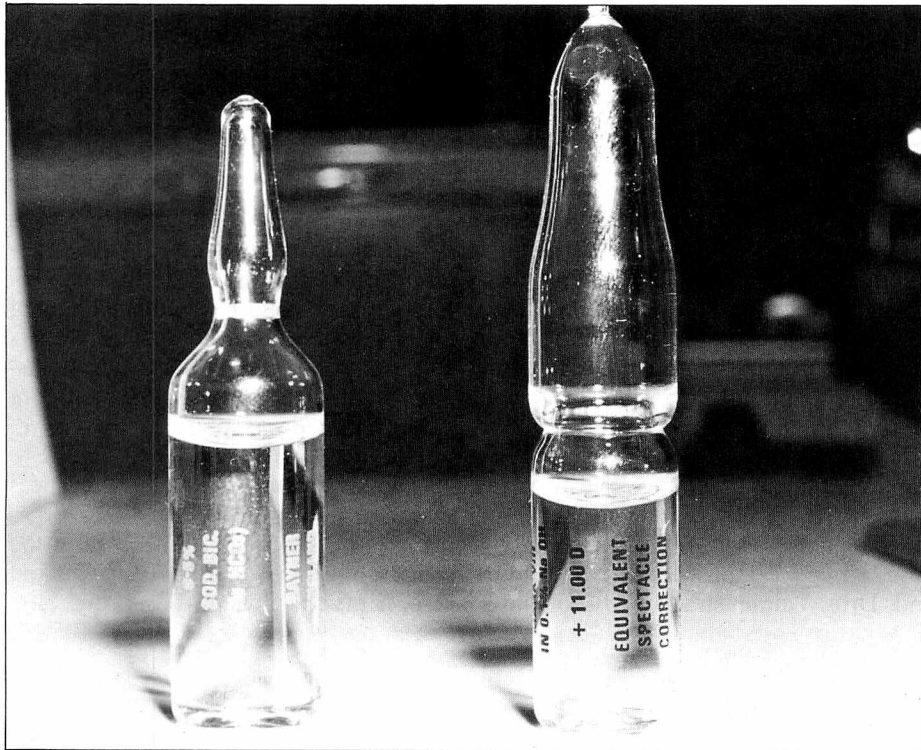
Although foreign manufacturers of electronic products are not required to

This imported frozen turtle meat was detained because the labels on the cartons in which it was packed claimed the contents also included shrimp and crabmeat. FDA inspectors found only turtle meat. The product was released for distribution after the turtle meat was removed from the mislabeled cartons.



Inspector Steve Tunks collects samples of imported frozen lobster tails at a Miami seafood processing firm and takes them to FDA's mobile laboratory, which is parked at the Port of Miami, where they are examined for possible decomposition.





This is part of a shipment of imported intraocular lenses that was detained by FDA at the U.S. Customs Office in Miami because the product lacked adequate directions for use. Intraocular lenses are implanted by a surgeon, usually in an elderly patient who has had cataract surgery. The vial on the right contains the solution used to clean the lens and the vial on the left contains the lens.

open their plants for inspection, they do have an incentive to "invite" FDA to check their facilities. A foreign manufacturer's products can be denied access to the U.S. market if FDA feels the firm's quality control is inadequate or its product fails to meet U.S. regulations for controlling emission of radiation. One of the best ways for FDA to determine if a firm meets U.S. standards is to conduct an on-site inspection.

Inspection of foreign food firms is a relatively new activity for FDA. The Agency is concerned primarily about low-acid canned foods such as pimientos, corn, pepper, green beans, olives, and asparagus because improper processing of these types of food can result in the growth of bacteria that cause food poisoning, including botulism, which often is fatal. A foreign firm's low-acid processing method must be reviewed and approved by FDA before its products are allowed into the U.S. market, as is the case with domestically manufactured products. In some cases this may require FDA inspection of the foreign firm's facilities. Foreign producers of other types of food are not required to permit inspection of their facilities, but regular import inspections procedures usually are adequate to deal with any problems

involving these products.

Inspection of foreign firms which manufacture medical devices is also done on an invitational basis.

Inspection of imported products and foreign firms is not the only method of protecting American consumers from dangerous or substandard products shipped from other countries. Increased emphasis is being given to the development of bilateral agreements on the regulation of consumer goods. These formally written agreements, negotiated for the United States by either the Department of State or FDA, are intended to foster mutual recognition of regulatory activities between FDA and countries exporting products to the United States.

Each agreement involves the United States and one foreign country. In effect, the agreement means that FDA has determined that the regulations and standards applied by the exporting company to the products covered by the agreement are equal to U.S. standards for similar products. As a result, products covered by the agreements are not subject to any special regulatory action or analysis when they are offered for import into the United States.

FDA negotiated the first bilateral agreement with Canada in 1948 in an

effort to assure the sanitary quality of imported Canadian shellfish. Thirteen additional agreements were negotiated between 1948 and 1975. Four of these active agreements are with Canada, and one each with ten other countries. They cover food, human drugs, and the exchange of information on electronic products. Seventeen more bilateral agreements are being worked out for possible implementation over the next three years. These agreements help assure the safety and quality of imports, reduce FDA's overseas inspection workload and the need for domestic import surveillance, and open or improve communication between FDA and foreign nations.

Many food, drug, and other FDA-regulated products produced and marketed in the United States are also exported for sale in other countries. FDA does not regularly monitor these exports, but does investigate all legitimate complaints from foreign firms or governments which receive products they feel are not up to that country's standards. FDA also alerts foreign governments when it initiates a recall of a product that has been exported by a U.S. firm.

James Greene is a staff writer with FDA's Office of Public Affairs.

Panel Reports On First Aid Ointments

An advisory committee has reviewed the ingredients used in nonprescription antibiotics that are sold for the treatment of minor skin wounds. Some of the ingredients are effective in keeping harmful germs from getting into the wound. But when it comes to treating infection by stopping or slowing the growth of bacteria, the Panel couldn't find enough evidence to determine whether any of the ingredients work.

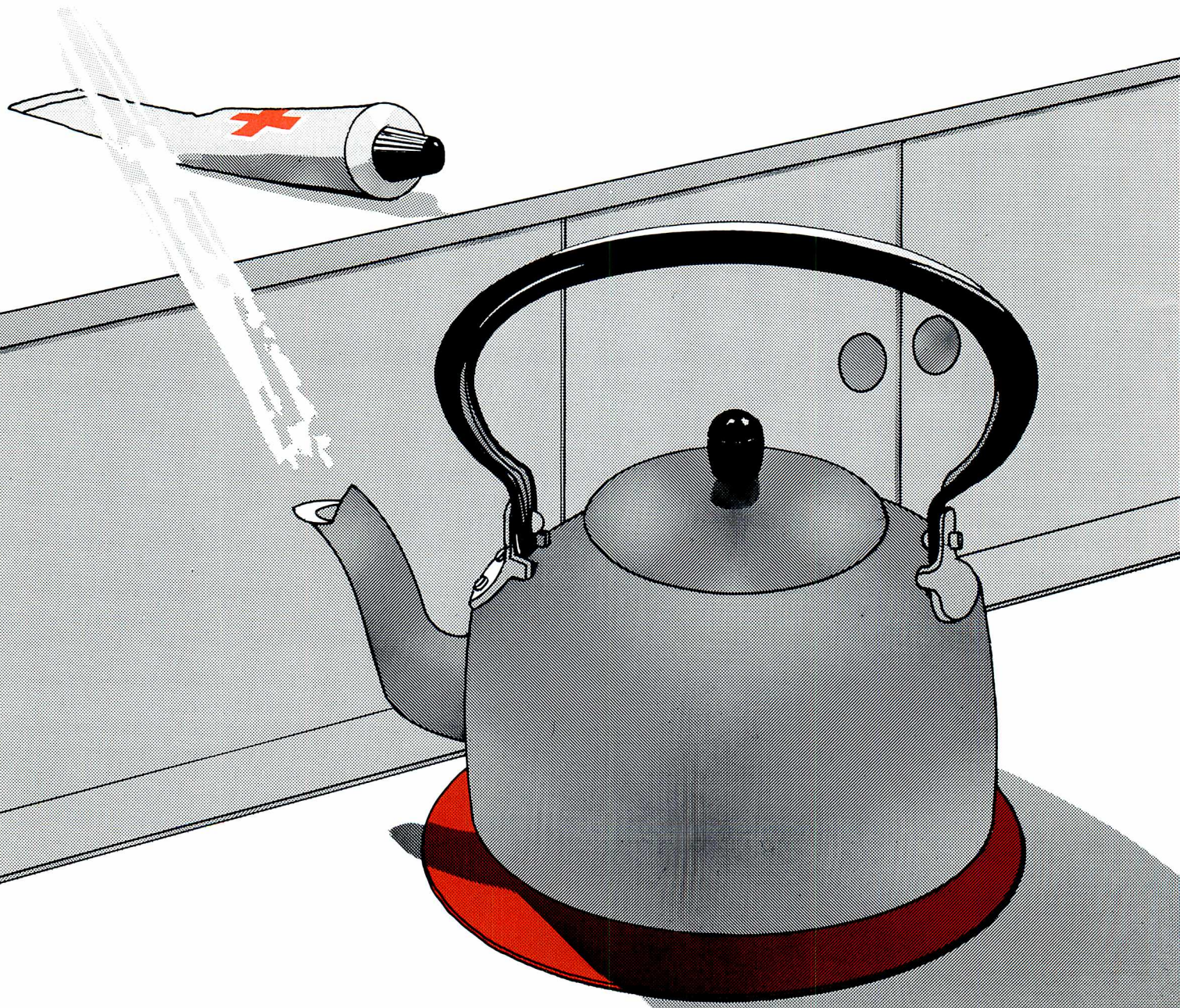
by Annabel Hecht

Psychologically speaking, as every child knows, a kiss from mommy will make a skinned knee all better. From a first aid standpoint, it does help to cleanse the scrape gently and then perhaps apply an ointment containing an antibiotic. So says a panel of experts who have been studying the safety and effectiveness of nonprescription topical antibiotics sold for use in treating minor skin wounds.

The panel is one of 17 such advisory groups established by the Food and Drug Administration to look into

the ingredients and the labeling claims of all nonprescription or over-the-counter drug products. After reviewing the report and recommendations of each panel, and soliciting comments from any interested party, FDA issues standards for the type of nonprescription drugs covered by the report.

Antibiotics are chemical substances which are produced by living organisms and which can kill or slow the growth of other bacteria. Penicillin and streptomycin are perhaps the best



known of the prescription antibiotics. Because they are manufactured through a biological fermentation process, antibiotics may vary in potency and purity from batch to batch. To insure uniformity, each batch of antibiotic drugs is tested and certified by FDA.

The Topical Antibiotic Advisory Panel concluded that nonprescription products containing antibiotics should be used only as part of the first aid treatment of small superficial wounds such as cuts, abrasions, and burns. The Panel defined first aid as "a process which includes initial adequate cleansing which may or may not be followed by application of a safe, non-irritating product which does not interfere with normal wound healing and which may reduce the bacterial numbers and help prevent infection."

The Panel reviewed five antibiotics: bacitracin, gramicidin D, neomycin sulfate, polymyxin B sulfate, and the tetracyclines (chlortetracycline hydrochloride, oxytetracycline hydrochloride, and tetracycline hydrochloride). The Panel studied each to determine its safety and effectiveness for two purposes:

- To provide a protective physical barrier that prevents potentially harmful bacteria from getting into a wound.
- To prevent or treat infection of skin wounds by retarding the growth of bacteria already present in the wound or that might get into it.

The Panel found that bacitracin and the tetracyclines are safe and effective as a protective barrier to prevent bacteria from getting into small, superficial skin wounds. There is not enough data available to determine whether gramicidin D and neomycin sulfate are safe and effective as physical barriers, the Panel said. Polymyxin B sulfate is not effective as a physical barrier when used alone, the Panel said, but it improves the effectiveness of bacitracin and the tetracyclines when used in combination with these ingredients.

The Panel found that not enough data were available from well-con-

trolled studies on any of the five antibiotics to establish their safety and effectiveness in preventing or treating infection of skin wounds by retarding the growth of bacteria.

Neomycin sulfate was of special concern to the Panel because of evidence that people who use it can, over time, develop allergic reactions to it and to related antibiotics. In addition, certain bacteria apparently can develop resistance to neomycin sulfate and its drug relatives. The Panel concluded that neomycin sulfate should remain on the market for treatment of minor skin wounds only if studies can show that less than 0.1 percent of the population is allergic to it, that germs are not developing resistance to it, and that it is effective as a wound protectant or a treatment for infection. If it is found that more than 0.1 percent of the population is allergic to neomycin sulfate it should be taken off the market, the Panel said.

The Panel recommended that in instances where there is not enough data to determine the safety and effectiveness of an ingredient, it should be permitted to remain on the market for two years during which time the manufacturer would be required to conduct studies to answer the questions raised by the Panel. Any that do not prove to be safe and effective would be removed from the market. The two-year period would begin when FDA issues its final standards for acceptable ingredients in nonprescription topical antibiotics.

More is involved in treating a minor wound than just smearing on a first aid product, the Panel pointed out. The kind of preparation the antibiotic comes in—cream, ointment, gel, etc.—may make a difference in how well it works. Some studies have shown that ointments are better, while other studies favor creams. The Panel said that a higher concentration of antibiotic can get to a wound from a cream formulation than from an ointment and recommended that certain cream formulations now sold only by prescription be considered for over-the-counter use, if

they are determined to be safe and effective.

To avoid possible misuse in the treatment of acute or chronic skin conditions or large wounds, the Panel recommended that products effective only as wound protectants be labeled as "first aid product," "protectant," or as first aid or protectant for small (minor) cuts, abrasions, and burns.

The Panel said that if testing shows any of the five antibiotics are safe and effective for retarding the growth of bacteria, their labeling should be permitted to include such phrases as "decreases bacteria," "helps prevent or guard against skin infection," or "treats infection."

Labels on nonprescription topical antibiotics should not be permitted to claim that the product helps kill bacteria, or speeds, helps, augments, or hastens healing, the Panel said. Claims that the product is "not an uncommon sensitizer" or that it is an antiseptic also should not be permitted, the Panel said.

The labeling of all nonprescription first aid preparations should recommend gentle washing of skin wounds before application and should carry warnings that they are not to be used longer than one week, and are not to be used in the eyes or on long-standing skin conditions such as leg ulcers, diaper rash, or hand eczema, the Panel said. It also recommended that the label advise that a physician should be consulted in the case of a deep or puncture wound or if itching, redness, swelling, pain, or other sign of infection or allergy develops when the product is used.

The conclusions and recommendations of the Panel, reached after more than two years of study, are being published in the *FEDERAL REGISTER* so interested parties may comment on them. FDA will issue final standards on acceptable ingredients and labeling after all comments have been reviewed.

Annabel Hecht is a staff writer with FDA's Office of Public Affairs.

The Medical Uses Of Sound

Ultrasound—high frequency sound waves—can produce “pictures” of the body for use in medical diagnosis. Sound pictures are better than x-ray pictures for distinguishing between soft body tissues, and high frequency waves do not travel through air so the person administering the ultrasound to a patient is not exposed to it. Ultrasound also is used for creating heat to relieve sore muscles and for a number of other therapeutic purposes.

by Phyllis Lehmann

What can locate submerged submarines, clean watches, detect brain injury, monitor development of an unborn child, destroy cataracts, and provide relief to a football player's aching knee? The answer is sound—the same physical energy that enables us to hear.

Sound waves bouncing off underwater objects are the basis of the military's sonar detection system, developed before World War II. In the past three decades, concentrated beams of sound energy have been put to dozens of peacetime uses, from cleaning watches to detecting structural flaws in buildings. But probably the most dramatic developments have been in medicine, where very high frequency sound waves—known as ultrasound—have become valuable for treating, and especially for diagnosing, illness.

The two major medical applications of ultrasound require very different approaches. In medical treatment or therapy, the purpose is to put enough sound energy into the body to produce an effect—such as heating—in order to relieve pain or loosen up stiff joints. In diagnosis, the goal is to use as little energy as possible to create a “picture” of what is going on in the body. Because in many cases it can significantly reduce the need for x

rays, the diagnostic use of ultrasound excited scientists the most. But even though many physicians seem convinced that ultrasound entails much less potential risk than x rays, FDA scientists caution that its effects are still under study.

Ultrasound was first used in medicine in the 1950's as a direct outgrowth of sonar. But another medical advance of that decade—radioactive tracers—captured scientists' fancy and most of the research money. It wasn't until the mid-sixties, when ultrasonic equipment had become more refined and concern about ill effects from x rays and radioactive materials had begun to mount, that ultrasound's popularity soared.

Today, ultrasound devices can be found in almost every major hospital, as well as in many doctors' offices. Ranging in cost from about \$1,000 to \$80,000, these units are much more widely affordable than other new diagnostic devices, such as CT scanners (computer-aided x-ray machines), which sell for \$250,000 to \$600,000.

The biggest advantage of ultrasound is that it represents a different form of energy, which unlike x rays can distinguish between soft body tissues and without injection of dyes or other invasive procedures can give physicians a picture of what is going on in such organs as the heart. And unlike x rays, high frequency sound waves do not travel through air; the physician or technician administering ultrasound can be exposed to it only through direct contact. Thus, ultrasound does not pose a potential hazard to the person administering it, as do x rays.

An ultrasound “scan” is a simple, painless procedure. The patient lies on a table, and a technician applies mineral oil to the area of the body to be scanned. (The oil assures that no air

will impede conduction of the sound waves into the body.) A small, hand-held transducer—a device that transforms electrical energy into sound energy—is then rubbed across the body. As sound waves emitted by the transducer travel through the body, they hit boundaries between tissues, which have varying acoustical properties. Some of the sound waves bounce off these boundaries back to the transducer, where they are reconverted to electrical signals that appear as lines or dots on a screen. The type of picture created by these lines and dots depends on the complexity of the machine being used.

The types of diagnostic equipment now in wide use fall into four broad categories. Described very simply, these are:

- *A-mode (A refers to amplitude.)* This is the simplest type of diagnostic unit, which gives information only along a pencil-thin sound beam, projected on a screen as a horizontal line with occasional peaks. It is commonly used to study the brain. When a transducer is placed at the side of the skull, the line on the screen peaks as sound bounces off the bone of the skull and again as it bounces off the midline structures of the brain. If the patient has a tumor, blood clot, or massive hemorrhage, the midline may be physically shifted, or pushed, off center. When the ultrasound scan, or echoencephalogram, shows a midline shift of three millimeters or more, doctors know something is pressing on the brain and can proceed with further tests.

The A-mode unit, which can be fairly small and portable, is used in emergency rooms and in some emergency vehicles for fast detection of brain injury.

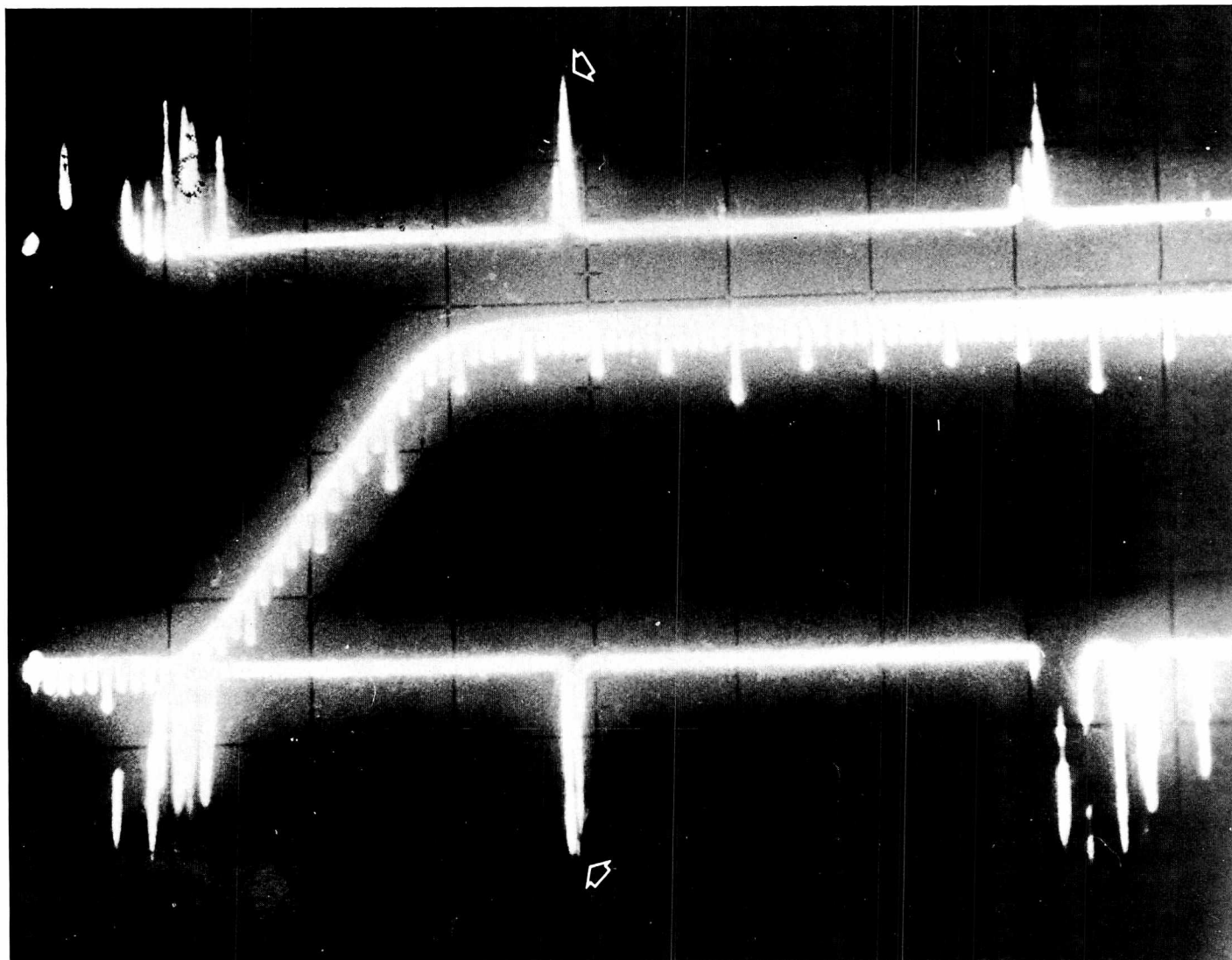
- *B-mode (brightness).* This type gives two-dimensional information



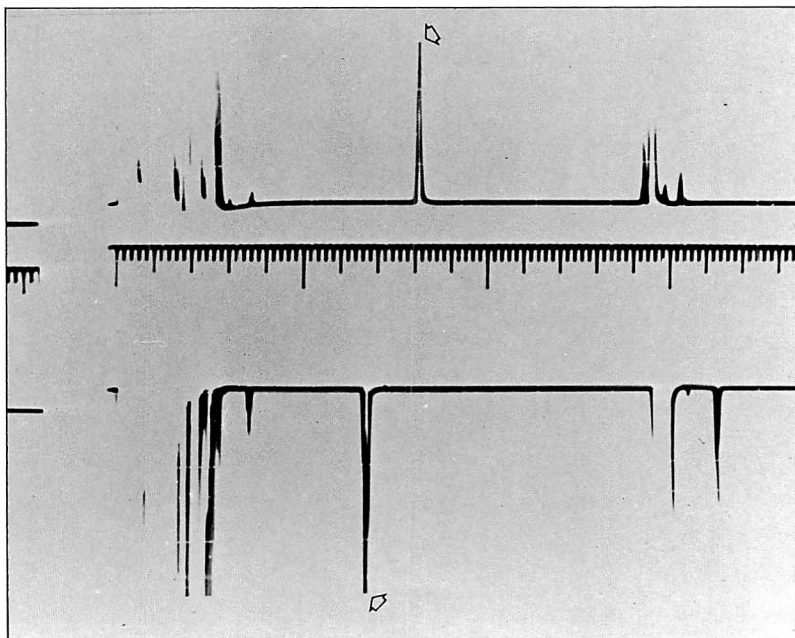
Mineral oil is rubbed on a patient's back in preparation for doing an ultrasound scan. Very high frequency sound waves do not travel through air but are easily conducted through liquid.

A hospital technician does a kidney scan by rubbing the transducer of the ultrasound machine across the patient's lower back. The ultrasound picture—called a sonogram—is projected on a screen on the ultrasound machine. A camera can be used to make a photograph of the sonogram when it is projected so it can be examined later by the doctor and can be made a part of the patient's medical record.





These two echoencephalograms, or brain scans, show how ultrasound can be used to help diagnose a head injury. The scan shown above is of a normal brain. The two parallel lines indicate the sound beam transmitted through each side of the skull. The middle peak in each line (arrows) is the echo of sound bouncing off the midline of the brain. When the middle peak on the top and bottom lines line up exactly, the scan is normal. In the scan shown at right the middle peaks do not line up, indicating a shift in the midline of the brain. This study was of a woman admitted to a hospital in a very confused state. She had fallen, but doctors did not know whether the fall had caused a brain injury or whether she had fallen as a result of a stroke. The midline shift indicated a blood clot between the brain and the skull, caused by the fall. A stroke would have caused bleeding within the brain and this would not have shown up as a midline shift. (The difference in the background color of the scans is due to the use of different types of film.)



about a slice or plane within the body. By moving the transducer across the entire abdomen, for example, the technician "paints" a picture with dots of varying brightness of the outline of body tissues. To the untrained eye, this picture—or sonogram—of a liver, gall bladder, or fetus looks like the lunar landscape, but to the diagnostician it reveals a great deal.

- *M-mode (motion)*. A more sophisticated machine, this type traces out the motion of rapidly moving structures within the body, such as heart valves. Doctors can analyze the shape of the lines that appear on the screen to diagnose various disorders of heart valves and distinguish such conditions as an enlarged heart or water around the heart.

- *Doppler*. This type of equipment makes use of what physicists call the "Doppler effect"—the change in the frequency of sound waves according to the speed at which the sender or receiver is moving. Doppler equipment measures sound reflected from such moving objects as a fetal heart or the blood flowing through an artery. The most common type of Doppler unit is continuous-wave, which means that sound waves are sent continuously through the body, creating, in effect, a motion picture. The waves reflected by the body are translated into an audible signal or "beat" that allows doctors attending pregnant women, for example, to listen to the fetal heartbeat. Continuous-wave units often are used to monitor the fetus during a difficult labor and delivery.

"When you consider all the types of equipment, the instances where ultrasound is preferable to other diagnostic methods probably run into the hundreds," says Dr. Roger Sanders, director of Abdominal Ultrasound in the Radiology Department at Johns Hopkins Hospital in Baltimore.

Probably the most widespread use of ultrasound is in obstetrics, where use of x rays is considered potentially more hazardous than ultrasound to a developing fetus. Doctors regularly scan women to detect pregnancy as early as the sixth or eighth week following conception, to find out if there is more than one fetus in the womb, to determine the exact stage of pregnancy by measuring fetal head size, to listen to the baby's heartbeat,

to see if the fetus is in the normal head-down position, and to determine the location of the placenta (if it is in front of the baby, a cesarean section would be necessary, since a regular delivery would cause excessive bleeding).

Doctors also use ultrasound as a painless, non-invasive screening method to determine the next step in diagnosing or treating disease. For example: A man enters the hospital complaining of blood in the urine, an indication of kidney disease. Doctors inject dye in a vein and take x rays, which show a mass on one kidney. It could be a cancerous tumor or a harmless cyst; both look the same on an x ray. Ultrasound can determine with 95 percent accuracy which it is, because the interior of a cyst is filled with fluid and therefore sends back few or no echoes, while a solid tumor clearly reflects sound waves. Doctors then know what to do next to confirm the diagnosis and treat the patient.

Ultrasound is much more capable than x rays of distinguishing between soft tissues in the body. Sound waves can detect a growth in soft tissue that would show up only indirectly on an x ray if it happened to be pushing against some other organ. An ultrasound scan revealed an apparent cyst and widespread pancreatitis in a 24-year-old woman recently admitted to Johns Hopkins Hospital with a vaguely palpable mass in her abdomen. Her condition would have been impossible to detect by any other means except a CT scanner.

Because it so clearly outlines soft tissues, ultrasound also can be used to "map" out the precise size, shape, and location of a cancer, so that radiation can be focused most efficiently where it is needed without damaging surrounding tissues.

Research indicates that ultrasound has promise in some other diagnostic areas as well. Scientists have found that ultrasound may be capable of detecting breast cancer in the very early stages, even before a palpable tumor exists, because changes in the elastic properties of breast tissue preceding development of a tumor change the velocity of sound waves directed at the breast.

Ultrasound also may prove to be a reliable way to detect build up of

cholesterol and other deposits in such crucial arteries as the carotid, which carries blood to the brain. If blockage in the carotid could be detected early, surgery could be performed in time to prevent a stroke. Ultrasound may provide doctors with the first opportunity to monitor the effects of drug therapy or changes in diet on blockage of the arteries.

The uses of ultrasound for therapeutic treatment are not as widespread as they are for diagnosis, but they go beyond relieving aching muscles and stiff joints. For instance, in a quick and relatively simple procedure, a doctor can use sound vibrations to "chop up" a cataract without endangering the eye. In dentistry, ultrasound is a handy device for removing the plaque, or hard deposits, from teeth.

The most widespread therapeutic use, though, is in physical medicine, where ultrasound is used to create heat to relieve pain and increase blood flow to injured tissues. Similar to the way a microwave oven uses radiant energy to cook food from the inside out, the sound waves cause molecules in the body to vibrate faster, creating friction that produces "deep heating". Most hospitals have one or two such ultrasound units for rehabilitating victims of arthritis, stroke, polio, or other disabling diseases.

There are other, more dramatic, treatment possibilities still in the research stages. Conceivably, ultrasound could be focused at high intensities to destroy cancer cells without damaging surrounding tissue. Some studies indicate, for example, that sound may be useful in treating malignant melanoma, a type of skin cancer that spreads rapidly and often is fatal.

In another study, ultrasound enhanced the effects of a cancer drug on leukemia cells of a mouse, apparently by increasing their uptake of the drug. Although ultrasound is not yet being used to treat cancer in humans, these studies indicate that it could become a valuable tool for fighting this dread disease.

With all its current and potential uses, ultrasound seems to have a bright future. But is it really safe? Most experts think so, but notes of caution are being sounded. After all, ultrasound has been widely used for



Food Additives And Hyperactive Children

by Timothy Larkin

Do the synthetic colors and flavors used in food cause some children to be unusually active and interfere with their ability to learn? One theory says they do, and FDA is seeking to simulate carefully controlled tests to determine whether there is a connection between artificial colors and flavors and hyperactivity.

As Dr. Benjamin Feingold describes it in his book, **WHY YOUR CHILD IS HYPERACTIVE**, one summer day in 1965 a middle-aged woman arrived at his office. Dr. Feingold, then chief allergy specialist at the Kaiser Permanente Health Care Program in San Francisco, found the woman to be "suffering from acute hives. Her face was swollen, mainly about the eyes. . . . She looked, and obviously felt, miserable."

Feingold had done research on certain chemicals found in the saliva of fleas whose bites produced comparable allergic reactions. He suspected that the woman might be suffering from an allergic reaction to a similar group of chemicals that are present in artificial colors and flavors used in foods, as well as in some 21 fruits and vegetables. He decided to put the patient on a diet free from such substances, which he called an "elimination diet," later also known as the Kaiser-Permanente or K.P. diet.

The diet worked. The woman's skin condition cleared up. Ten days after the woman's initial visit, Feingold received a call from Kaiser-Permanente's chief of psychiatry who informed him that the allergic patient had been undergoing psychotherapy for two years for some serious personality disorders. But now, in less than two weeks, these symptoms had disappeared.

"How did you treat that patient?" he was asked.

That question started a train of thought that consumed a great deal of Dr. Feingold's time during the follow-

ing years, led to his book, started a scientific controversy that still continues, stimulated hearings in the U.S. Congress, and kindled hope in thousands of parents and teachers driven to, and often over, the edge of patience by children who seemingly cannot sit still, be quiet, listen to instructions, or learn at rates in keeping with their intelligence.

Dr. Feingold began by wondering whether the same diet that produced such a direct psychological, as well as physical, change in his female patient might have similar impact on persons with other problems of apparently psychological nature, among them the hyperactive or, as Feingold calls them, "hyperkinetic" children with learning disabilities (H-LD children).

As he became more aware of the extent of the problem of overactive children, Feingold's interest became locked onto a search for ways by which a change in diet might also lead directly to a change in behavior. Shortly after he explained his still incomplete theory on a San Francisco television show, Feingold was contacted by a mother whose otherwise intelligent son was a bundle of tireless and misdirected energy leading him to such bizarre behavior as trying to run his tricycle into an oncoming car. Young Johnny had all the usual H-LD symptoms, and his exhausted parents were now contemplating a physician's recommendation that he be given a stimulant drug that, for reasons yet unclear, often has a calming effect on H-LD children.

Worried that this treatment might make their son dependent on drugs, the parents were ready to grasp at straws. They brought Johnny to Dr. Feingold who began with a physical exam. Since the lad proved to be normal physically, Feingold suggested the elimination diet, to be strictly monitored by the parents. Since Johnny was well within the normal boyhood behavior in his love of sweets, Feingold also advised that

such "sweet tooth" demands be responded to by homemade candy, ice cream, and pastries, all free from artificial flavors and colors.

In addition, Feingold asked the parents to maintain a meticulous "diet diary," writing down *everything* that Johnny ate or drank, with particular attention being paid to lapses from the diet and any subsequent alteration in behavior. The diary later showed that Johnny's behavior improved markedly when he followed the diet and that he resumed his overactive behavior when he ate something—a candy bar, artificially-flavored cereal or vitamin tablets—not prescribed by the diet.

Based on these and similar experiences with other "Johnnies," Feingold became convinced of a direct relationship between H-LD and diet. His book contains a detailed explanation of his theory and how he arrived at it, buttressed with case histories and testimonial letters. It also provides sample menus for those who wish to follow the elimination diet. Feingold currently also proposes three actions by Government and industry: full disclosure on food labels of the use of artificial flavors and colors; an educational effort by the Food and Drug Administration to tell consumers about what Feingold calls the "inherent potential" of chemical color and flavor additives; and a requirement that food free of synthetic colors and flavors be designated by a special, easily recognized package symbol.

In September 1975 the Senate Subcommittee on Administrative Practice and Procedure held hearings on the Feingold theory. Testimony was heard from Dr. Feingold and from children and parents who had endured the destructive symptoms of H-LD and who had tried the elimination diet with beneficial results. FDA's position on the Feingold thesis and his suggestions about labeling foods and beverages was given by the then Commissioner of Food and Drugs Alexander M. Schmidt, M.D.

Commissioner Schmidt emphasized that the FDA takes the Feingold thesis very seriously. For that reason the Agency was instrumental in getting an intergovernmental task force set up to concentrate expertise and to attempt to find funds for testing the thesis. This Interagency Collaborative Group on Hyperkinesis is composed of 29 specialists from FDA, the National Institute of Mental Health, the U.S. Office of Education, and the National Institute for Child Health and Human Development.

In regard to Dr. Feingold's specific recommendations, FDA already requires all foods and beverages (except a limited number of standardized foods exempted by law) to state on the label when artificial colors or flavors have been used. The Commissioner also said in his testimony that FDA has no objection if food manufacturers wish to use a symbol or logo on the labels of their products signifying the absence of artificial colors and flavors, provided that the food products are in fact free of artificial colors and flavors. The Commissioner explained, however, that under present law FDA cannot require that such a symbol be used, nor is it in a position to recommend changing this law or in any additional way acting on the basis of the Feingold theory until certain questions about the theory are answered.

It is these answers that the Interagency Collaborative Group on Hyperkinesis was set up to pursue.

The questions all center about whether what Dr. Feingold is presenting will remain interesting theory or can move from theory to established fact. There are two major obstacles to that movement: lack of a demonstrated connection between cause and effect, and failure to conduct a so-called double blind study of the theory.

If a scientist believes something, y, causes something else, x, it is necessary to prove this by experiment. Before being accepted by the scientific community as fact, the experiment must be capable of being repeated a number of times and always produce the same result. (This is called replication.) If it is suggested, for example, that adding a certain catalyst, iron, to a proper amount of hydrogen and

nitrogen, will cause ammonia to be produced far more rapidly than would be the case without iron, this can be tested and retested. If it is believed that light bends due to the pull of gravity, repeated astronomical measurements can check it out.

Unfortunately, the link between the effect, hyperkinesis, and what Dr. Feingold believes to be a cause—certain chemicals—is far from being so clear cut, easily demonstrated, or replicated.

One difficulty involves the need to know exactly what an experiment is supposed to be measuring. Hyperactivity is not a well-defined affliction and there is no simple diagnostic test to detect it. Hyperactivity is a collection of symptoms that have widely varying causes. Taken together, such symptoms may indicate that a child has a genetic makeup that produces overactive behavior when stimulated by a particular group of chemicals.

But the symptoms could mean something entirely different, not a hyperactive child, but rather a child who is behaving hyperactively because of hunger or from boredom with uninteresting or badly conveyed learning matter. The child could simply be reacting to too many other children crammed into one class, or the symptoms could be the result of a multitude of other factors—social, psychological, biological, or environmental. The Council on Child Health of the American Academy of Pediatrics points out that in some cases what a frustrated adult describes as hyperactivity might be normal behavior for an energetic, curious child.

Another difficulty involves designing an experiment that will demonstrate a clear relationship between cause and effect. For example, it has been found that the foods eliminated by the Feingold diet lower the intake of a number of other substances, such as vitamin C and carbohydrates. It could therefore be argued that what is actually being demonstrated is not a cause and effect relationship between certain chemicals used in food additives and hyperactivity, but between carbohydrates and hyperactivity. Unless experiments can be designed to demonstrate the effect of eliminating only the suspect chemicals from the diet, it will be difficult to prove that

these chemicals are the cause.

A related cause-and-effect difficulty stems from the way parents and children involved in the elimination diet interact. The diet involves giving children a great deal of attention—attention of an entirely different kind than merely irritated response to irritating behavior. Parents work with their children on such constructive projects as devising menus, recording detailed information in diaries, checking on progress, and making cookies and other foods at home.

If, after some days or weeks of this kind of close, loving attention and interaction, a child's behavior changes, is the cause the elimination diet or the new and positive atmosphere of parental concern enveloping the use of the diet? Or is it both? Again, there is no single isolated cause to account in a scientifically convincing way for any effect. Studies have shown that when children are found to be diabetic and a change in diet is accompanied by increased attention from their parents, the children's behavior changes even though the diet is intended solely to control the disease.

Another set of difficulties arises from the lack of a double blind study. Dr. Feingold certainly believes wholeheartedly in the usefulness of his diet, and he is articulate, enthusiastic, and convincing. Parents who try it with their overactive children certainly want to believe in it. And there must be at least some children who want to please their parents and live up to expectations that the diet will improve their behavior. There is nothing wrong in any of this, but it has long been known that when sick people are given a pill that they believe will help them they may get better even if the "medicine" is only a sugar pill or so-called placebo.

It is relatively easy to eliminate this "expectation" factor in experiments involving vaccines or drugs. Two groups are established, a control group and an experimental group. Only the experimental group gets the substance whose effect is being studied. The control group gets a neutral substance, a placebo. None of those in a position to affect the data being gathered know which is the control group and which the experimental, which the placebo



and which the real thing. This is called a double blind study, because both giver and receiver are "blind" to the true nature of what is being given and received.

Lack of these kinds of proof is why scientists question even the most convincing array of testimonials and letters of appreciation, such as those which appear in Dr. Feingold's book and were presented to the Senate subcommittee.

What is needed then are carefully conducted and objective experiments. A number of these have been initiated or are underway. To date, they have succeeded primarily in determining exactly how a study should be conducted to produce a scientifically valid assessment of the Feingold theory. It is now agreed that the experiment should:

- Assure random assignment of the children being tested.
- Include enough children to make the data meaningful.
- Include careful examination of the children to assure that they are in fact hyperkinetic.
- Use the double blind and placebo technique.
- Establish standardized ways to

measure the children's behavior, with measurement to include the period before the experimental diet is used in order to establish a "baseline" or normal behavior level.

- Develop ways to make sure that the children do not deviate from the diet.
- Establish methods of statistical analysis appropriate to the experiment.

Earlier studies of the Feingold theory, because they did not meet all these requirements, are considered inconclusive, although all were useful in clarifying study requirements.

In one experiment carried out to test the Feingold theory by the Food Research Institute of the University of Wisconsin, 36 boys between the ages of 6 and 12 were used for the study population. The preliminary findings show no significant overall effect from the Feingold diet either as measured by classroom behavior or by parents. FDA is supplying the funds needed to complete the analysis of the data from this study.

Also, the Interagency Collaborative Group on Hyperkinesia prepared and approved two additional study proposals, one to be carried out at the

University of Wisconsin and the other at the Kaiser-Permanente Center in California. The former involves school-age hyperkinetic children; the latter, children from 1 to 5 years old. Both involve so-called "challenge" studies: children identified as having improved while using the elimination diet will be given food containing (are challenged with) a mixture of artificial colors to see if they then revert to hyperactivity. In addition, the National Institute of Mental Health is funding a study at the University of Pittsburgh.

It is hoped that these studies will provide the scientific data needed to answer some of the questions concerning the possible association of dietary factors and H-LD.

Until a final and conclusive evaluation of the theory is in hand, the American Academy of Pediatrics urges parents not to use the elimination diet on any long-term basis simply because no one yet knows its long-term effects.

Timothy Larkin is a special assistant to the Commissioner of Food and Drugs.

New Standards For Test Laboratories

Before any new drug can be tested in people, it must be tested in laboratory animals to show that it is safe. Food additives also are tested in animals for safety before they are permitted on the market. The results of animal tests always have been reviewed carefully by FDA, but the labs that carry out the tests were not subject to regular inspection. Now, as part of a major new research monitoring program, FDA has proposed strict standards covering the operation, maintenance, and personnel of laboratories that test drugs and food additives in animals.

by Annabel Hecht

Under the laws regulating the marketing of medicines in the United States, the manufacturer is responsible for testing a drug to show that it is safe and effective for its intended use.

How animals are cared for and handled could make a difference in the outcome of a laboratory study. The Animal Welfare Act of 1970 and the U.S. Department of Health, Education, and Welfare's Guide for the Care and Use of Laboratory Animals are cited in the proposed regulations as the standards to be followed by testing labs.



Experiments to determine safety are one of the first steps in the development of a new drug. FDA requires that carefully controlled animal tests be conducted to find out whether the product has any toxic effects and whether it can cause birth defects or cancer. Such animal tests are crucial because it is based on this evidence that FDA gives the manufacturer permission to go ahead with tests in humans to determine the product's effectiveness in treating specific diseases.

Food additives also are tested in animals for safety before they are permitted on the market.

The results of animal safety tests submitted by manufacturers of drugs and food additives always have been carefully reviewed by FDA. But the laboratories that actually carried out the tests have not been inspected in the

past unless serious questions were raised about the data. There were no standards or regulations covering acceptable laboratory procedures and no systematic way to check out testing facilities.

Now, however, research laboratories and the work they do are subject to much closer scrutiny by FDA. This new approach stems largely from findings by FDA that some testing laboratories were not doing their job well and in some cases were falsifying and withholding important information about the animal studies. As a result, FDA received incorrect or inadequate information and several drugs that could cause harmful side effects were allowed on the market without adequate warnings.

This problem was not an isolated one. FDA's investigation revealed that not only one large drug company

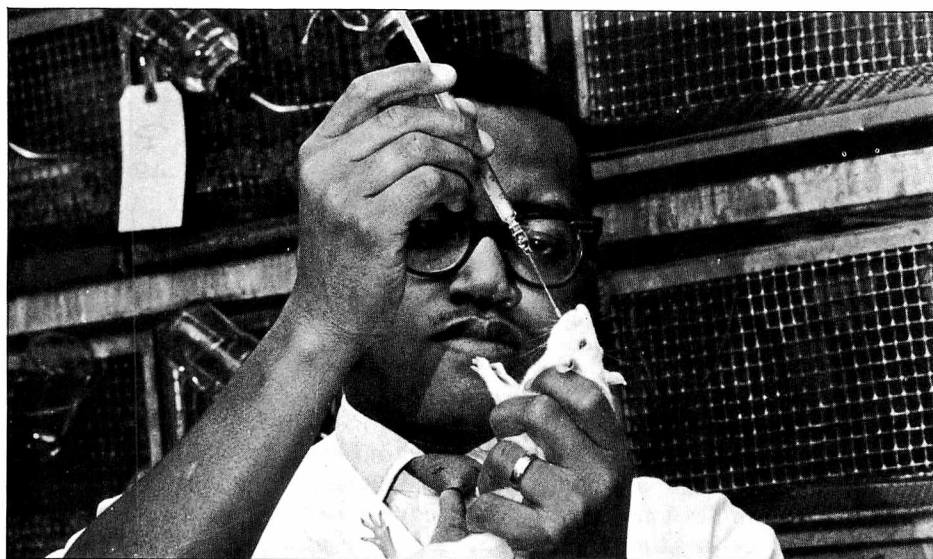
laboratory, but several independent testing facilities as well, had serious deficiencies in their procedures. The Agency found that in some laboratories:

- Experiments were poorly conceived, carelessly executed, and inaccurately or incompletely analyzed.

- Technical personnel were unqualified and failed to follow test procedures, make accurate observations, keep accurate records, and properly handle the animals during the study and at autopsy.

- Management of the laboratories failed to supervise their employees and the sponsors of the research—the companies who were paying to have the studies done—did not monitor the work in progress.

The problem is not unique to FDA; it is one shared by all Federal agencies regulating or evaluating chemi-



The proposed Good Laboratory Practice Regulations require that equipment used to administer test substances be designed to assure that the animal gets the correct dose.



Careful preparation, cutting, sectioning, and mounting of animal tissues that are to be examined is crucial to a good laboratory study. Much valuable information has been lost because laboratories have not had written instructions covering these procedures.

To make certain that diseased animals are not used in laboratory studies and to prevent the spread of infection to animals already in the facility, newly arrived animals should be quarantined until their state of health has been determined.



Separate areas for mixing feed are a "must" under the proposed laboratory regulations. This worker, filling boxes with feed containing a potentially hazardous substance, is protected from exposure to the test material by a plastic hood.



icals. And its full dimensions are still unknown.

To insure that medical products and food additives are as safe as their makers claim them to be, FDA has put into operation a comprehensive Bioresearch Monitoring Program. The \$16 million effort provides not only for the monitoring of testing facilities, but the people carrying out the actual research and the firms or organizations sponsoring it.

One of the first steps taken under the new program was development of proposed Good Laboratory Practice Regulations, popularly called GLP's. Like the Good Manufacturing Practice Regulations governing actual production of drugs for medical use, the proposed GLP's set standards for every aspect of animal or other laboratory studies from operation of the laboratory and maintenance of equipment to personnel and recordkeeping.

For instance, the proposed regula-

tions call for an adequate number of appropriately qualified people to conduct the studies and a scientist or other qualified professional, designated the study director, to oversee the work. Clearly written "protocols" are required which define the objectives of the study and the minimum information to be obtained. Written operating procedures are to describe in detail the methods for performing the various laboratory operations.

A quality assurance unit, headed by someone other than the study director, is required to make sure that the written procedures are being followed. And a professional staff person is to be on hand at all times to assist technicians when questions or problems come up.

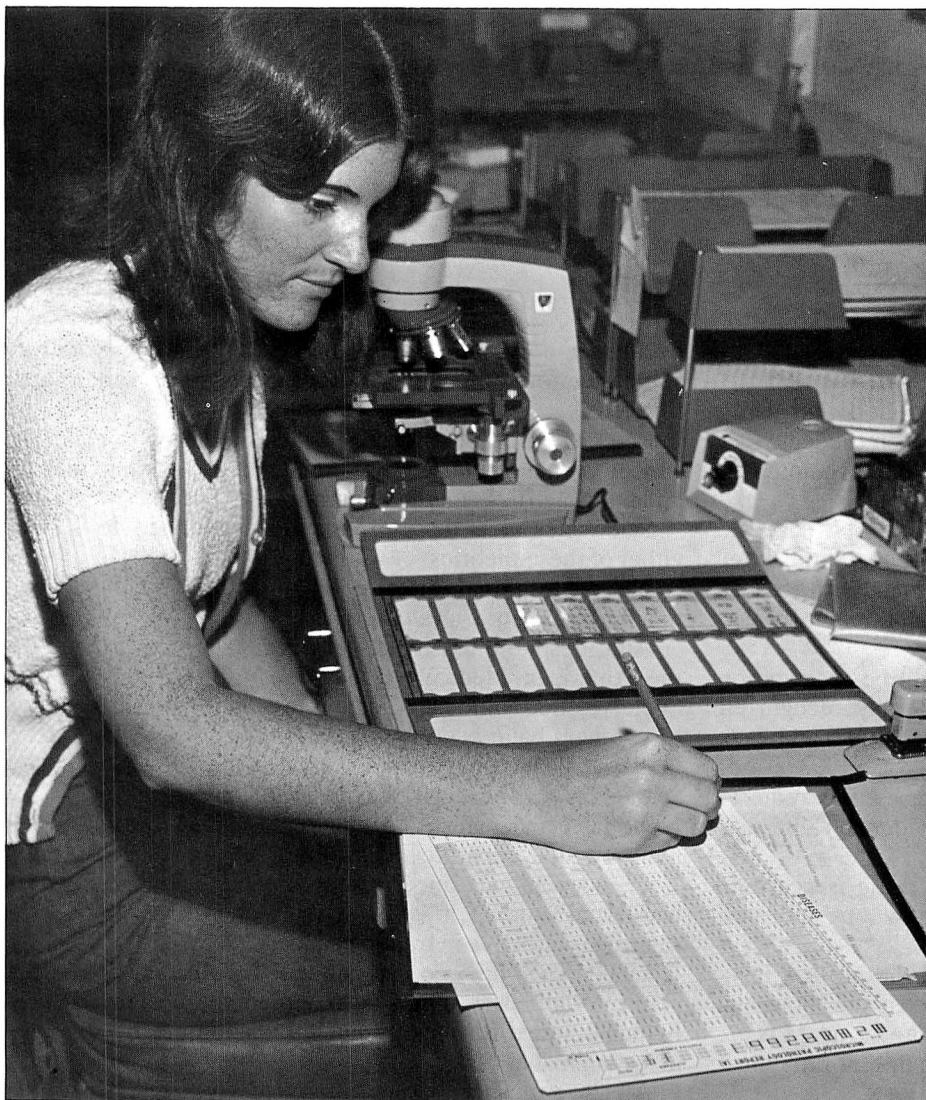
The proposed regulations covering laboratory facilities specify that separate areas or well-defined areas be provided for different on-going studies and that separate sections be set aside

for work with radioactive or other hazardous materials. Newly-received animals and sick or diseased animals require isolated quarters. Separate areas are also required for storage of feed and other supplies and for handling of test substances.

Concern for the working conditions of the staff and the comfort of the test animals is reflected in the requirement that facilities be constructed to minimize noise that might interfere with the collection of data or cause distress to the animals.

What goes into the test animals is the crux of the matter and the proposed GLP's specify that the identity, purity, quality, and strength of substances to be tested, as well as control material, be known and documented before the study begins. Feed samples should be tested periodically to be sure that test substances have been thoroughly and uniformly mixed.

When it comes to the final report to



FDA's investigation of testing laboratories revealed that in some cases test data were not recorded accurately or were actually lost before a record could be made. The proposed regulations specify that such information is to be recorded immediately and accurately in bound books with numbered pages or on worksheets that can be bound later.

FDA on the tests, the proposed regulations call for some 14 items starting with who did the work, why, and how it was done. Unforeseen circumstances that may affect the quality of the study are to be included, and each researcher involved must date and sign his segment of the report. The study director is responsible for the final document. Raw data, documentation, and specimens are to be kept in an archives for certain periods of time.

The proposed Good Laboratory Practice Regulations will apply to most laboratories conducting studies in support of any product regulated by FDA, including prescription and non-prescription drugs, biological and radiological products, medical devices, and food and color additives. Not to be included are laboratories involved in basic research on the causes of disease, studies to determine physical or chemical characteristics of a test substance or the pharmacological activity

of drugs, and tests involving human volunteers as subjects. About 550 testing laboratories in this country and some abroad will be affected by the proposed regulations.

Adherence to the standards should help laboratories avoid some of the scientific "horror stories" unearthed by FDA investigations: long-term studies carried out with no one in charge; dead animals recorded as being alive and well; mixing equipment encrusted with material from previous studies; autopsy reports altered and signed by people who did not participate in the work.

Laboratories that do not follow the proposed regulations may find that their work will not be accepted by FDA as supporting data for requests to market a new drug or other product. Failure to comply with the regulations also could result in a laboratory being disqualified as a testing facility. In extreme cases, such as submission

of false data, criminal prosecution could result.

The proposed Good Laboratory Practice Regulations were published in the November 19 FEDERAL REGISTER. A four-month period—ending in mid-March—was allowed for written comment from interested persons. In addition, a public hearing was held February 15 by FDA to provide an opportunity for an exchange of views on the scientific soundness and practicability of the proposed regulations. All comments, written and oral, will be taken into consideration in developing the final regulations.

In the meantime, FDA investigators have inspected about 40 animal laboratories to look at current practices in light of the proposed GLP's and to get a broader view of the quality of current research.

Annabel Hecht is a staff writer with FDA's Office of Public Affairs

News Highlights

Testimony Invited on Status of Laetrile

In response to a court directive, the Food and Drug Administration has invited public testimony on the legal and scientific status of Laetrile, a substance widely promoted as a cancer "cure."

Also known as amygdalin and vitamin B-17, Laetrile occurs naturally in the pits of apricots, peaches, and bitter almonds. The substance has been promoted as a cancer "cure" for about 25 years. Recent promoters claim it also prevents cancer.

Written testimony and oral argument will be received on two specific questions: 1) Is Laetrile generally recognized by experts as a safe and effective anticancer drug?; and 2) Is Laetrile, by virtue of its marketing before the 1962 Food, Drug, and Cosmetic Act, exempt from that law's requirement that a drug be shown by scientific evidence to be safe and effective before it can be marketed?

FDA will accept written testimony on these issues until March 25. Written replies to that testimony will be accepted until April 22.

Oral argument on the issues raised by the written testimony will be held before a representative of the Commissioner of FDA in Kansas City, Missouri, on May 2. Anyone who wants to make a presentation at that time must file a written notice by April 22.

FDA's Bureau of Drugs will participate in the proceedings as a proponent of the position that Laetrile has not been proved safe and effective as an anticancer drug and that it is not exempt from FDA regulation.

In announcing the invitation for public testimony, FDA emphasized that "this proceeding . . . is being undertaken by FDA solely because the Agency was directed to do so by the Court of Appeals."

FDA made clear that the proceedings will not deter the Agency from continuing to take regulatory action against commercial distribution of Laetrile.

The Court of Appeals for the Tenth Circuit, in October 1976, ordered FDA to compile an administrative rulemaking record concerning Laetrile. The written testimony and oral arguments are to be a part of this record. When complete, the record will be submitted to the U.S. District Court in Oklahoma City. The case before the district and appeals courts involves a cancer patient seeking to obtain Laetrile.

Several cases similar to this one have been instituted in other Federal courts. In the majority of these cases, the court has ruled in FDA's favor. No court has authorized the sale of Laetrile in the United States or its importation for commercial distribution.

Early promoters of Laetrile claimed that it worked by seeking out cancerous cells and destroying them with cyanide, a deadly chemical contained in Laetrile. The promoters claimed that healthy cells were safe from Laetrile

because the cyanide release could only be triggered by a substance found in cancerous cells but not present in healthy cells.

Later the promoters changed their approach to claim that cancer is caused entirely by a deficiency of "vitamin B-17" and that Laetrile is this "vitamin."

Scientists have never found any evidence to support either of these theories.

No professional dietetic or nutrition group has ever recognized Laetrile as a vitamin.

And, despite intensive effort over many years, the FDA, the American Medical Association, the American Cancer Society, the National Cancer Institute, and independent researchers have been unable to find any scientific evidence that Laetrile has any effect on cancer.

Laetrile is the most tested of all cancer "cures." The National Cancer Institute alone has tested Laetrile in animals on five separate occasions between 1957 and 1975. Four independent cancer research centers which undertook additional studies in 1975 have found no evidence that Laetrile is effective in treating cancer.

Under U.S. law, no drug intended for use against cancer or any other disease can be regarded as safe for testing in humans until it first shows some indication of effectiveness in test animals.

All 26 anticancer drugs approved by FDA since 1962 were first shown to be effective in animals before being tested for safety and effectiveness in humans.

Notice of the Laetrile proceedings was published in the *FEDERAL REGISTER* February 18, 1977.

Written testimony can be submitted to the office of the FDA Hearing Clerk, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20857. Copies of all testimony will be maintained there and at FDA offices in Brooklyn, New York; Atlanta, Georgia; Chicago, Illinois; Kansas City, Missouri; Los Angeles, California; and Seattle, Washington.

Cutback Urged in Antibiotics in Feed

The National Advisory Food and Drug Committee has recommended to FDA that certain antibiotics no longer be added to animal feed as growth promotants, but instead be limited to treatment of animal disease and illness.

Antibiotics are used in feeds to assure healthy animals with good growth characteristics. There has been concern over the effect such antibiotics might have when they are fed to meat animals, then carried forward to humans as residues in that meat. Another problem is that the bacteria in and around animals could become resistant to the antibiotics used in animal feed. If those same antibiotic-resistant bacteria caused disease in people, then the antibiotics might not work in treating the disease.



The committee urged that FDA prohibit the low-level uses of penicillin in animal feed for growth promotion, and prohibit use of penicillin for prevention of disease to the extent that substitutes are available. It further recommended that the mixing of animal feed containing tetracycline and penicillin be limited to feed mills and livestock producers holding specific approval from the Agency, and to veterinarians.

The committee affirmed that the long-term goal of FDA should be to eliminate from animal feed the use of any drugs used to treat disease in people.

The Committee report is now under review by the Agency. After the evaluation is completed, FDA will announce its policy on the use of antibiotics in animal feed.

FDA to Review All Food Additives

The Food and Drug Administration has announced a new and far-reaching program to provide for the periodic review of all food additives to make sure they are safe by modern standards.

Under the program, all substances added to foods—including preservatives, colors, flavors, and substances that may get into food from packaging—will undergo a regular scientific re-evaluation.

If new tests are indicated by the review, FDA will require that the tests be made by the manufacturers who make or use the additives.

If re-evaluation indicates that an additive needs to be restricted or removed from the market, FDA will take that action.

The program was announced by Sherwin Gardner, Acting Commissioner of FDA, in testimony before the Senate Select Committee on Small Business.

“Under the law, the FDA must decide on the basis of the best available science if a proposed food additive is safe for human use. If it is, then FDA must approve that additive. The law does not specifically require periodic re-

evaluation of a safety decision once made,” said Gardner.

“But science is dynamic and a food additive judged safe by the science of 1970 may very well be suspect by the science of 1977.”

Gardner said the new program is made possible by new resources given FDA by Congress. Under this program, FDA will periodically re-check its past scientific decisions about food additives against the latest scientific information and methods.

The re-evaluation process will start in March when a team of FDA scientists will begin to develop a priority list for the 2,100 substances added directly to foods. Each substance on the list will be given a review priority based on the potential health risk posed by that substance.

In April, the Agency will begin an industry-wide survey to ascertain how much of each additive a consumer might be exposed to. The result will provide one criterion for establishing review priorities. Within 18 months the Agency expects to establish profiles for each additive and to make preliminary judgments about its regulatory status.

The program also will include reviews of indirect additives—that is, substances that may leach into food from packaging.

The program will incorporate several FDA efforts already underway, including the review of additives that are Generally Recognized As Safe (GRAS), the development of criteria for evaluating the safety of flavors, and the recently-completed evaluation of all colors which have been provisionally approved by the Agency.

Label Notice Proposed on Use of Yellow 5

The Food and Drug Administration has proposed a series of actions to assure that people allergic to Yellow No. 5, the most widely-used color additive, will be able to avoid it in foods and drugs.

FDA estimates that 47,000 to 94,000 people in the United States may be allergic to Yellow No. 5, also known as tartrazine. Allergic reactions to Yellow No. 5 include asthmatic symptoms, such as wheezing and difficulty in breathing; hives; and stuffy or runny nose.

The Agency proposed that:

- The labels of foods containing Yellow No. 5 identify the color by name in the list of ingredients. Previously, all colors used in food products only needed to be identified in the ingredient listing as “artificial coloring,” as provided for by law. The principal uses of Yellow No. 5 in foods are in beverages, candy, desserts, cereals, bakery goods, ice cream and sherbet, dairy products, and snack foods.

- Yellow No. 5 be prohibited in drugs used frequently by allergic people. The ban would apply to five categories of nonprescription drugs (pain relievers, antihistamines, cough-cold remedies, anti-asthmatic drugs and nasal decongestants taken by mouth) and to seven categories of prescription drugs (the previous five plus steroidal and nonsteroidal anti-inflammatory drugs).

- Drugs that continue to be colored with Yellow No. 5 be required to carry on the front label the warning statement: “This product contains FD&C Yellow No. 5 which may cause allergic-type reactions in certain susceptible people.” Coloring is used in drugs to help identify medicines by kind and dosage.

Sherwin Gardner, Acting Commissioner of Food and Drugs, said: "Yellow No. 5, as currently used, poses no hazard to the general population. But those people who are allergic to Yellow No. 5 ought to be able to identify it in their foods and drugs and avoid products containing it. The proposals we are issuing are designed to accomplish these objectives."

Estimates of the number of people allergic to Yellow No. 5 are based on the number of people estimated to be allergic to aspirin. Allergic responses to Yellow No. 5 seem to occur primarily in people allergic to aspirin. About half of the people who have had allergic reactions to aspirin are also allergic to Yellow No. 5.

There is no evidence of allergic reactions to Yellow No. 5 from its use on the skin, so the proposed regulations do not apply to externally-applied drugs or cosmetics.

The proposed labeling requirements would take effect one year after the issuance of a final regulation. The ban on Yellow No. 5 in certain drugs would take effect six months after a final regulation is published. No product recalls would be required.

The proposals were published in the February 4, 1977 *FEDERAL REGISTER*. Comments may be submitted within 60 days of that date to the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20857.



Survey Finds Little Kepone in Seafood

A special survey conducted by FDA has shown that seafood from the Chesapeake Bay and Atlantic and gulf coast waters generally contained either no residues of the pesticides Kepone and Mirex or residues well below current FDA legal limits.

In late 1975, it was discovered that discharges during the manufacture of Kepone, a pesticide used as an ant poison, contaminated fish from the James River in Virginia. In mid-1976, it was shown that Chesapeake Bay seafood may also have been contaminated by Kepone. Mirex, which is chemically similar to Kepone, is used to control fire ants in many Southern States.

FDA conducted its survey from July to December 1976 to see the extent to which these two pesticides have left residues in fish in areas of the country where they have contaminated the environment, and to assure that fish do not contain these contaminants in amounts above the FDA action level.

The action levels set by FDA, based on recommendations from the Environmental Protection Agency (EPA), are 0.1 parts per million (ppm) for Kepone and Mirex in finfish; 0.3 ppm for Kepone in clams and oysters; and 0.4 ppm for Kepone in crabs. Any seafood containing amounts above the action level would be subject to FDA regulatory action.

The survey consisted of 300 samples, collected mainly from wholesale seafood markets. Each sample contained about 10 fish. The survey showed:

- Of 102 Chesapeake Bay samples, two contained Kepone residues above the action level. The two samples, both at 0.14 ppm, were of bluefish and spot.
- Overall, finfish samples from the Chesapeake Bay, representing nine species, contained an average Kepone

residue in the 0.03-0.05 ppm range. Bluefish from the Bay averaged 0.05 ppm.

- All crabs tested from the Bay contained measurable Kepone, but none exceeded the action level. Clams and oysters contained no Kepone or trace amounts.

- For bluefish caught along the Atlantic coast, the average Kepone level was 0.02 ppm or less. The highest levels were found in samples from the Virginia coast, ranging from 0.01 to 0.06 ppm. None of the 66 bluefish samples from the Atlantic coast exceeded the action level.

- Of 132 samples from the South Atlantic and gulf coast, one contained Kepone. This was a finding of a trace amount in a crab sample from Georgia.

- One of the 132 samples from the South Atlantic and gulf coast contained Mirex above the action level. Most other samples contained no Mirex or just trace amounts.

FDA has supplied its report to EPA and all affected States. FDA will continue to monitor Kepone in fish, coordinating sampling efforts with Virginia, Maryland, and EPA. The Agency will continue also to provide assistance to New York and Pennsylvania for studies of Mirex and Kepone contamination in fish from waters in those States.

EPA now is re-evaluating the action levels for Kepone. EPA expects to complete its review in March and make recommendations to FDA.

Group Named to Advise on Cancer Agents

A group of 30 people drawn from outside the Government has been named by the National Cancer Institute to help it in identifying and evaluating cancer-causing chemicals in the environment.

The group, called the Clearinghouse on Environmental Carcinogens, will consider: 1) chemicals that should be tested in animals to determine cancer-causing potential; 2) appropriate experimental conditions for the conducting of

tests; 3) the significance of test results; and 4) the risk to humans from those chemicals found carcinogenic. Clearinghouse membership is divided into subgroups to address each of these areas. In addition, the Clearinghouse will respond to requests for advice on environmental causes of cancer from Congress, the President's Cancer Panel, the National Cancer Advisory Board, and other Federal agencies.

Voting membership of the Clearinghouse is limited to 30 non-Government persons, drawn from academic, medical, and scientific research institutions, as well as from industry, organized labor, and public interest groups. The members are selected on the basis of their knowledge and experience in the many aspects of cancer causation as related to environmental chemicals. Collectively, they provide expertise in medicine, law, laboratory animal sciences, chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology.

Chairman of the Clearinghouse is Dr. Arnold L. Brown, chairman of the department of pathology and anatomy at the Mayo Clinic in Rochester, Minnesota. Dr. James M. Sontag of the National Cancer Institute serves as the executive secretary for the Clearinghouse.

In addition to the voting membership, representatives of various Government agencies concerned with environmental causes of cancer also will participate in the activities of the Clearinghouse. These agencies include the Food and Drug Administration, Environmental Protection Agency, Occupational Safety and Health Administration, Department of Agriculture, and a number of institutes of the National Institutes of Health.

All meetings of the Clearinghouse and subgroups will be open to the public.

Label Warning Proposed for Bubble Bath

The Food and Drug Administration has proposed that bubble bath labels be required to carry the following statement: "Caution—Use only as directed. Excessive use or prolonged exposure may cause irritation to skin and urinary tract. Discontinue use if rash, redness or itching occur. Consult your physician if irritation persists. Keep out of reach of children."

For bubble bath sold as powder, FDA proposes to require an additional cautionary statement saying: "Avoid inhalation of dust to prevent respiratory discomfort."

Sherwin Gardner, Acting Commissioner of Food and Drugs, said: "The Food and Drug Administration has received many complaints from consumers and physicians about adverse reactions from bubble baths. The reactions range from rashes and itching to injuries to the urinary tract, bladder and kidney, and genital disorders, particularly in girls. Other reports are of eye irritation and respiratory disorders. Many of these reactions required medical attention.

"The cautionary label we are proposing will alert consumers to the potential for these reactions and will advise them to consult with their physicians if irritation persists. We hope this caution label will reduce misuse of bubble baths and lower the number of injuries to consumers."

FDA has met several times with bubble bath manufac-

turers in an effort to reduce the number of injuries. In 1971 FDA asked the manufacturers to remove all harsh ingredients from bubble baths.

The number of adverse reactions reported since then, however, has been relatively constant.

In a 1974 survey of cosmetic adverse reactions, FDA found the rate of adverse reactions to bubble baths was 14 per 10,000 product uses, compared to a rate of 6.9 for all cosmetics.

The proposal to require the cautionary statement appeared in the *FEDERAL REGISTER*, January 28, 1977. Comments will be accepted for 60 days and may be sent to the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20857.



FDA X-ray Training Materials Get Wide Use

By 1980, an estimated 50,000 users of diagnostic x-ray equipment will have benefitted through use of training materials produced by FDA. As part of its efforts to reduce unnecessary exposure to radiation, FDA's Bureau of Radiological Health has developed a series of training and educational programs for health care professionals in medical and dental radiology. These programs include:

- A self-contained teaching system covering the major segments of diagnostic radiology. The system—called the Diagnostic Radiology Health Sciences Laboratory—now is being used in 44 medical and osteopathic schools in the United States, and soon will be in use in 22 more. It is expected to reach the entire medical school community by 1980.

- A series of five slide/tape packages designed to teach radiologic technologists how to protect patients and themselves from unnecessary x-ray exposure. The series is entitled Radiation Protection During Medical X-ray Examinations.

- A program that enables users to determine their areas of weakness and to identify materials to correct deficiencies. This Self-Assessment Program will be fully implemented in 1977.

FDA also has publications, slides, videotapes, audio cassettes, and movies on such subjects as basic principles of radiological health, Federal and industry standards and guidelines on x-ray equipment, and patient protection during x-ray examinations.

Regional Reports

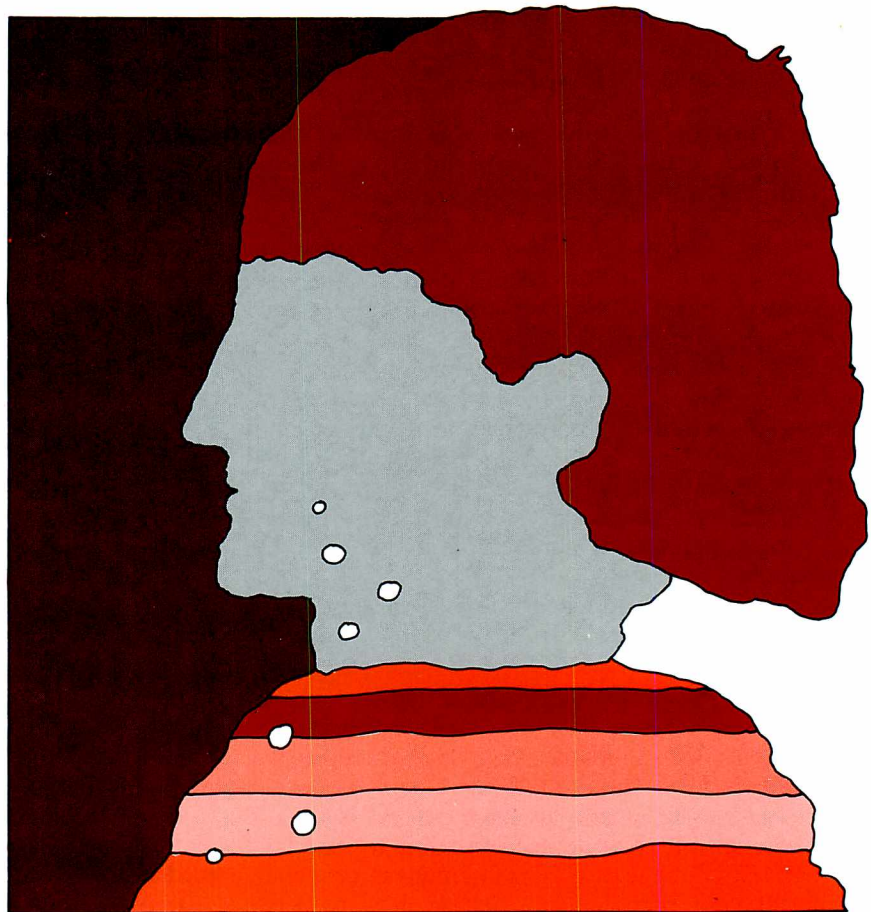
"Regional Reports" consists of important information on inspections, product seizures, court proceedings, and other regulatory and administrative actions initiated by FDA's regional and district field offices across the country to provide protection to consumers under Federal laws. "State Actions," the section immediately following "Regional Reports," consists of similar information about the consumer protection activities of State and local governments.

REGION I

Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont

Home of the Herbert Candies, Inc., Shrewsbury, Massachusetts, voluntarily destroyed 109 pounds of french style caramels and hard candies following an inspection by FDA's **Boston District** which revealed the candies contained the color additive Red No. 2. Red No. 2 was banned by FDA in 1976. FDA supervised the destruction of the candy.

A variety of foods from Portugal, Bangladesh, and Hong Kong were detained by FDA's Boston District after investigations and lab tests confirmed that the products were in violation of FDA regulations. The detentions included biscuits contaminated with rodent hairs and short in weight, worth about \$4,700, and marmalade, also short in weight and valued at about \$6,700. These products were offered for import from Portugal. In addition, \$40,000 worth of frog legs, offered for import from Bangladesh, were detained because of *Salmonella* contamination. Decomposed shrimp, offered for import from Hong Kong and valued at \$15,000, also was detained.



REGION II

New Jersey, New York, Puerto Rico, Virgin Islands

FDA's **New York District** was called upon to help in the treatment of an eight-year-old boy who was suffering from the symptoms of acrodynia, a form of mercury poisoning. The Mount Sinai Hospital in New York City asked FDA's New York District to analyze seven urine samples taken from the young patient. Chemists from FDA's Brooklyn-laboratory used a relatively new scientific tool called a flameless atomic absorption spectrophotometer to detect the amount of mercury in the child's system. Results showed that the patient's mercury level

was somewhat higher than normal but still below the amount considered toxic. Proper followup treatment by the physicians, based partly on FDA's urine analyses, allowed the youngster to return home.

Four shipments of various specialty candies made in France, Hungary, and Switzerland were refused entry by FDA's resident post at Champlain, New York. The candies, which included chocolate-covered cherries as well as hollow chocolates in the shape of miniature bottles and kegs, were found to contain cordials and other liqueurs. Such a product violates a provision of the Food, Drug, and Cosmetic Act which does not permit con-

fections to contain alcohol other than that which occurs in flavoring extracts. The alcohol was discovered in tests performed at FDA's Buffalo District laboratory. The shipment, valued at more than \$27,000, also had several labeling violations, including incomplete or nonexistent ingredient declarations and lack of a statement of net contents.

U.S. marshals in Buffalo seized about 8,000 pounds of raisins and currants, valued at \$4,000, at the Federal Bakers Supply Co., Buffalo. Routine inspection by FDA's **Buffalo District** disclosed that the lots were insect infested, and thus adulterated and unfit for use as human food.

Tablicaps, Inc., Franklinville, New Jersey, has begun a recall of more than 600,000 tablets of diethylstilbestrol (DES) because the product did not meet uniformity requirements. DES is a synthetic estrogen used in replacement therapy for estrogen deficiencies. FDA's **Newark District** learned of the problem when a sample of the 5-milligram tablets was analyzed by the National Center for Drug Analysis and failed to meet content requirements specified by the United States Pharmacopeia. Such analysis by the Center is part of a continuing program to check drugs for proper content. The firm sent letters to drug wholesalers in eight States who had received shipments of the lot in question, requesting them to return their stock to Tablicaps, where it will be destroyed by burial in a landfill.

Various food products valued at about \$100,000 and including cheese spread, herbs and spices, malted milk balls, croutons, melba toast, and soybeans were seized by the Federal Government at Corradetti Enterprises, Cinnaminson, N.J. The seizure resulted from a routine inspection of the firm by investigators from FDA's **Newark District** who discovered extensive insect infestations in various lots of food stored in the firm's warehouse.

REGION III

Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia

The Sheppard X-ray Co., Fairless Hills, Pennsylvania, has become the first company to pay a civil penalty for violating x-ray regulations under the Radiation Control for Health and Safety Act of 1968. The firm signed a consent decree in the U.S. District Court for the Eastern District of Pennsylvania to pay a \$2,000 fine for failure to certify and report the assembly of certified components which go into diagnostic x-ray systems as required by Federal regulations. The company also agreed to refrain from similar acts of noncompliance in the future. The legal action was recommended by FDA's **Philadelphia District** and FDA's Bureau of Radiological Health following two separate incidents in which the company failed to submit to FDA and to the purchaser of an x-ray system a report which lists all certified components installed in the system. This information, which must be supplied to FDA and to the purchaser within 15 days after the system is assembled, certifies that the components used in the system meet FDA performance standards. As a result, FDA forwarded a formal complaint which led to the court action. After a pretrial hearing, the company decided to pay the fine and not contest the case in court.

The Federal Government seized a variety of drugs including aspirin, isopropyl rubbing alcohol, and mineral oil at a distributor in York, Pennsylvania, because they violated FDA's Good Manufacturing Practice Regulations. The drugs were manufactured by Davis Manufacturing Co., Knoxville, Tennessee, where a U.S. marshal earlier had seized about \$40,000 worth of the same type of drugs following a series of inspections by FDA's **Nashville District**. Investigators found numerous GMP violations, including failure to identify and assay all active ingredients, failure to provide adequate space for storage of drug components, and failure to maintain clean equipment. The **Nashville District** discovered some of the drugs had been shipped to the Pennsylvania distributor and promptly notified FDA's **Philadelphia District** which initiated seizure action. Included in the seizure were 22 cases of aspirin, 325 cases of isopropyl rubbing alcohol, and a quantity of mineral oil in pint bottles.

FDA's **Baltimore District** has detained 18 body scanners, valued at \$5.5 million, at Washington, D.C., because of noncompliance with FDA standards for diagnostic x-ray equipment. The scanners are manufactured by EMI Medical, Inc., Hayes, Middlesex, England, for EMI Medical, Inc., Northbrook, Illinois. The diagnostic x-ray equipment, which is used by hospitals, was recalled by the Illinois firm because the beam-limiting device, which controls the amount of radiation emitted, failed to operate as required by FDA standards. The manufacturer submitted a proposal for bringing the equipment into compliance and this was accepted by FDA's Bureau of Radiological Health. Those units not in compliance are being detained by FDA until the firm makes the necessary corrections.

A U.S. marshal seized approximately 2,000 bags of flour destined for the Norfolk City School Board and valued at \$15,000, at the Norfolk Southern Railway Co., Virginia Beach, Virginia, because of insect infestation. An FDA inspector from the **Baltimore District** had noticed that the boxcar in which the flour was shipped was insect infested.

REGION IV

Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee

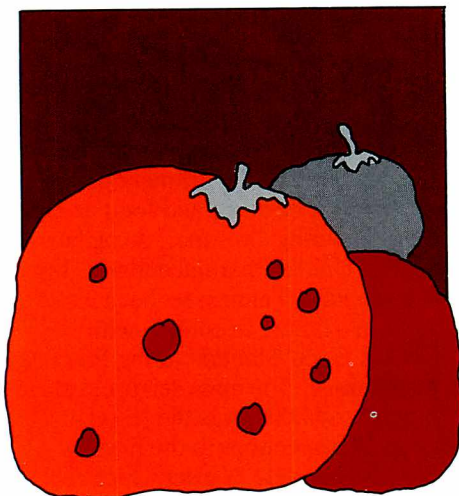
The Federal Government seized the entire stock of drugs and food at Davis Manufacturing Co., Inc., doing business as United Pharmaceuticals, Inc., in Knoxville, Tennessee, because of the firm's failure to comply with FDA's Good Manufacturing Practice Regulations. The mass seizure, valued at nearly \$44,000, was the result of a series of inspections at the firm by FDA's **Nashville District** which revealed the company's failure to identify and assay all active ingredients; failure to provide adequate space for storage of drug components to minimize the risk of mix-ups; and failure to keep equipment clean and orderly. FDA inspectors also found inadequate production and control records. The seized goods consisted of raw and in-process materials and finished products, isopropyl alcohol, hydrogen peroxide, mineral and castor oil, iodine,

Mercurochrome, calamine lotion, saccharin, and many other products.

U.S. marshals seized two lots of green coffee beans packed in 130-pound bags and valued at nearly \$80,000, at JFG Coffee Co., Knoxville, Tennessee, following an inspection by FDA's **Knoxville District** which revealed the coffee was adulterated with rodent excreta pellets and urine. A total of 114 bags of coffee beans were offered for import from Nicaragua, and 192 bags from Germany.

The Federal Government seized over 95,000 pounds of Seablest brand frozen shrimp at a cold storage warehouse in Ocala, Florida, after inspections by the National Marine Fisheries Service and FDA's **Orlando District** disclosed that the shrimp was decomposed. The shrimp, valued at \$189,000, was packed by Parry Murray Foods, Malaysia, and stored for a New Orleans-based trading company.

A shipment of 4,500 cans of Orlando brand peeled tomatoes, offered for import from Spain, was detained by FDA's Orlando District because the tomatoes contained mold and because the cans did not have a net contents



statement on the front of the label. The tomatoes, in six-pound cans, and valued at about \$5,000, were imported by Orlando Food Corp. of New York.

REGION V

*Illinois, Indiana, Michigan,
Minnesota, Ohio, Wisconsin*
Hemo-Blend Research Corp.,

Canton, Ohio, has stopped promotion of Hemo-Blend, a mixture of vitamins which the company claimed could improve the performance of race horses. The current promotion ended when the U.S. District Court for the Southern District of Indiana ordered the seizure and destruction of \$400 worth of the product in possession of a dealer in Indiana. The seizure was based on action taken by FDA's Bureau of Veterinary Medicine in 1970 after the bureau sent a magazine ad for the product to the FDA's **Cincinnati District** for investigation. That investigation resulted in court action after the Federal Government established by expert opinion that all of the labeling claims made by the company for improving the performance of race horses were false.

REGION VII

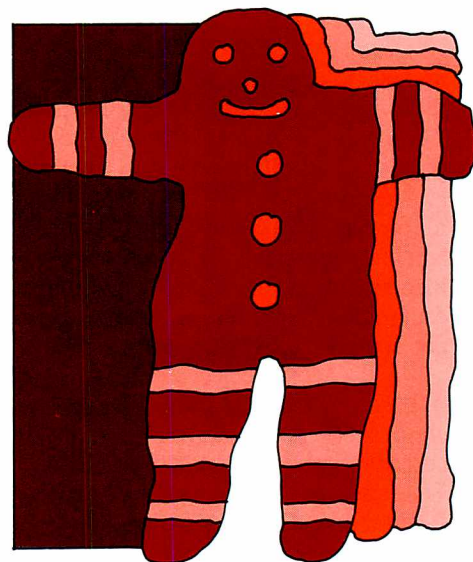
Iowa, Kansas, Missouri, Nebraska

Food and paper products valued at approximately \$100,000 were seized by the Federal Government at Acme Foods, Inc., a wholesale food warehouse in St. Louis, after an inspection by FDA's **Kansas City District** revealed bird and insect contamination of the products. Packaged goods including sugar, crackers, rice, and cereals, along with paper plates, cups, and other paper products, were found contaminated with insect and bird excreta. FDA inspectors, in agreement with the owners, and by order of the U.S. District Court for the Eastern District of Missouri, examined and segregated the contaminated goods. The firm eventually disposed of nearly 14,000 pounds of adulterated products and completed extensive structural repairs of the storage facility before resuming distribution of stock.

REGION VIII

*Colorado, Montana, North Dakota,
South Dakota, Utah, Wyoming*

Little Dutch Boy Bakeries, Inc., Draper, Utah, initiated a ten-State recall of 16,500 cases of cookies which contained the banned color additive Red No. 2. The illegal use of the color was discovered during a routine inspection of the bakery by FDA's **Denver District**. Red No. 2 was prohibited from use in foods in February 1976.



Oriental Foods, Inc., a processor of fresh bean sprouts and egg rolls, in Denver, has been ordered by the U.S. District Court in Denver not to process or sell its products until insanitary conditions found at the firm by FDA's Denver District have been eliminated. The order was the result of an FDA inspection which revealed insanitary conditions and practices which could lead to bacterial contamination of the bean sprouts. FDA laboratory analysis of bean sprout samples showed a high level of bacterial contamination.

REGION IX

*Arizona, California, Guam, Hawaii,
Nevada*

A U.S. marshal seized a lot of 184 135-pound bags of green coffee beans at a public storage facility in San Francisco because they were defiled with pigeon excreta. The seizure was the result of an investigation by FDA's **San Francisco District** which revealed that the beans, imported from Indonesia, had been discharged from the carrying vessel onto the port's Pier 27, which is operated by the Pacific Oriental Co. While stored on the pier, the coffee was exposed to pigeon contamination.

FDA's **Los Angeles District** moved its trailer laboratory to a new U.S. Customs Truck dock in Nogales, Arizona, for use in monitoring produce, offered for import from Mexico, for illegal pesticide residues. The new location is the major entry point for trucks carrying Mexican

produce into this country for sale throughout the United States. The laboratory had been located at an older, smaller truck dock in the same area.

REGION X

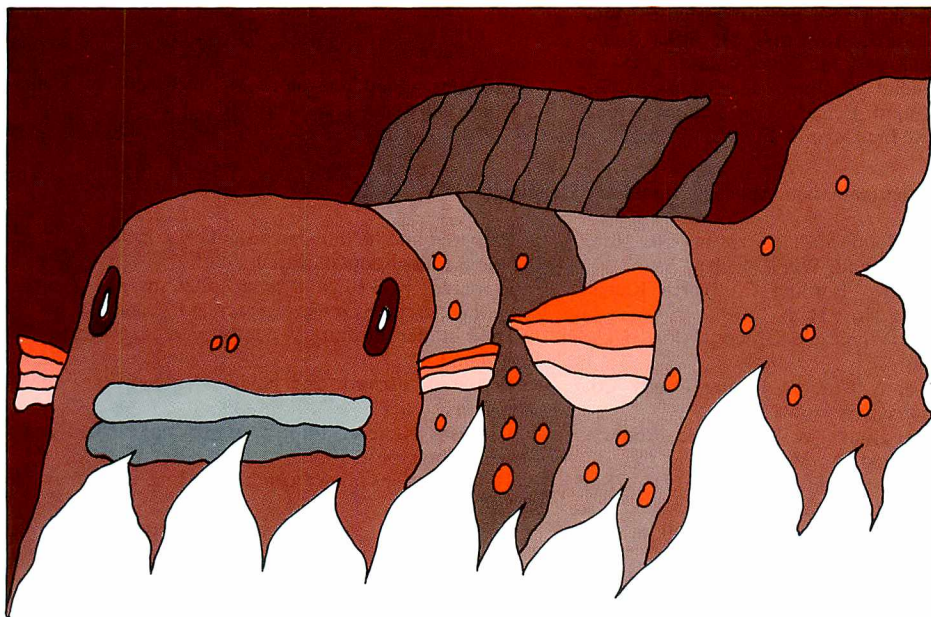
Alaska, Idaho, Oregon, Washington

Cargill, Inc., Portland, Oregon, and its responsible officials entered into a consent decree of injunction, filed in the U.S. District Court of Oregon at Portland, as a result of inspections by

FDA's **Seattle District** which disclosed that the firm was holding food under insanitary conditions in a rat-infested facility and that the food was contaminated with rodent filth. The firm operates a grain receiving facility for the storage and distribution of wheat and barley for use as human food. Most of the grain is exported. Under the consent decree, Cargill, Inc., agreed, among other conditions, to bring its operation into compliance with FDA regulations by establishing an effective sanitation control program, eliminating

vermin from its facility, cleaning and renovating its facility and equipment, repairing structural defects, and selecting a qualified person to be responsible for the firm's sanitation work. The consent decree also requires weekly inspection of the firm by management personnel who will take appropriate corrective action whenever necessary. If the firm fails to comply with the decree, it could be subject to closure or whatever additional remedies the court deems necessary to effect compliance with the law.

State Actions



Frozen Catfish Destroyed

Farmers Seafood Co., Shreveport, Louisiana, voluntarily destroyed 550 cartons of frozen catfish which caught fire and burned after the truck carrying the fish to Dallas was involved in a highway accident near the east Texas town of Van. After the fire was brought under control, the fish were removed from the truck under supervision of sanitarians from the Tyler County Health Department and returned to Shreveport, where the contents of 550 of the original 750 cartons, weighing 50 pounds each, were found unfit for human consumption. Shreveport city sanitarians and FDA's

Shreveport resident investigator witnessed the incineration of the damaged goods, which were valued at about \$29,000.

Reconditioned Grain Tested

The Food and Drug Protection Division of the North Carolina Department of Agriculture monitored the testing of more than 90,000 bushels of reconditioned corn and soya beans for aflatoxin contamination, after the products were involved in an explosion and fire of unknown origin while stored in a grain elevator at the Continental Grain Co., Elizabeth City, North Carolina. Aflatoxin is a highly toxic substance

produced by some molds. Tests performed by a private firm in Edenton, North Carolina, and paid for by the grain company, revealed no high levels of aflatoxin and all grain was salvaged for animal use.

Doctor's License Revoked

The State of California has revoked the license of Dr. John A. Richardson of Albany, California. The State's Bureau of Medical Quality Assurance found Richardson guilty of nine offenses against the code of medical ethics, including gross negligence, aiding and abetting the unlicensed practice of medicine, and unlawful sale of drugs for alleviating cancer. California law provides for an appeal to the courts of the license revocation. The courts also will determine whether Richardson will be permitted to practice during his appeal. Meanwhile, Richardson has filed suit in the Federal District Court in San Francisco against various members of the medical bureau and is asking an award of \$93 million for violation of his civil rights, defamation of reputation, and other alleged offenses. Richardson is a strong proponent of Laetrile, an unapproved drug advocated by some individuals and organizations for the treatment of cancer. An investigation by FDA's San Francisco District in early 1975 revealed interstate shipments of Laetrile by Dr. Richardson. This information was relayed to the State board and was included in the allegations argued before the administrative law judge in the Federal court.

Seizures and Postal Service Cases

SEIZURE ACTIONS charging violation of the Federal Food, Drug, and Cosmetic Act are published when they are reported by the FDA District Office.

A total of 31 actions to remove from the consumer market products charged to be violative was reported in January. These included 20 seizures of foods; 3 involved charges concerning poisonous and deleterious substances, 17 involved charges concerning contamination. Other seizures included 1 of food additive, 7 of drugs (including 1 of veterinary/medicated feed), and 3 of medical devices.

PRODUCT, PLACE & DATE SEIZED	MANUFACTURER (M), PACKER (P) SHIPPER (S), DEALER (D)	CHARGES
FOOD/Poisonous and Deleterious Substances		
Halibut, frozen/Bellingham, Wash. 12/20/76	Excursion Inlet Packing Co., Inc./Excursion Inlet, Alaska (P,S)	Contains the added poisonous and deleterious substance mercury.
Bellingham, Wash. 12/20/76	Petersburg Fisheries, Inc./Petersburg, Alaska (P,S); Seward Fisheries, Inc./Seward, Alaska (P,S); Sitka Sound Seafoods, Inc./Sitka, Alaska (P,S)	"
Mahi Mahi fish fillets, frozen/Santa Clara, Calif. 1/6/77	Sociedad Nacional de Galapagos/Guayaquil, Ecuador (P); National Freezers, Inc./Miami, Fla. (S)	Contains added poisonous or deleterious histamine-like substances; decomposed.
Contamination, Spoilage, Insanitary Handling		
Barley, malted/West Bend, Wis. 9/28/76	West Bend Malt & Grain Co., Inc./West Bend, Wis. (M,D)	Prepared and held under insanitary conditions; insect and rodent contaminated.
Beverage, carbonated, 7 Up/Olathe, Kans. 10/28/76	Seven Up Bottling Co./North Kansas City, Mo. (M,S)	Prepared, packed, and held under insanitary conditions; contains mold, yeast, and foreign material.
Cake mixes, cornmeal, cereal, and lasagna noodles/Altus, Okla. 11/22/76	Moore Wholesale Grocery/Altus, Okla. (D)	Held under insanitary conditions; insect contaminated.
Candy bars, Twin Bing/Omaha, Nebr. 8/13/76	Palmer & Co., t/a Palmer Candy Co./Sioux City, Iowa (M,S)	Prepared, packed, and held under insanitary conditions.
Chili peppers, green, frozen/El Paso, Tex. 11/22/76	Martin Bouvet & Sons Chile Products/Garfield, N. Mex. (P,S)	Contains bacterial filth; prepared and packed under insanitary conditions.
Chili peppers, indian, dried/San Francisco, Calif. 11/12/76	Pacific Oriental Terminal Co./San Francisco, Calif. (D)	Held under insanitary conditions; bird contaminated.
Crabmeat, claw/Port Arthur, Tex. 8/31/76	Shell Key Packing Co./Franklin, La. (M,S)	Prepared and packed under insanitary conditions; contains <i>E. coli</i> , staphylococci, and bacterial filth.
Cuttlefish, canned/Pawtucket, R.I. 11/16/76	Conservas Independencia, Lda./Matosinhos, Portugal (M,S)	Rodent and insect contaminated.
Flour/Allston, Mass. 12/28/76	Thurman Co./Allston, Mass. (D)	Processed in insect-infested milling and packing equipment.
Green beans, canned/Pasco, Wash. 12/23/76	Shipped from Salem, Oreg.	Unfit for food due to metallic odor and in cans which are internally detinned.
Mushrooms, canned, and steak sauce with mushrooms, Fred's/Wichita, Kans. 10/26/76	Fred's Mushroom Products Co./South Lebanon, Ohio (M,S)	Contained in swollen cans; label lacks name and place of business of the manufacturer and common or usual name of the food.
Peanuts, shelled/Indianapolis, Ind. 11/10/76	Central Indiana Supply Co./Indianapolis, Ind. (D)	Held under insanitary conditions.
Peanuts, spanish, jumbo/Minneapolis, Minn. 11/8/76	Martin Brokerage Co./Minneapolis, Minn. (D)	"
Peanuts, spanish, small/Buffalo, N.Y. 11/9/76	Buffalo Nut, Div. of Dan-Dee Pretzel & Potato Chip Co./Buffalo, N.Y. (D)	"
Rice/Cambridge, Mass. 12/30/76	Dollar Food Store, Inc./New York, N.Y. (S)	Held under insanitary conditions; insect contaminated.
Shrimp, frozen/San Francisco, Calif. 12/16/76	Imported from Rizal, Philippines.	Contains decomposed shrimp.
Soup, lentil, canned/Brooklyn, N.Y. 11/24/76	Florio & Co./Salerno, Italy (M,S)	Contains insects; quantity of contents statement not within bottom 30% of display panel area.
FOOD ADDITIVE		
Vita-Life Vitamin B-15 tablets/Tulsa, Okla. 12/15/76	Belvedere Laboratories/Hayward, Calif. (M,S)	Contains the nonconforming food additives calcium pangamate and dimethyl glycine; false and misleading claims concerning nutritional properties, use, and identity of calcium pangamate; and lacked name of each ingredient.

PRODUCT, PLACE & DATE SEIZED	MANUFACTURER (M), PACKER (P), SHIPPER (S), DEALER (D)	CHARGES
DRUGS/Human Use		
Chlorpheniramine maleate tablets, U.S.P./Hayward, Calif. 1/11/77	Stayner Corp./Berkeley, Calif. (M)	Strength and quality below U.S.P. standard; circumstances of production not in conformity with current good manufacturing practice.
Cough syrup, Benylin/Skokie, Ill. 11/30/76	Parke Davis & Co./Detroit, Mich. (M,S)	New drug without an effective approved New Drug Application; labeling fails to bear adequate warnings or prescription legend.
Glucose tolerance test cola, Abco-dex/ Baltimore, Md. 11/12/76	Custom Laboratories, Inc./Baltimore, Md. (D)	Circumstances of production not in conformity with current good manufacturing practice.
Quinidine sulfate tablets; sulfisoxazole tablets, U.S.P./Broomfield, Colo. 11/1/76	Cord Laboratories, Inc./Broomfield, Colo. (M)	Labeling fails to bear adequate directions for use; new drugs without effective approved New Drug Applications.
Triple Sulfa suspension/St. Louis, Mo. 10/6/76	Cord Laboratories, Inc./Broomfield, Colo. (M,S)	New drug without an effective approved New Drug Application.
Various drugs, including merthiolate, Mercurochrome, alum, aspirin tablets, and epsom salts/ Hickory, N.C. 12/22/76	Davis Manufacturing Co., Inc./Knoxville, Tenn. (M,S)	Circumstances of production not in conformity with current good manufacturing practice.
Veterinary/Medicated Feed		
Furosemide injection/Dallas, Tex. 11/23/76	D-M Pharmaceuticals, Inc./Rockville, Md. (M,S)	New animal drug and no approved New Animal Drug Application was in effect with respect to its use and intended use.
MEDICAL DEVICES		
Panels containing antibiotics for tests, and antibiotics for manufacturing in vitro test devices/Cleveland, Ohio 10/7/76	Medical Specialties, Inc./Cleveland, Ohio (D)	Subject to antibiotic certification on enactment of Medical Device Amendments of 1976, and lacked such certification.
Electrosedation units/Euless, Tex. 11/10/76	Tri-Tronics Labs/Euless, Tex. (M)	False and misleading claims; inadequate directions for use, and inadequate warnings against unsafe use.
Therapuncteur and Punctoscope devices/Denver, Colo. 11/8/76	Shores Medical Electronics/Tulsa, Okla. (S)	False and misleading claims; fail to bear adequate directions for use.

U.S. POSTAL SERVICE actions taken in medical cases as authorized in the Mail Fraud Statute (18 U.S.C. 1341) and/or the False Representation Statute (39 U.S.C. 3005) as reported by the Chief Postal Inspector.

Complaints Filed by Law Department Under 39 U.S.C. 3005 (False Representation)

December 23, 1976: **Golden Peacock Products**, 1155-B Triton Drive, Foster City, California. Advertising and sale through the mail of the product "Magic Health Slippers," representing the ability to stimulate nerve endings and improve health.

January 14, 1977: **PRO-B-5-DIV**, 210 Fifth Avenue, New York, New York, and **M.K.S. Enterprises, Inc.**, and **Growing Glory**, 50 Bond Street, Westbury, New York. Advertising and sale through the

mail of a hair lotion product, representing the ability to thicken and strengthen human hair.

January 14, 1977: **JMH Enterprises**, P.O. Box 35814, Houston, Texas. Advertising and sale through the mail of the product "Whole Bath Loofa With Poly Handles," representing the ability to reduce cellulite.

False Representation Orders Issued by Judicial Officer Under 39 U.S.C. 3005

December 10, 1976: Against **Select Items**, 1236 S. La Cienega Blvd., Los Angeles, California 90035. Advertising and sale through the mail of the product, "Linga Pendulum," representing the ability to enlarge the male organ and strengthen and stiffen male erections.

December 10, 1976: Against **Mark Hunter**, P.O. Box 2608, Sepulveda, California. Advertising and sale through the mail of an alleged method for assured potency and a larger male organ.

December 23, 1976: Against **Ginseng II**, 1 Wolfs Lane, Pelham, New York. Advertising and sale through the mail of the product "Ginroy" capsules, representing the ability to increase and restore vitality in persons of all ages.

December 28, 1976: Against **E-Pill**, Box 6712, Miami, Florida. Advertising and sale through the mail of the product "High Potency Vitamin E" tablets, representing the ability to increase sexual ability and potency in both sexes.

January 4, 1977: Against **Fran-Mar Enterprises**, P.O. Box 130, Rockvale, Colorado. Advertising and sale through the mail of the product "The Franmar," a pamphlet containing information representing the ability to cause weight loss.

Notices of Judgment

NOTICES OF JUDGMENT on Seizure Actions

FOOD/Poisonous and Deleterious Substances

Apricot kernels, bulk and retail packages, at Portland, Dist. Oreg.

Charged 8-25-76: when shipped by Earth Products, Inc., Marina Del Rey, Calif., the article, labeled in part "Lange's Mello-Gold Apricot Kernels . . . Maximum Consumption 3 to 5 kernels Per Day . . . Packed by NuVita Foods, Inc., Portland, Oregon", and (bulk) "Natural Apricot Kernels Packed For Earth Products Marina Del Rey, Ca", contained the poisonous and deleterious substance hydrocyanic acid (hydrogen cyanide) in such quantity as might render it injurious to health, and the article was unfit for food due to the presence of hydrocyanic acid; 402(a)(1), 402(a)(3). Default decree ordered destruction. (F.D.C. No. 60869; S. No. 76-53-346; N.J. No. 1)

Fish oil, at Meckling and Vermillion, Dist. S. Dak.

Charged 7-3-75: when shipped by Progressive Distributing Co. (a/k/a Stoller Fisheries), Spirit Lake, Iowa, the article (6,100 gallons at Vermillion and 3,200 gallons at Meckling) contained the added poisonous and deleterious substance polychlorinated biphenyls in excess of the tolerance prescribed for animal feed components; 402(a)(2)(A). The article was claimed by Sioux Alfalfa Meal Co., Meckling and Vermillion, S. Dak., who claimed the article and denied the charge. The Government served written interrogatories on the claimant. The claimant answered the Government's interrogatories and served written interrogatories on the Government. Subsequently, the claimant withdrew its claim and answer; and a default decree ordered the article destroyed. (F.D.C. No. 60393; S. Nos. 81-033 H, 76-336/7 H; N.J. No. 2)

FOOD/Contamination, Spoilage, Insanitary Handling

Beans, pinto, kidney, and small red, dried, at Owensboro, W. Dist. Ky.

Charged 10-20-75: while held for sale, all of the articles except the kidney beans contained rodent filth; and all the articles were held under insanitary conditions; 402(a)(3), 402(a)(4). Grant L. Kuhn & Co., Lansing, Mich., who had shipped the pinto and kidney beans, filed an appearance and moved for representative samples of the articles. The Government opposed such motion on the ground that the shipper had not filed a claim to the articles. However, the court ordered a representative sample delivered to the shipper. Owensboro Canning Co., Inc., Owensboro, Ky., the dealer, filed an answer to the complaint. Subsequently, the Government moved for a default decree of condemnation on the ground that neither the shipper nor the dealer had filed a claim to any of the articles. The court granted the Government's motion for a default judgment. Thereafter, the dealer claimed the articles and moved to set the default decree aside. The court set the default decree aside, since the claimant agreed to pay all inspectional, salvaging, and court costs. Ultimately, a consent decree authorized release to the claimant for salvaging. (F.D.C. No. 60510; S. Nos. 76-34-303/5; N.J. No. 3)

Candy bars, Twin Bing, 2 seizure actions, at Omaha, Dist. Nebr. and Omaha, Dist. Nebr.

Charged 8-10-76 and 8-10-76: when shipped by Palmer Candy Co., Sioux City, Iowa, the article had been prepared, packed, and held under insanitary conditions; 402(a)(4). Default decrees ordered destruction. (F.D.C. Nos. 60831, 60843; S. Nos. 76-24-735, 76-24-739; N.J. No. 4)

Coconut, dessicated, at Jersey City, Dist. N.J.

Charged 10-27-72: while held for sale, the article contained moldy, rancid, and decomposed coconut; 402(a)(3). Consent decree authorized release to claimant for salvaging. (F.D.C. No. 58462; S. Nos. 55-827/8 F; N.J. No. 5)

Cornmeal, at Detroit, E. Dist. Mich.

Charged 3-5-74: while held by Borman's, Inc., Detroit, Mich., the articles contained rodent filth and were held under insanitary conditions; 402(a)(3), 402(a)(4). Consent decree authorized release to claimant for salvaging. (F.D.C. No. 59686; S. Nos. 43-437/8 G; N.J. No. 6)

Crackers, rice, farina, corn flakes cereal, black-eyed peas, and other food stocks, at San Sebastian, Dist. P.R.

Charged 3-18-76: while held by Alamacenes Rivera, San Sebastian, P.R., the named articles contained rodent and/or insect filth, and all of the articles were held under insanitary conditions; 402(a)(3), 402(a)(4). Consent decree authorized release to Juan Bautista Rivera Guerrero for salvaging. (F.D.C. No. 60695; S. No. 76-51-041; N.J. No. 7)

Crepe mixes of various types, at Fairfield, Dist. N.J.

Charged 1-27-76: while held by SEB of France, Inc., Fairfield, N.J., some types of the crepe mixes contained rodent filth and all types of the article had been held under insanitary conditions; 402(a)(3), 402(a)(4). Consent decree authorized release to dealer for salvaging. (F.D.C. No. 60630; S. No. 76-34-620; N.J. No. 8)

Peanuts, shelled, and chestnuts, shelled, at New York, S. Dist. N.Y.

Charged 1-7-75: while held by A. L. Bazzini Co., Inc., New York, N.Y., the articles contained insect filth, and the peanuts had been held under insanitary conditions; 402(a)(3), 402(a)(4). Consent decree authorized release to claimant for salvaging. (F.D.C. No. 60129; S. Nos. 42-174/7 H; N.J. No. 9)

Peanuts, unshelled, at St. Louis, E. Dist. Mo.

Charged 7-13-76: while held by Rethemeyer Coffee Co., St. Louis, Mo., the article was held under insanitary conditions; 402(a)(4). Default decree authorized donation to a conservation commission for animal feed. (F.D.C. No. 60795; S. No. 76-24-014; N.J. No. 10)

Poppyseeds, at New York, S. Dist. N.Y.

Charged 2-15-73: while held by Baker and Williams Bonded Warehouse, New York, N.Y., the article contained insects and had been held under insanitary conditions; 402(a)(3), 402(a)(4). Consent decree authorized release to claimant for salvaging. (F.D.C. No. 58841; S. No. 59-128 F; N.J. No. 11)

Salmon, canned, Frosty, at San Juan, Dist. P.R.

Charged 4-9-76: when shipped by Frosty Fish Co., Wilmington, Calif., the article contained decomposed salmon; 402(a)(3). Default decree ordered destruction. (F.D.C. No. 60707; S. Nos. 76-50-688/96; N.J. No. 12)

Sesame seeds, at Santurce, Dist. P.R.

Charged 6-13-75: while held by Luis V. Pino, Santurce, P.R., the article contained rodent filth and was held under insanitary conditions; 402(a)(3), 402(a)(4). Default decree ordered destruction. (F.D.C. No. 60388; S. No. 25-539 H; N.J. No. 13)

Soybeans, at San Francisco, N. Dist. Calif.

Charged 9-17-76: while held by Azumaya, Inc., San Francisco, Calif., the article was held under insanitary conditions; 402(a)(4). Consent decree authorized release to dealer for salvaging. (F.D.C. No. 60888; S. No. 77-73-908; N.J. No. 14)

FOOD/Economic and Labeling Violations

Nuts, mixed, at Albany, N. Dist. N.Y.

Charged 9-30-76: while held by Empire State Nut Co., Inc., Albany, N.Y., who packed the article using cashews, brazils, and filberts shipped in interstate commerce, the article (labeled in part "Capitol Brand . . . Mixed Nuts Fancy Contains 60% Cashew Nuts with Brazil Nuts, Filberts, Almonds, and Pecans Added. No Peanuts . . . Contents: Virginia Peanuts, Cashews, Brazil Nuts, Filberts, Almonds, Pecans . . . Empire State Nut Co., Albany, N.Y.") failed to conform to the definition and standard of identity for mixed nuts containing 60 percent cashews, since the article contained approximately 40 percent cashews; and the label statement "Contents: Virginia Peanuts" and the label vignette showing peanuts were false and misleading, since the article contained no peanuts; 403(g)(1), 403(a). Default decree authorized delivery to FDA for donation to charitable institutions. (F.D.C. No. 60872; S. No. 77-58-027; N.J. No. 15)

Pizza pie kits, Lenora's, at Buffalo, W. Dist. N.Y.

Charged 6-23-76: while held by Lenora's Pizza, Buffalo, N.Y., who assembled the kits using tomato sauce shipped in interstate commerce, the labels of the kits (which each contained two pizza crusts, and sauce, pepperoni and pizza cheese for two pizzas) lacked the name and place of business of the article's manufacturer, packer, or distributor—403(e)(1); and the article was in violation of the Fair Packaging and Labeling Act, since the quantity of contents statement, appearing on the kits' principal display panel area of more than 100 square inches, was in a type size less than 1/4 inch high—15 U.S.C. 1453(a)(3)(C)(i). Default decree ordered destruction. (F.D.C. No. 60765; S. No. 76-57-921; N.J. No. 16)

Prune concentrate and water mix, and other fruit concentrate and water mixes, at Lafayette, W. Dist. La.

Charged 6-28-76: when shipped by Florida Home Juice Co., Avon Park, Fla., the articles, labeled in part (case) "Prune Juice [or "Cranberry", "Orange", "Grapefruit", "Pineapple", "Grape", "Apple", "Apricot", "Tomato", "Peach", "Pear"] Individual Portions . . . Checkerboard Juices St. Louis, Mo."



consisted of individual 4-oz. cups whose labels lacked the name and place of business of the manufacturer, packer, or distributor—403(e)(1); the articles, whose cups were labeled “Grape Juice From Concentrate”, “Apple Juice From Concentrate”, and “Tomato Juice From Concentrate”, lacked the common or usual name of each ingredient—403(i)(2); and the article, whose cups were labeled “100% Pure Pineapple Juice”, lacked the common or usual name of the food since “pineapple juice” was not the common or usual name for “pineapple juice from concentrate”—403(i)(1). Consent decree authorized donation to charitable institution. (F.D.C. No. 60766; S. No. 76-37-795; N.J. No. 17)

FOOD/COLOR ADDITIVES

Caviar from whitefish, at New York, S. Dist. N.Y.

Charged 7-27-76: while held by Purepak Foods, Inc., New York, N.Y., who prepared the article using the color additive “Jetine Black” and salted lake fish rose shipped in interstate commerce, the article, labeled in part “Poriloff Caviar EUUH . . . Whitefish,” contained the delisted color additive FD&C Red No. 2; 402(c). Default decree ordered destruction. (F.D.C. No. 60801; S. No. 76-42-078; N.J. No. 18)

Red food coloring, bulk and repacked, at Des Moines, S. Dist. Iowa.

Charged 7-27-76: while held by Tone Bros., Inc., Des Moines, Iowa, the bulk coloring, and the repacked coloring labeled in part “Pure Red Food Color . . . Tone Bros., Des Moines, Iowa”, or “Pure Red Food Color . . . Spartan Dist. By Spartan Stores, Inc. Grand Rapids, Mich.,” contained the delisted color additive FD&C Red No. 2; 402(c). Default decree ordered destruction. (F.D.C. No. 60826; S. No. 76-25-237 et al.; N.J. No. 19)

Red No. 2 amaranth color, and Olender's dark red color solution, at Hamtramck, E. Dist. Mich.

Charged 6-21-76: while held by Philip Olender & Co., Hamtramck, Mich., the solution (which had been manufactured by the dealer using the bulk FD&C Red No. 2) and the bulk color contained the delisted color additive FD&C Red No. 2; 402(c). Default decree ordered destruction. (F.D.C. No. 60757; S. No. 76-67-182; N.J. No. 20)

DRUGS/Human Use

Chlorothiazide tablets, at New Britain, Dist. Conn.

Charged 8-2-76: when shipped by Bolar Pharmaceutical Co., Inc., Copiague, New York, the article, labeled in part “Chlorothiazide 250 mg. [or “500 mg.”] . . . Tablets Manufactured for H. L. Moore Drug Exchange New Britain, Conn.,” was a new drug without an effective approved New Drug Application; 505(a). Default decree ordered destruction. (F.D.C. No. 60830; S. Nos. 76-56-810/1; N.J. 21)

Chlorothiazide tablets, at Newington, Dist. Conn.

Charged 8-2-76: when shipped by Bolar Pharmaceutical Co., Inc., Copiague, New York, the article, labeled in part “Chlorothiazide 500 mg. . . . Tablets . . . Distributed by David A. Rosow, Inc., Newington, Conn.,” and “Chlorothiazide 250 mg. . . . Tablets . . . Bolar Pharmaceutical Co., Inc., Copiague, New York,” was a new drug without an effective approved New Drug Application; 505(a). Default decree ordered destruction. (F.D.C. No. 60823; S. Nos. 76-56-808/9; N.J. No. 22)

Lidocaine hydrochloride injectable, and bacteriostatic sodium chloride injection, at Indianapolis, S. Dist. Ind.

Charged 5-1-72: when shipped by Maizel Laboratories, Div. of Myers Carter Laboratories, Inc. (subsidiary of Chromalloy-American Corp.), Chicago, Ill., the circumstances used in the manufacture, processing, packing, and holding of the articles (which were labeled in part “L-Caine 1% Brand of Lidocaine Hydrochloride USP . . . [or “Bacteriostatic Sodium Chloride Injection”] Manufactured for Century Pharmaceuticals, Inc., Indianapolis, Indiana . . . Maizel Laboratories . . . Chicago, Ill.”) failed to conform with current good manufacturing practice; 501(a)(2)(B). The articles were claimed by Ross A. Deardorff, president, for Century Pharmaceuticals, Inc., Indianapolis, Ind. After some correspondence with Mr. Deardorff and after Mr. Deardorff failed to file an answer to the complaint, a default decree of condemnation was entered. Century Pharmaceuticals, Inc., moved to set aside the default decree. After a hearing, the court denied the motion but granted additional time to file an amended motion. Century Pharmaceuticals, Inc., subsequently filed an answer to the complaint and a motion to amend the motion to set aside the default decree. The court again denied the motion to set aside the default decree saying:

“The articles in question were purchased by the intervenor claimant, Century Pharmaceuticals, Inc., an Indianapolis, Indiana, based corporation, from Myers Carter Laboratory, Inc. (who was a wholly owned subsidiary of Chromalloy-American Corporation of St. Louis, Missouri). The articles in question were actually manufactured by Maizel Laboratories, Inc. After manufacturing the articles, Maizel Laboratories, Inc. became a division of Myers Carter Laboratory, Inc. The plaintiff instituted seizure proceedings in many jurisdictions against the drug known as ‘Lidocaine’ manufactured in Chicago, Illinois, wherever it could be found. The articles seized in this case are the subject of one of the actions and a small part of the total seizure of the drug ‘Lidocaine’. The ‘Lidocaine’ drug was used in the manufacture of the seized articles in this case. The value of the seized articles in this case was approximately one thousand dollars (\$1,000.00). They were seized after they were shipped on or about March 6, 1972 in interstate commerce from Chicago, Illinois, to Indianapolis, Indiana. The intervenor used the drug ‘Lidocaine’ in its package products for four (4) or five (5) years for resale to its customers under the trade name or brand name of ‘L-Caine’.

“The plaintiff has been advised in writing that the seller would reimburse intervenor for the seized articles which was in turn communicated to the intervenor. . . .

“This Court on May 1, 1972 issued a monition order providing for notice by publication and a warrant for the attachment and seizure of the articles also issued on May 1, 1972. . . .

“On May 25, 1972 a *pro se* pleading of the corporation intervenor claimant, Century Pharmaceuticals, Inc., entitled, ‘Claim Upon Intervention’ was filed The intervenor claimant corporation failed to appear by counsel and no pleadings were filed until March 1, 1973 when the United States of America filed its motion for a default decree of forfeiture and on March 2, 1973 a default was entered, a decree of condemnation was entered, and the United States Marshal was ordered to forthwith destroy the seized articles. . . .

“On March 6, 1973, the intervenor filed an appearance by counsel and filed a motion to set aside the default judgment. Intervenor requested a hearing thereon which the Court granted and scheduled it for March 7, 1973. It was rescheduled for March 15, 1973 at the request of the intervenor. The March 5, 1973 motion was denied at the March 15, 1973 hearing . . . with leave to intervenor to file an amended motion together with a proposed answer to the merits of the action within five (5) days. The default of the intervenor was explained in the March 15, 1973 hearing Thereafter on March 20, 1973 the intervenor filed the motion and the proposed answer on the merits to the complaint which presented the issues of this hearing of July 3, 1973.

“The intervenor was clearly in default and no justifiable reason or excuse for being in such default has been proven to the Court.

“Furthermore, there has been no sufficient showing that the intervenor has a meritorious claim or defense to the seizure of the articles, or that the United States of America's claim is not meritorious. The Court finds that the articles in question are drugs within the meaning of the Federal Food, Drug and Cosmetic Act, Title 21 U.S.C.A. Sections 331 et seq.; that such articles were adulterated as charged in the complaint as defined in such Act, Title 21 U.S.C.A. Section 351(a)(2)(B); that such articles were shipped in interstate commerce and received by the intervenor as charged in the complaint in violation of such Act, Title 21 U.S.C.A. Section 331(a); and the Court has jurisdiction of the subject matter and of the articles pursuant to such Act, Title 21 U.S.C.A. Section 334.

“On or about February 15, Myers Carter Laboratory, Inc. had taken over Maizel Laboratories, Inc. and it then became a division of the acquiring corporation under the name of Maizel Laboratories, Inc. In February and March of 1972, Maizel Laboratories, Inc. had been inspected at least twice by agents of the Food and Drug Administration of the United States of America. These agents found sixteen (16) specific violations of ‘current good manufacturing practices’. On February 17, 1972, Maizel Laboratories, Inc. and Dr. Ben Maizel, the former President of Maizel Laboratories, Inc., were found guilty of contempt of a court of record in Chicago, Illinois, for producing drugs in a plant which was not in compliance with good manufacturing practices. Dr. Maizel was produced by the intervenor as a witness in the July 3, 1973 hearing. Dr. Maizel has had no connection with that business since February 15, 1972. Myers Carter Laboratory, Inc. and its division, Maizel Laboratories, Inc., have not appeared in this action and present no claim and indeed have offered to reimburse their customers including this intervenor. The intervenor ordered the articles from Myers Carter



Laboratory, Inc. on or about March 6, 1972.

"Under the facts and circumstances a spot checking of certain packages of the articles seized for adulteration would only prove the status of the particular item contained in the fifty-nine (59) cases of many sub articles. The fidelity of the manufacturing lot numbers of 'Lidocaine' have also not been supported by the evidence and the credibility of the witness used to establish such under all of the facts and circumstances is questioned.

"The March 20, 1973 motion to vacate the default judgment of March 2, 1973 be and is hereby denied."

Century Pharmaceuticals, Inc., appealed. Upon appeal, the court of appeals reversed the district court, saying:

"This appeal is from the district court's denial of claimant-appellant's motion to vacate a previously entered default judgment. As indicated at oral argument, we reverse.

"The Government has now conceded that claimant-appellant was entitled under Fed.R.Civ.P. 55(b)(2) to written notice 'at least 3 days prior to the hearing' on the application for entry of the default judgment and that said provision was violated in this case. Despite the Government's claim of lack of prejudice, we find that the failure to comply with this procedural requirement placed the appellant in a different and less advantageous posture. The discovery of this error necessitated that the default judgment be vacated and it was an abuse of discretion not to do so.

"The judgment of the district court is reversed and the cause remanded with directions to vacate the default judgment and proceed accordingly."

Accordingly, the original default decree was vacated and the claim and answer were allowed. Subsequently, Century Pharmaceuticals, Inc., moved that the claim and answer be withdrawn. Such motion was thereafter allowed. Accordingly, the Government moved for a default decree. Ultimately, the second default decree was granted and the article was ordered destroyed. (F.D.C. No. 57990; S. Nos. 35-033/5 F; N.J. No. 23)

Phenobarbital sodium and pentobarbital sodium elixir, and phenobarbital sodium and pentobarbital sodium combination sedative in an elixir, at Norfolk, E. Dist. Va.

Charged 6-21-76: while held for sale, the strengths of the articles differed from their declared strengths, since the elixir contained less than the declared $\frac{1}{8}$ gr. of phenobarbital sodium in each 5 cc., and the combination sedative contained less than the declared $\frac{1}{8}$ gr. of phenobarbital sodium, more than the declared $\frac{1}{8}$ gr. of pentobarbital sodium, and more than the declared 12% alcohol; and the labeling of the articles was false and misleading as to the declared amounts of the above ingredients; 501(c), 502(a). Default decree ordered destruction. (F.D.C. No. 60751; S. No. 76-02-780; N.J. No. 24)

Viro-Zyme protein hydrolysate injectable, at Anaheim, C. Dist. Calif.

Charged 5-31-73: when shipped by Marcen Laboratories, Inc., New Rochelle, N.Y., the article was a new drug without an effective approved New Drug Application; 505(a). The article was claimed by the shipper who denied the charge. Upon stipulation of the parties, the action was removed to the District of Connecticut. The action was held in abeyance pending disposition of a criminal action. Ultimately, the criminal action was terminated, the claimant withdrew the claim and answer, and a default decree ordered the article destroyed. (F.D.C. No. 59271; S. No. 52-651; N.J. No. 25)

DRUGS/Veterinary

Probios Plus boluses for beef animals, at Gainesville, N. Dist. Ga.

Charged 7-27-76: when shipped by NuLabs, Inc., Portland, Oreg., the article was a new animal drug and no approval of a New Animal Drug Application was in effect with respect to the use or intended use of the drug; 501(a)(5). Default decree ordered destruction. (F.D.C. No. 60803; S. No. 76-61-531; N.J. No. 26)

Silogen fermentation product for silage and Zymaferm fermentation product combination for animal nutrition, at Lincoln, Dist. Nebr.

Charged 9-5-74: while held by BZD Livestock Products, Inc., Lincoln, Dist. Nebr., (who printed and used the accompanying brochure entitled "BZD Zymaferm The Enzyme Culture for Animal Nutrition . . . Silogen The Enzyme Culture for control of Silage and High Moisture Grains") the articles, labeled in part "BZD Silogen Dried 'A. Oryzae' Fermentation Product . . . BZD Livestock Products, Inc. . . . Lincoln, Nebraska," and "BZD Zymaferm . . . Ingredients Dried 'A. Oryzae' Fermentation Product . . . BZD Livestock Products, Inc., . . . Lincoln, Nebraska," were new animal drugs and no approval of a New Animal Drug Application was in effect with respect to the use and

intended use of such drugs; 501(a)(5). The dealer claimed the articles, denied that the articles were drugs, and alleged that the articles were not intended for consumption by humans and that the articles posed no danger or threat to health or safety of humans or animals. The Government served written interrogatories on the claimant. After the claimant answered the interrogatories, the Government moved for summary judgment. The court ruled in favor of the Government saying:

"Several courts have had occasion to examine the intended scope of the definition of a drug under § 321(g). The United States Supreme Court did so in *United States v. Bacto-Unidisk*, 394 U.S. 784 (1969). At issue was whether antibiotic sensitivity discs, which never came into contact with the patient's body, were drugs within the prior version of 21 U.S.C. § 321(g)(1)(D) or alternatively whether they were merely devices under that section and § 321(h). Prior to holding that the discs were drugs, the court stated: ' . . . Congress fully intended that the Act's coverage be as broad as its literal language indicates—and equally clearly, broader than any strict medical definition might otherwise allow.'

"The touchstone under the statute is the intended use of the product. Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims show intended uses that bring it within the drug definition. *United States v. Article . . . Consist. of 216 Carton. Bot.*, 409 F.2d 734, 739, n. 3 (C.A. 2nd Cir. 1969). That case cites the Senate Report 361, 74 Cong., 1st Sess. (Dunn p. 240), and the language of that report is particularly applicable here That case considered whether a cosmetic product called 'Sudden Change,' which was advertised as providing a face lift without surgery, would fall within the definition of drug. In stating the standard for determining whether a product is intended to affect the structure of the body of man, the court said: ' . . . [T]he question . . . is to be answered by considering, first, how the claim might be understood by the "ignorant, unthinking or credulous" consumer, and second, whether the claim as so understood may fairly be said to constitute a representation that the product will affect the structure of the body in some medical—or drug-type fashion, i.e., in some way other than merely "altering the appearance." ' 409 F.2d at 742.

"Here, the argument of the plaintiff seems directed more to the products' intention to affect a function of the body of an animal. The definition is no less applicable.

"The promotional materials distributed with the two products involved were submitted to the court. The parties also submitted these materials to their respective experts in animal sciences. The two products are Zymaferm and Silogen.

"The Zymaferm bag tag describes the substance as 'Dried "A. Oryzae" Fermentation Product grown on wheat bran.' It is billed as 'The enzyme culture for animal nutrition.' The accompanying materials describe the general functioning of enzymes as substances producing a change without themselves undergoing a change. It is represented that in highly bred animals possessing exacting nutritional requirements, deficiencies in diet can occur; that when this happens, prolapses in chickens, wobbles in horses, and ketosis in cattle may result; and that it is an enzyme culture like Zymaferm that can correct that loss. Another document states: ' . . . Zymaferm helps break down the fibrous cells of plants ingested by the animal which permits better and faster utilization of feed nutrients ' Various statistics are cited to show increased production and lower feed costs from use of the product.

"Silogen is described on the bag tag as 'Dried "A. Oryzae" Fermentation Product for Developing Proper Conditions to Control Silage and High Moisture Grains.' It is billed as 'The enzyme culture for control of silage and high moisture grains.' It is said to be a fermentation culture to be added to silage and produces enzyme organisms, accelerating the carbon dioxide process which controls the temperature of the silage. The promotional materials report that Silogen-treated silage is more palatable and more digestible, contains more of proper fermentation, retains more dry matter, more TDN, and more nutrients, and results in less silage consumed per animal; that a test concluded that the additive resulted in significant improvement in milk fat content, protein digestibility, and efficiency of milk production; and that the animals' digestibility of protein was increased by 7.9 per cent when the animals were fed Silogen-treated silage.

"A defendant's argument that the products were nutritive and therefore food, rather than drugs, was specifically rejected by Judge Robinson of this district in *United States v. Articles of Drug, Etc.*, 263 F. Supp. 212 (U.S.D.C. Neb. 1967). There, even though laxative products were described as food, the court looked to the labeling of the product and the oral representations made.



The court observed that it was represented to cure everything from backaches to cancer, and said: "When healing powers are attributed to 'foods,' they become drugs within the meaning of the Act." 263 F. Supp. at 215.

"A similar defense was presented in *United States v. Nutrition Service, Inc.*, 227 F. Supp. 375 (U.S.D.C. W.D. Pa. 1964) (aff'd on basis of lower court opinion, 347 F.2d 233 (C.A. 3rd Cir. 1965)). The defendant argued that 'Mucorhycin' was not a drug, but rather a 'food product of biologically processed whole wheat grain . . . sold and distributed for special dietary purposes through licensed members of the healing arts for special dietary uses.' The court held that this product was at most a catalyst, causing food to become absorbed and alimentary to the tissues in the human body, and that its food value, as such, was nil. The court stated that the 'real test was how was this product being sold?' and held that it was being sold for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and that the defendant's designation of Mucorhycin as a food supplement, while recommending its merits in curbing death-gripping diseases, did not make it a 'food' under 21 U.S.C. § 321(f).

"It is difficult to understand how the defendant can stand by its promotional claims that Zymaferm acts similarly to the natural enzymes of the body in breaking down the fibrous cells of plants ingested by the animal and thus increases the speed of the digestive process, while still contending that it does not affect 'any function of the body of man or other animals.' Clearly, the use of the product is intended to affect the functions—namely the digestion—of animals. The product sold here is sold, not for its food value, but for its enzyme effect on the functioning of the body. As such, Zymaferm is clearly a 'drug' under § 321(g)(1)(C). . . . Furthermore, it seems clear that the defendant has intended the use of Zymaferm for the prevention of various diseases in chickens, horses and cattle. Accordingly, it is also a 'drug' under § 321(g)(1)(B). . . .

"Silogen is also designed to affect the structure or functioning of the animal's body and is intended to affect both digestion and milk production. It too, then, is a 'drug' under § 321(g)(1)(C). * * *

"Thus, there remains no genuine issue of any material fact and the plaintiff is entitled to judgment as a matter of law. The plaintiff shall submit a proposed judgment of condemnation."

The claimants filed a motion for a new trial and for an amendment and revision of the court's findings of fact and conclusions of law. The Government opposed such motion, arguing: that there had been no "trial," that (although claimant might appropriately seek to vacate, alter, or amend a summary judgment) the claimant had introduced nothing that was new, had reiterated and varied their previous assertions, and had merely assigned error as a *matter of law* to the court's grant of summary judgment. The court denied the claimant's motion, and subsequently entered a decree of condemnation ordering the articles destroyed. (F.D.C. No. 59901; S. Nos. 74-470/1 H; N.J. No. 27)

Vitamin E Plus Hemo-Blend supplement for horses, at Muncie, S. Dist. Ind.

Charged 9-9-76: when shipped by Dr. J. B. Davidson, Canton, Ohio, the article was a new animal drug and no approval of a New Animal Drug Application was in effect with respect to its use and intended use; 501(a)(5). Default decree ordered destruction. (F.D.C. No. 60859; S. No. 77-66-461; N.J. No. 28)

MEDICAL DEVICES

Panels containing antibiotics for minimum inhibitory tests, and antibiotics intended for manufacture of such in vitro diagnostic devices, at Cleveland, N. Dist. Ohio.

Charged 9-30-76: the panels (which were manufactured, or in the process of manufacture, by Medical Specialties, Inc., Cleveland, Ohio, using the antibiotics for manufacturing use) and the antibiotics for manufacturing use were devices intended for human use which, on the enactment of the Medical Device Amendments of 1976, were subject to antibiotic certification, and no antibiotic certificate, release, or exemption was in effect; 502(l). Default decree ordered destruction. (F.D.C. No. 60857; S. No. 76-12-060 et al.; N.J. No. 29)

COSMETICS/BEAUTY PRODUCTS

Skin cream, medicated, at St. Louis, E. Dist. Mo.

Charged 4-14-76: while held by Lander Co., Inc., St. Louis, Mo., who manufactured the article using menthol crystals, phenol, glycerin, and stearic acid shipped in interstate commerce, the

circumstances used in the manufacture, processing, packing, and holding of the article lacked current good manufacturing practice; 501(a)(2)(B). The manufacturer claimed the article, denied the charge, and stated that there was no jurisdiction and no equity in this case. The Government served written interrogatories on the claimant, which the claimant answered. Subsequently, a consent decree of condemnation authorized release to the manufacturer, who was to have taken all necessary steps to conform with current good manufacturing practice and to bring the article into compliance with the law under FDA supervision. (F.D.C. No. 60709; S. No. 76-23-714; N.J. No. 30)

NOTICE OF JUDGMENT on Criminal Action

FOOD

Sarjit S. Sikand, t/a India Gifts & Foods, Chicago, N. Dist. Ill.

Charged 12-23-75 in probation revocation petition: moong wariar, moong beans, and gramflour were held in an insect-infested building and were contaminated with insect filth; 402(a)(3), 402(a)(4). After a hearing, the court revoked the defendant's probation, and ordered him placed on three years of probation with the special condition of probation being the service first of 60 days in a jail under the work release program. In revoking the probation, the court said:

"I don't recall that I imposed conditions of probation that had to do with the maintenance of the cleanliness of this operation, but it's implicit that probationers do not continue to commit the same crime for which they were placed on probation, so that condition is implicit in any event. * * *

"Evidence taken in this hearing reveals continuing violations of federal law while on probation, violations of the same nature the defendant was originally convicted of. * * *

"Mr. Sikand has testified as to the measures taken which he testified satisfied him that he is now doing business in compliance with the regulations and laws enforced by the Food & Drug Administration. If this is true, it must have occurred since the May, 1975 inspection, and if probation after a criminal conviction did not compel these measures before May of 1975, they come too late at this time to make any impression on the Court; there obviously has been more than an adequate cause shown for revocation of probation.

"Mr. Sikand seems to be a capable and successful businessman and a family man, but his presence in the food business is a menace to the public health, and he has displayed an unwillingness or inability to conduct that business, even under the compulsion of criminal probation, free of law violations. His probation opportunities have not been taken advantage of, there's no justification for a second chance.

"Whether or not this is a criminal or specific intent statute no longer is relevant after a conviction and after an order of Court that the conditions of probation, or at least the implicit conditions of probation, be to conduct his business in a law observant manner. So, the reinspection idea does not solve any problems.

"If, under reinspection under his present circumstances, Mr. Sikand is not found in substantial compliance, he belongs in the penitentiary, which is a circumstance I don't have to advert to—perhaps, better he should get out of the food business.

"In any event, I order a revocation of the probation of the defendant Sikand, and impose what is called in this Court a split sentence." (F.D.C. No. 59845; S. No. 96-859 H; N.J. No. 31)

NOTICE OF JUDGMENT on Criminal Action

DRUGS

Marcen Laboratories, Inc., and Raphael A. Marotta, president, New Rochelle, S. Dist. N.Y.

Charged 12-15-75: when shipped, Ossonate Plus chondroitin sulfate combination injectable (count 21), Normotensin pancreas extract and mucopolysaccharide combination injectable (count 22), Viro-Zyme sodium nucleate combination injectable (count 24), Lipo-K pancreas extract and chondroitin sulfate combination injectable (count 30), and Lipo-K pancreas extract and chondroitin sulfate combination capsules (count 31), were new drugs without effective approved New Drug Applications; 505(a). The corporate defendant pleaded guilty to the above counts 21, 22, 24, and 30, and the individual to count 31; but both stipulated the withdrawal of their pleas if their motion to dismiss should prevail. The defendants had moved to dismiss the information on the ground that the statute's definition of "new drug" was unconstitutionally vague. The court denied the defendants' motion, saying:

"The information charges that defendants introduced into



interstate commerce 'new drugs,' in violation of the Federal Food, Drug and Cosmetic Act The FDA is to determine the status of a drug pursuant to the definition set out in § 321(p) of the Act. That section provides that a 'new drug' is any drug 'not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof Defendants contend that this definition of 'new drug' is unconstitutionally vague and therefore cannot support a criminal conviction.

"It is a basic principle of due process that a criminal statute must give a person of ordinary intelligence a reasonable opportunity to know what is prohibited so that he can act accordingly. A statute will be void for vagueness if its prohibitions are not clearly defined.

"In non-First Amendment cases, however, a vagueness challenge must be examined in the context of the facts of each case. Here, the fact that the general public is unable adequately to protect itself in the purchase of food and drugs imposes a high degree of responsibility on those who profit from their manufacture and sale and affects their obligations under regulatory legislation. A regulatory statute in the food and drug industry is not invalid because there may be difficulty in determining whether certain marginal offenses fall within the prohibited area. A person who has received fair warning of the criminality of his own conduct cannot attack a statute because the language would not give similar fair warning to other individuals that their conduct is also prohibited.

"The facts cannot support defendants' claim that they did not know that the drugs sold by them were 'new' within the meaning of the Act. The FDA has complete authority to determine which drugs are 'new' and require an approved NDA in order to be sold to the public. Defendants were aware, with respect to every count to which they pled guilty, that the drugs were considered to be 'new drugs' without an approved NDA.

"Defendant corporation admitted, with respect to each drug mentioned in Counts 21, 22, 24 and 30, that there had been at least one seizure by the FDA and that the FDA considered the drug to be a 'new drug.' Moreover, there had been at least one hearing under § 355 of the Act where defendant was able to contest the 'new drug' designation. As to Count 31, to which defendant Marotta pled guilty as an individual, there was a § 355 hearing, publication in the *Federal Register*, and a letter to defendant Marotta stating that the FDA considered the drug to be a 'new drug.' Since both defendants received actual notice that the FDA considered the subject drugs 'new drugs' and knew that there was no effective NDA permitting their sale, defendants are in no position to claim that they were unable to guide their conduct so as to avoid criminal liability.

"Accordingly, defendants' motion to dismiss the information is denied."

Subsequently, the court sentenced the corporation to a \$1,000 fine on each of counts 21, 22, 24, and 30, and the individual to 10 days imprisonment and \$1,000 on count 30. The defendants appealed the denial of their motion and the sentence of imprisonment as to the individual was appealed as excessive. After hearing argument, the court of appeals, ruling from the bench, affirmed the district court's decision, thus upholding the Federal Food, Drug, and Cosmetic Act's new drug provisions as applied in a criminal context. (F.D.C. No. 59347; S. No. 29-022 F et al.; N.J. No. 32)

NOTICE OF JUDGMENT on Criminal Contempt Action

Magnolia Grocery Co., and William E. Hook, partner, Carthage, E. Dist. Tex.

Charged 1-15-76 in criminal contempt petition: that, in violation of a consent decree of permanent injunction, flour, cornmeal, and cornmeal mix were held under insanitary conditions, and one lot of cornmeal was contaminated with insect filth; 402(a)(3), 402(a)(4). Upon motion of the Government, the court issued an order limiting the maximum imprisonment and fine, and ordering (in view of such limitation) that the defendants were not entitled to a jury trial. Upon stipulation as to the facts of the case by the parties, the court found the defendants in criminal contempt and sentenced the individual to seven days imprisonment. But such imprisonment was suspended and the individual was placed on probation for six months with special terms and conditions. The court ordered that the firm permit FDA inspection of all food on the premises within the next two weeks, ordered destroyed any food designated by FDA as being adulterated, ordered the firm to cease to make further orders of food, ordered the liquidation of the existing inventory of food, and ordered the firm's complete

liquidation and permanent cessation of operations within six months. (Inj. No. 655; N.J. No. 33)

NOTICE OF JUDGMENT on Injunction Action

Barnett & Sons Salvage, Ltd., and Jesse P. Barnett, Jr., secretary & treasurer, and Noel Brett Barnett, president, Opelousas, W. Dist. La.

Charged 11-18-75 in complaint for injunction: that the defendants were engaged in the business of marketing, distributing in interstate commerce, and holding for sale after interstate shipment, salvage grains and other feed ingredients, such as cottonseed meal, cottonseed oil, and cottonseed hulls; that FDA investigation showed that the defendants had agreed with Planters Oil Mill, Inc., Tunica, Miss., for such mill to receive and process poison-treated cottonseed, and to deliver the derived oil, meal, and hulls to the defendants or their designated agent; that the mill's invoices for such feed ingredients bore the disclaimer "Fertilizer, chemical and industrial use only" and the shipping records bore the disclaimer "Fertilizer use only"; that the defendants (without advising concerning lack of suitability for feed use) sold such cottonseed meal to a supplier of feed ingredients, Southern Feed Ingredients Co., Memphis, Tenn., who in turn directed the delivery of the meal to feed mills and dealers in Macon, New Albany, and Hattiesburg, Miss.; Mobile, Ala.; and Arcola, La.; that such cottonseed oil was similarly sold to a Denison, Tex., supplier of feed ingredients, and the hulls had been ordered shipped to the defendants; that FDA found samples of such meal, oil, hulls, and finished feed to be contaminated with pesticides, fungicides, and other poisonous or deleterious substances, such as Disyston, pentachloronitrobenzene, mercury, Chloroneb, Methoxychlor, and Captan; that, as of November 14, 1975, 14 railcars of adulterated finished animal feed and cottonseed meal were en route to Tunica, Miss.; 84,000 pounds of adulterated cottonseed oil was in a tank at Denison, Tex., and quantities of adulterated cottonseed hulls were at Opelousas, La., which adulterated feeds or feed components were the subject of varying degrees of control of the defendants; that the articles containing pentachloronitrobenzene, Disyston, and Chloroneb thereby contained nonconforming food additives, and the articles containing mercury thereby contained an added poisonous and deleterious substance; that, although invoices and bills of lading for the cottonseed meal and oil, to the defendants bore disclaimers such as "fertilizer use only," the defendants failed to inform their customers that such cottonseed meal and oil were not for food use, and such cottonseed meal and oil were misbranded by false and misleading labeling; that the defendants caused the interstate shipment of such violative foods, received in interstate commerce such violative foods, and caused the delivery for pay of such food, and by their acts of failing to inform Southern Feed Ingredients Co. that the cottonseed meal was not suitable for food use caused Southern Feed Ingredients Co. to resell and reship the cottonseed meal without such statement on its labeling and resulting in the cottonseed meal being misbranded; 402(a)(2)(C), 402(a)(1), 403(a). Consent decree enjoined the complained of violations and enjoined the interstate shipment, the interstate receipt and delivery for pay, and the holding for sale after interstate shipment, of any cottonseed meal, oil, and hulls whose invoices and other labeling failed to restrict such articles to nonfood use, unless and until: all contaminated foods under the defendant's control were destroyed or diverted to nonfood use under FDA supervision; procedures and controls were established and in operation to sample and analyze each shipment, and to destroy or appropriately dispose of contaminated articles; or, in the case of railcarloads or truckloads sold and distributed in the same railcars or trucks as received, the defendants obtained the guaranty specified in 21 U.S.C. 333(c)(2); and a shipment coding system was established and in operation. (Inj. No. 713; S. No. 76-38-331 et al.; N.J. No. 34)

NOTICE OF JUDGMENT on Miscellaneous Actions

Hypoglycemic drugs for oral use for diabetics, and warnings statement on cardiovascular mortality, Boston, Dist. Mass.; and disclosure requirement regulations for product labeling, U.S. Court of Appeals, First Circuit, Boston, Mass.

Charged 8-11-72 and amended 8-16-72, 11-3-72, and 7-31-75, by Robert F. Bradley, Boston, Mass.; Samuel Beaser, Boston, Mass.; and Leo P. Krall, Boston, Mass. (on behalf of themselves and 175 other physician members of the Committee on the Care of the Diabetic); and Samuel Landa, Boston, Mass. (on behalf of himself and all fellow diabetic users of oral hypoglycemic drugs), against HEW Secretary Elliot L. Richardson, FDA Commissioner



Charles C. Edwards, and specified manufacturers of oral hypoglycemic drugs (Upjohn Co., Kalamazoo, Mich.; Eli Lilly & Co., Indianapolis, Ind.; Ciba-Geigy Corp., Ardsley, N.Y.; USV Pharmaceutical Corp., New York, N.Y.; and Pfizer, Inc., New York, N.Y.), in complaint for declaratory judgment and injunction; that FDA had issued an order entitled "Final Labeling Approved for Oral Hypoglycemic Drugs"; that compliance with such order by the manufacturers of oral hypoglycemic agents would result in irreparable and great damage in that physicians would be prevented from treating diabetic patients using their best clinical judgment; that the defendants' decision to order the alteration of the labeling of oral hypoglycemic agents was based on a single clinical study, the University Group Diabetes Program, which had been the subject of prolonged and unresolved scientific and medical controversy; that the major finding of the study—increased cardiovascular hazard—was faulty on the basis that patients treated with oral hypoglycemic agents had more cardiovascular disease to begin with than patients treated with diet or insulin; that the number of diabetics in all treatment groups dying of cardiovascular disease was too small for any conclusions; that the FDA order would cause great fear, consternation, and mental anguish on the part of diabetic users of oral hypoglycemic drugs; that the physician-patient relationship would be damaged and impaired; that the order would expose physicians to the hazards of malpractice litigation; that further enforcement of or compliance with FDA's order would cause increased morbidity and might cause increased mortality among patients suffering from diabetes mellitus; that plaintiffs prayed for a declaratory judgment declaring: FDA's order to be rescinded immediately; all other FDA communication based on the finding of the University Group Diabetes Program to be repudiated and such repudiation to be widely disseminated; FDA's best efforts to be used to restore the confidence of patients in physicians who use tolbutamide and sulfonylureas generally; FDA to refrain from making any further recommendations related to oral hypoglycemic drugs based on the University Group Diabetes Program pending corroborative studies; the baseline data of the University Group Diabetes Program including the total patient record of each patient be made available to the plaintiff physicians; clinical opinions of disagreeing expert diabetologists and other controverting studies be disseminated with equal emphasis and frequency by FDA; and that the court enjoin the defendants Richardson and Edwards from enforcing the FDA order.

The court temporarily restrained the H.E.W. Secretary from taking official action to compel the alteration of the existing labeling of oral hypoglycemic drugs pending hearing of the plaintiff's prayer for a preliminary injunction. The Government moved to dismiss the complaint because it failed to state a claim upon which the court could grant relief. The Government also, in the alternative, moved for a summary judgment. Meanwhile, the court denied the plaintiff's motion for a preliminary hearing, saying:

"This matter is before the Court [District Judge L. H. Campbell presiding] on plaintiffs' motion for a preliminary injunction enjoining the defendants from implementing, enforcing or complying with an 'order' of the Food and Drug Administration. For the reasons set forth below, the motion must be denied. ***

"Plaintiffs request the Court to enter a declaratory judgment that the order requiring the relabeling of oral hypoglycemic drugs be rescinded immediately; that the Food and Drug Administration rescind and repudiate all other statements of any kind which have been distributed to the scientific communities, to the press or the public which are based on the findings of the study known as the University Group Diabetes Program; that the Food and Drug Administration use its best efforts to restore the confidence of patients in their physicians who prescribe tolbutamide and the sulfonylureas generally; that pending corroborative studies the Food and Drug Administration refrain from making any further recommendations related to oral hypoglycemic drugs based on the University Group Diabetes Program; that the Food and Drug Administration disseminate with equal emphasis the results of all other studies reported by qualified researchers as well as the clinical opinions of expert diabetologists who disagree with the UGDP study; and that the Court decide other similar matters of a peripheral nature.

"Plaintiffs' dispute with the Food and Drug Administration centers around the proper interpretation of a ten-year study of oral hypoglycemic agents known as the University Group Diabetes Program (UGDP). The study began in 1961 and eventually included over 800 patients in 12 university medical clinics. The study compared the results of various hypoglycemic treatment regimens in patients with recently diagnosed adult onset mild diabetes who were not insulin dependent. All patients were placed

on an antidiabetic diet. One group was given Orinase (tolbutamide) in addition to diet; a second group was given insulin in fixed dosages; a third group was given varying dosages of insulin; and a fourth group was given a placebo.

"At the end of an eight-year period, death rates from cardiovascular diseases were $2\frac{1}{2}$ times as high in the tolbutamide group (127%) as in the placebo group (4.9%). The mortality rates for the two insulin treatment groups were nearly the same as those for placebo treated patients. The UGDP study concluded: 'The findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or than diet and insulin at least insofar as cardiovascular mortality is concerned.' As a result of the UGDP study, the FDA decided to suggest certain changes in the labeling of oral hypoglycemic agents (see Appendix A). No formal order, as such, has been issued. But plaintiffs urge, and I would agree, that the FDA's 'recommendations' carry with them very substantial impact, and in fact the manufacturers have agreed to comply, although none has yet done so.

"Plaintiffs disagree vigorously with the results of the UGDP study, particularly with regard to the purported association between oral hypoglycemic drugs and heart disease. Plaintiffs argue that: 'Conclusions drawn from this study, which form the basis of the action of the Food and Drug Administration, are unsound. The major finding of the study—increased cardiovascular hazard—is faulty on the basis that patients treated with oral hypoglycemic agents had more cardiovascular disease to begin with than patients treated with diet or insulin, and, further, there was no attempt to assess degree and frequency or coronary artery disease as baseline in all patients of the UGDP study. Further, the data indicates that more patients with diabetes of longer duration were treated with oral hypoglycemic agents than those treated with diet or insulin. Lastly the number of diabetics in all treatment groups dying of cardiovascular disease is far too small for any conclusions to be drawn.' . . . Plaintiffs have submitted numerous letters and affidavits of eminent physicians and scientists, together with evidence of scientific studies, in support of their contention that the UGDP study is invalid. Other evidence, contained in the FDA's Reply of June 5, 1972, and in affidavits filed with the Court, tends to indicate substantial professional support for the methodology and findings of the UGDP study, and of the FDA's actions based thereon.

"For the plaintiffs to obtain a preliminary injunction, they must demonstrate both that they will suffer irreparable injury absent preliminary relief, and that they have a reasonable probability of prevailing on the merits. . . . Although the plaintiffs may indeed suffer some degree of irreparable injury absent preliminary relief, the same can be said with respect to the defendants Secretary and Commissioner (who are, by law, required to promote and protect the public's interest) if an injunction is granted. Both sides are asserting positions in the public interest. There is nothing the Court can do, whether it grants injunctive relief or not, which cannot be said to result in irreparable harm to the party whose views, at this early stage, are given the lesser weight.

"Thus the Court must rely particularly on its assessment (necessarily preliminary) of the probability that the plaintiffs will or will not prevail on the merits; and in view of the serious conflict among experts over the validity of the UGDP study, and of the usually restricted role of a court in reviewing decisions of administrative agencies, I conclude that the plaintiffs have failed to demonstrate at this time a sufficient likelihood of ultimate success to warrant relief.

"Plaintiffs, in their Motion For Preliminary Injunction, seek to enjoin the defendants from implementing, enforcing or complying with the 'order' altering the labeling of oral hypoglycemic drugs. They argue that unless the relief sought is granted, they will suffer irreparable injury in two ways. First, relabeling will interfere with the physician-plaintiffs' exercising their best clinical judgment in the treatment of patients suffering from diabetes mellitus. Second, relabeling will cause fear, consternation and mental anguish on the part of the patient-plaintiff. Plaintiffs have submitted the affidavits of Doctors James M. Moss, Henry Dolger, and Robert F. Bradley, and of Samuel Landa in support of these assertions. . . .

"There are several points raised by these affidavits which bear discussion. It is not clear why the FDA's relabeling requirements should prevent Dr. Bradley from exercising his 'best clinical judgment.' The papers on file in this case indicate that Dr. Bradley is well aware of the alleged defects of the UGDP study, and indeed has expended considerable effort in publicizing his awareness to other physicians. Many reputable physicians apparently share his belief. The pendency of this lawsuit, even absent a preliminary injunction, serves to reinforce the fact that differing



views exist among those qualified to assess the medical and scientific issues. It is not certain, therefore, that the proposed relabeling will substantially inhibit Dr. Bradley from prescribing oral hypoglycemic drugs. So far as malpractice litigation is concerned, if the UGDP study is as faulty as Dr. Bradley believes, and there is insufficient evidence to link oral hypoglycemic drugs with increased heart disease, then one might expect such malpractice suits to result in a defendant's verdict. In any event, neither the UGDP study nor the FDA's opinions will disappear simply because preliminary relief is granted. These will continue to be available to attorneys who represent plaintiffs in malpractice litigation.

"Similar considerations apply to the affidavit of Mr. Landa. He too is well aware of the alleged defects of the UGDP study. It is difficult to understand why he will experience more anxiety returning to oral hypoglycemic drugs if the labeling is changed than if the labeling is unchanged. In either case, he is cognizant of the controversy among physicians concerning whether these drugs cause heart disease, and must decide for himself what course of action to follow.

"All of this is not to say that there is no irreparable injury to the plaintiffs, or to those less well informed whom plaintiffs may represent, if the relabeling occurs and if the plaintiffs' view of the underlying medical question should turn out to be the better one. However, it would appear that the magnitude of the injury pending a decision on the merits has been somewhat overstated. That plaintiffs will suffer a degree of irreparable injury pending decision does not by itself compel the issuance of a preliminary injunction. . . .

"It can as readily be said that there will be irreparable injury to the defendant officials (or rather, to the members of the public whom they have a duty to protect) if the relabeling is enjoined. For if defendants Richardson and Edwards are correct, and oral hypoglycemic drugs do increase the possibility of heart disease, then what of those patients who ought to be warned of this danger before taking the drugs? If plaintiffs obtain a preliminary injunction, these patients might use the drugs in ignorance of the risks, thereby increasing the likelihood of their suffering heart disease. On a motion for a preliminary injunction, the Court must balance the equities, and weigh the consequences to each party of its decision. In view of the considerations discussed above, it does not appear that on the issue of irreparable injury plaintiffs are entitled to a preliminary injunction.

"Plaintiffs have not demonstrated a reasonable probability of prevailing on the merits. Plaintiffs are before this Court seeking review of the action of the FDA, as reflected in its May 1972 *Drug Bulletin*, requiring relabeling of oral hypoglycemic drugs. . . .

"The Federal Food, Drug and Cosmetic Act only provides a right of hearing to the drug manufacturers. . . . Plaintiffs, however, are not manufacturers but rather are physicians and patients aggrieved by agency action. Accordingly, they sue under provisions of the Administrative Procedure Act. . . . Plaintiffs rely upon [5 U.S.C. 706(2) i.e., hold unlawful and set aside agency action, findings, and conclusions found to be (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law; . . . (E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute.]. They argue that the action of the FDA has been arbitrary and capricious and constitutes an abuse of discretion in that the agency has 'not fairly considered the facts which form the basis for their decision, and [has] not given an opportunity for an impartial investigation of both sides of this question.' However, the FDA received plaintiffs' 600 page Petition, submitted on October 7, 1971, and replied in detail to the various issues raised therein by a 100 page Reply dated June 5, 1972. Thus, it is not strictly accurate to argue that the FDA has considered only one side of the question. . . . It is important to focus upon the precise administrative action being challenged as arbitrary and capricious. The UGDP study itself is not agency action. Thus, whether or not the UGDP study team acted in every instance on a rational basis is not in issue so much as whether the FDA could rationally conclude that there was a possibility of a link between oral hypoglycemic drugs and heart disease, and that therefore it was the FDA's duty, pursuant to statute, to make certain that the labeling reflected this possibility. That the FDA decided to resolve doubts in favor of requiring a warning cannot be viewed as an irrational act or a 'clear error of judgment.' . . . Considering the conflict of scientific views before the Court over the interpretation of the UGDP study, it does not appear at the moment that the plaintiffs have shown a reasonable probability of proving at trial that the FDA's action is unsupportable on any rational basis.

"Although the case at bar does not arise under §§ 556 and 557

of the Administrative Procedure Act, plaintiffs argue that *Citizens to Preserve Overton Park*, [401 U.S. 402 (1971)] requires a similar standard in this case. . . . On the present showing, I am unconvinced that a reasonable mind might not accept the UGDP study as adequate to support the proposed relabeling of oral hypoglycemic drugs.

"This is not to say that after further hearing, the Court might not conceivably reach a conclusion favorable to the plaintiffs. But on a motion for preliminary relief the plaintiffs must demonstrate that the probabilities of success are on their side. This they have not done.

"For the reasons stated above, plaintiffs' motion for a preliminary injunction is hereby denied."

After the original temporary restraining order had lapsed and the original motion for a preliminary injunction had been denied, the plaintiff filed another motion for a temporary restraining order and another motion for preliminary injunction, alleging that such motions were based upon the above opinion, together with a serious change of circumstances.

The District Court denied the motion for a temporary restraining order saying:

"Plaintiffs filed motions for a temporary restraining order and preliminary injunction on September 21, 1972 following the denial of an earlier motion for preliminary injunction by Judge Campbell, sitting as emergency judge, on August 30, 1972. (The temporary restraining order issued August 11, 1972 'pending hearing of the plaintiff's [sic] prayer for a preliminary injunction at 10:00 A.M., Thursday, August 17, 1972' had no force and effect after the denial of the preliminary injunction.) The September 21 motion for temporary restraining order is supported by a memorandum which asserts that the basis of the relief now sought is Judge Campbell's opinion 'together with a serious change of circumstances. . . .

"No new evidence by way of affidavit was presented with the motion, nor was any motion to amend the complaint offered to substantiate the assertion of the 'serious change of circumstances'. The regulation 21 C.F.R. § 1.3 (erroneously cited as 21 C.F.R. § 1.1 in plaintiffs' supporting memorandum) is not referred to in either the complaint or the substitute complaint. It does not appear from Judge Campbell's opinion that plaintiffs sought relief before him predicated on that regulation, but they could have done so. . . . Rather they sought to enjoin the order of the Food and Drug Administration on the ground that it 'is arbitrary, unreasonable and capricious'.

"It appears to the court that plaintiffs are seeking the relief in the present motion only because they failed to obtain greater relief before Judge Campbell.

"Accordingly, as a matter of discretion the motion for temporary restraining order is denied."

Subsequently, the plaintiffs renewed their motion for a preliminary injunction and moved to amend their complaint. The plaintiffs based these motions on the new argument that FDA's proposed label was itself misleading because it failed to reveal the existence of a "material weight of contrary opinions among qualified experts", as required by law. After oral argument, the court granted the plaintiffs' motion to amend and motion for a preliminary injunction.

The Government appealed; and, upon appeal, the circuit court vacated the injunction and remanded the case to the FDA, saying:

"The district court granted a preliminary injunction, being persuaded that there was a reasonable likelihood of success in showing that the FDA had failed to comply with the statutes and its own regulation requiring that under some circumstances labeling make reference to the existence of a serious medical controversy. We vacate the injunction for reasons important to the proper judicial role in reviewing administrative actions.

"This controversy revolves around a long-term, federally funded study undertaken by the University Group Diabetes Program (hereafter the UGDP study) to determine the effects of oral hypoglycemic agents on vascular complications in patients with adult-onset diabetes. The study, involving twelve clinics and 1,200 patients, consisted of four treatment groups: diet alone, diet plus regular insulin doses, diet plus varying insulin doses and diet plus fixed doses of either tolbutamide or phenformin (two hypoglycemic agents). After monitoring the patients for from five to eight years, the study concluded that the combination of diet and either tolbutamide or phenformin was no more effective than diet alone in prolonging life but that those oral agents might be more hazardous than diet or diet plus insulin insofar as cardiovascular mortality was concerned. The latter conclusion, which led the investigators to discontinue use of the agents in the study as an unethical risk, was based on findings that patients treated with the two agents used in the study suffered more than twice as many



cardiovascular deaths than patients receiving the other treatments.

"After the study received much publicity and criticism, the FDA convened an ad hoc committee of experts on May 21, 1970 to evaluate the study's findings and the following day issued a press release agreeing with the UGDP study's conclusions and indicating that the agency would require labeling changes to reflect those views. After more extensive evaluation, the FDA concluded that protection of the public required a strong warning to physicians recommending use of an oral agent only if other treatments were inadvisable and noting the UGDP's findings regarding the apparently increased danger of cardiovascular mortality. This evaluation and proposed labeling change was first formally published in the *FDA Drug Bulletin* of June, 1971. ***

"This suit was filed on August 11, 1972 and a temporary restraining order issued that day. After a hearing and submission of affidavits of experts by both sides, the emergency district judge denied the preliminary injunction on August 30, finding that whatever irreparable injury might be suffered by the plaintiffs did not outweigh that suffered by the public represented by the defendants and that the plaintiffs had not demonstrated 'a reasonable probability' of showing that the FDA's decision to require the warning was arbitrary or capricious. A second motion for a preliminary injunction was denied on September 21 by the judge to whom the case was permanently assigned because no new evidence or amendment of the complaint had been presented.

"On October 17, 1972, the litigation entered an entirely new phase. On that date, plaintiffs filed a motion for leave to amend their complaint, supported by 13 affidavits by diabetes experts attesting to the controversy over the UGDP study, and new motions for a temporary restraining order and a preliminary injunction. The motions presented for the first time the argument that the FDA's proposed label was itself misleading and thus rendered the drug misbranded in violation of the statute, because it failed to reveal the existence of a 'material weight of contrary opinion' among 'experts qualified by scientific training and experience' as allegedly required by the agency's own regulation, 21 C.F.R. § 1.3. After oral argument, at which plaintiffs' counsel admitted this was an unprecedented case, being brought by the doctors and seeking to apply that regulation to the agency's own labeling recommendation, the district court in a Memorandum and Order granted on November 3, 1972, the motions to amend the complaint and for a preliminary injunction. It noted that 'The application for preliminary injunction was heard on the affidavits filed by plaintiffs and defendants, and their arguments both oral and written' and stated that 'the court is satisfied plaintiffs have made a showing that there is reasonable likelihood upon a full hearing on the merits they would be successful in establishing the defendants . . . have not in the order described in the May 1972 *Bulletin* complied with 21 C.F.R. § 1.3; 21 U.S.C. § 321(n) and 21 U.S.C. § 352(a)', and that 'there is [absent an injunction] a likelihood of irreparable injury to the plaintiffs' greater than would be visited upon the defendants by such relief.

"The district court had jurisdiction to review the administrative action under the Administrative Procedure Act (APA) . . . There is no dispute over the scope of review—whether the agency action was 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.' . . . The action challenged was informal agency action, subject to judicial review under that standard. . . .

"Significantly, there is also no controversy over the basis for judicial review—the full administrative record that was before the [Commissioner] at the time he made his decision.' . . . Yet, as the district court's brief memorandum indicates, the preliminary injunction was based not on a review of that record but on the affidavits presented by both sides to the court. As the Supreme Court has only recently reiterated, 'the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court.' . . . There are strong policy reasons behind this requirement. Litigation affidavits are often 'merely "post hoc" rationalizations . . . which have traditionally been found to be an inadequate basis for review.' . . . Moreover, this rule is significant in limiting courts to their proper role. Courts are to determine whether an agency's action was arbitrary or capricious in light of the information it confronted. It is a re-view, a second look at the same material, not a re-doing. And, of course, limiting review to the existing administrative record also saves judicial time.

"The requirement that review be on the administrative record parallels and supports the exhaustion of administrative remedies doctrine which reflects similar policies. To the extent that the record reflects consideration of arguments made and evidence submitted, it also reflects the focus which the agency had in bringing to bear its expertise. The exhaustion requirement, as it applies to administrative agencies, is no mere technical rule to enable courts to avoid difficult decisions. It is grounded in

substantial concerns not only of fairness and orderly procedure, . . . but also of competence. Courts are not best equipped, as both sides here readily agree, to judge the merits of the scientific studies and the objections to them. Specialized agencies like the FDA are created to serve that function. In this case, the regulation which, in their motion to amend, plaintiffs contend specifically governs the content of a balanced label, 21 C.F.R. § 1.3, was never presented to the Commissioner nor referred to in the administrative record. It is the significance of this omission that governs our disposition.

"Plaintiffs argue that while this regulation was never mentioned in the administrative proceedings, the concept of 'fair balance' which it represents was fully presented and argued by them in their initial petition, was explicitly rejected by the Commissioner in his initial letter, and that the specific statutes under which this regulation was promulgated were mentioned in plaintiffs' letter of response. While we recognize that the concept was put forward, are fully aware of the disadvantages of further delay, and do not wish to render the exhaustion doctrine a rigid and technical barrier, several factors in this case lead us to insist that the specific argument now pressed be first thrashed out in the administrative arena.

"Most significantly, this is an unprecedented argument. As plaintiffs' counsel readily admitted in oral argument before the district court, there appears to be no prior case in which an FDA drug labeling decision was challenged not by the producer but by concerned medical practitioners, and no case in which the misbranding statutes and regulations were sought to be applied not to the manufacturer's label but to the FDA's proposal for alteration of the label in light of new information. It is thus not surprising that the dialogue that did occur regarding 'fair balance' was on an entirely different plane. The Food, Drug and Cosmetic Act as amended in 1962 requires that applicants seeking approval for marketing of new drugs present 'substantial evidence' of the drug's effectiveness as well as evidence of its safety. The term 'substantial evidence' is defined in the statute to mean 'adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved'. . . . Yet the statute provides that approval of an application may be refused or withdrawn not only because 'there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have', . . . or there is 'insufficient information to determine whether such drug is safe' . . . but also if 'based on a fair evaluation of all material facts', the drug's labeling is 'false or misleading in any particular.' . . .

"The Commissioner, in his ruling on plaintiffs' petition, rejected the argument for 'fair balance' because he said that Congress had determined in 1962 that 'unsubstantiated expert opinion could no longer suffice to establish the effectiveness of drugs', and that 'Except perhaps in rare instances where there is substantial evidence on both sides of an issue, therefore, it is inappropriate to utilize the package insert to present all aspects of the evidence relating to safety and effectiveness.' Since he found that not the situation here, he saw 'no basis' for a balanced label. . . .

"Now, aware of the stringency of the substantial evidence test, . . . the plaintiffs argue that the misbranding statutes and regulation apply. Section 502 of the statute, 21 U.S.C. § 352, declares that 'A drug . . . shall be deemed to be misbranded—(a) if its labeling is false or misleading in any particular.' The definitional statute (21 U.S.C. § 321(n)) provides: 'If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things) not only representations made or suggested . . . but also the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates.' Implementing the latter definition is regulation 1.3. . . . One reading of this regulation would suggest that unsubstantiated individual clinical opinions of qualified experts, which are insufficient under the 'substantial evidence' test enacted in the effectiveness section, might be sufficient to create a fact omission of which might render the labeling misleading.

"The Commissioner never considered the meaning of this regulation, its relationship to the substantial evidence test, the intersection of the safety, effectiveness, and misbranding requirements, or the applicability of the misbranding requirements, both statutory and regulatory, to an FDA proposal for re-labeling, for the simple reason that the issue was not presented to him. Arguably these are simply issues of law which we are fully capable of resolving without administrative assistance. But as the Supreme Court has very recently noted in similarly resolving a closely analogous case, the interpretation of even definitional



sections in the drug law will often involve expert knowledge and the ability to evaluate the scientific evidence that becomes relevant. . . . Moreover, we have here not only novel issues concerning the interpretation of the statute, which the specialized enforcement agency should first undertake, but also unprecedented inquiries as to the meaning of the agency's own regulations. It is thus no answer to say that an agency need not be reminded of its own regulations. Finally, both the definitional statute and its implementing regulation on which the district court relied explicitly anticipate the exercise of administrative discretion, since they require only that the omission of expert differences of opinion be considered, along with all other relevant facts, in determining whether a label is misleading. . . .

"An equally important reason for insisting on exhaustion here is that insofar as the record reveals the administrative process seems to have been working well in this instance. The initial ad hoc advisory committee convened by the agency included several eminent critics of the UGDP study, indeed some of the plaintiffs here. While the response to Dr. Bradley's initial communications may not have been fully satisfactory, the response to the Committee's petition was both lengthy, detailed, and technical. Even the rebuttal letter, essentially in the form of a petition for reconsideration, a useful procedure in insuring that objections to even the supposedly final agency decision are first brought to its attention, received a specific and complete response. Arguments, studies, and materials, were not ignored; difficult problems were not swept under the rug. The communications evidenced agency recognition of the plaintiffs' expert status, and, as the concession of standing indicates, receptivity to criticism. Additionally, we were informed at oral argument that extensive negotiations between the parties to arrive at a mutually acceptable solution to the labeling problem had been carried on during much of this litigation. We thus have more than a pious hope that a remand to the agency will not only not be futile, but could well produce the most informed and responsible solution possible.

"Because the plaintiffs failed to exhaust their administrative remedies regarding the issues they now present and, consequently, the district court reviewed the agency decision on something other than the administrative record, we must vacate the injunction.

"Injunction vacated; case remanded for further proceedings consistent with this opinion."

Prompted by the opinion of the court of appeals, FDA promulgated in 40 Fed. Reg. 28582 of July 7, 1975, a revision of the regulations concerning failure to reveal material facts—21 CFR 1.3.

The plaintiffs moved to file, in the district court, a supplemental complaint seeking to enjoin enforcement of the amendments to the regulation 21 CFR 1.3 (alleging that such revised regulation effectively eliminated the basis of the plaintiff's cause of action), seeking declaratory judgment, seeking a temporary restraining order, and seeking a preliminary injunction postponing the effective date of such revised regulation pending proceedings before the district court. Although the court permitted the supplemental complaint to be filed, the court denied the request for a temporary restraining order saying:

"Plaintiffs seek injunctive relief to maintain the status quo of 21 C.F.R. § 1.3 pending review of the final administrative determination of the amended regulation. The burden is on plaintiffs to make a strong showing (1) of the probability of prevailing on the merits of the complaint, (2) of irreparable harm to plaintiffs if the restraining order is not granted pending judicial review, and (3) that the public interest will not be adversely affected by the injunctive relief.

"Plaintiffs have made no sufficient showing of the likelihood of success on the merits or that they will suffer irreparable harm absent the injunctive relief they request. The interest to be served by regulations relating to the labeling of oral hypoglycemic drugs is the protection of the health and safety of these members of the public likely to use or to be exposed to the drugs. Plaintiffs contend that the drugs must be deemed misbranded unless it is shown on the label that there is a great difference of opinion, a great controversy among doctors and scientists, concerning the drugs or the use of them. This contention has been made known to defendants over a period of many months and the administrative record demonstrates that defendants have not overlooked or ignored it. Appraisal of the contention and the data adduced in

support of it is the function of the agency and not the court. Where the decision of the agency, made in the midst of the controversy, has not been shown to be lacking in support of substantial evidence, the required presentation for equitable intervention by the court by issuance of injunctive relief to prevent enforcement of the regulation has not been demonstrated. Furthermore, nothing has been demonstrated by plaintiffs to persuade the court that the defendants have proceeded to violate the express rulings or even the spirit and intent of the opinion of the Court of Appeals in *Bradley v. Weinberger*, *supra*.

"Plaintiffs are three doctors, and Samuel Landa, a patient alleged to be 'suffering from diabetes mellitus and who has been using oral hypoglycemics under the direction and supervision of [plaintiff] Dr. Robert F. Bradley'. The plaintiffs' argument that the doctors will sustain irreparable harm absent injunctive relief because of the likelihood of their being exposed to tort liability as a result of the application of the amended regulation is at best speculative. Furthermore, nothing was demonstrated or argued as to irreparable harm to the alleged patient Landa if injunctive relief does not issue."

Subsequently, the plaintiffs moved to dismiss their supplemental complaint without prejudice, on the basis that they intended to file a petition for judicial review of the revised regulation 21 CFR 1.3 in the circuit court. The court of appeals considered the plaintiffs' motion to postpone the effective date of the revised regulations, plaintiffs' motion for summary reversal, and other memoranda. The court of appeals, assuming *arguendo* that there was appellate jurisdiction, denied the plaintiffs' motions because the court was not able to say that the district court erred in holding that there had been an insufficient showing of irreparable harm.

Petitioned 10-6-75 in the U.S. Court of Appeals for the First Circuit by Robert F. Bradley, Samuel Beaser, and Leo P. Krall (as members of the Committee on the Care of the Diabetic) and Samuel Landa, against the Food and Drug Administration: that direct judicial review by the court of appeals be granted as to the FDA regulation 21 CFR 1.3 which defined certain disclosure requirements for product labeling. Upon motion of the Government, the petition was dismissed (without prejudice to petitioners' right to seek review in the district court), because the courts of appeals have no original jurisdiction to review administrative actions in the absence of a special statutory provision conferring jurisdiction. Although, under the Federal Food, Drug, and Cosmetic Act, certain FDA regulations are singled out for direct appellate review. Regulations issued under § 371(a) are not included in this specification, and the omission appears to have been deliberate. Accordingly, pre-enforcement review of FDA regulations issued under § 371(a) has uniformly been initiated in the district courts."

Ultimately, the FDA regulations 21 CFR 310.510 and 21 CFR 1.3 (as revised) were promulgated and effectuated; and special warnings for oral hypoglycemic drugs on cardiovascular mortality were required. (Misc. Nos. 198, 313; N.J. No. 35)

Notices of Judgment are given pursuant to section 705 of the Federal Food, Drug, and Cosmetic Act. Notices of Judgment report cases involving seizure proceedings, criminal proceedings, and injunction proceedings. Seizure proceedings are civil actions taken against *goods* alleged to be in violation, and criminal and injunction proceedings are against *firms* or *individuals* charged to be responsible for violations. The cases generally involve foods, drugs, devices, or cosmetics which were alleged to be adulterated or misbranded or otherwise violative of the law when introduced into and while in interstate commerce, or while held for sale after shipment in interstate commerce.

Notices of Judgment are prepared by Food and Drug Division, Office of the General Counsel, DHEW.

Published by direction of the Secretary of Health, Education, and Welfare.

Sherwin Gardner, *Acting Commissioner of Food and Drugs*
Washington, D.C., March 1, 1977

You Can't Find Cholesterol on the Nutrition Label?

Could be. Because food labels are not required to show cholesterol content. But many of them do, and that's important to people who have been advised by their doctors to restrict their cholesterol intake. When the information is given, the amount (in milligrams) of cholesterol in each serving of the food is shown and also the amount in each 100 grams of food. For example, a product label may show:

Cholesterol (14 MG/100 G) 34 MG

This means there are 14 milligrams of cholesterol per each 100 grams of the product and 34 milligrams of cholesterol in each serving of the product.

Another optional item on the Nutrition Label is sodium content. Some manufacturers put the sodium content of their products on the label for the benefit of people on salt-restricted diets. This information also must be shown both in milligrams per serving and per 100 grams of food.

And some labels tell you what percent of the total calories in the product are supplied by fat and how much of the fat in the product is polyunsaturated and how much is saturated. A label that provides this information might show:

Fat (Percent of Calories 53%) 33 G
Polyunsaturated 2 G
Saturated 9 G

This means that 53 percent of the total number of calories in one serving of the food are supplied by fat. The rest of the calories are supplied by protein or carbohydrate. One serving of the food contains 33 grams of fat. Of this, 2 grams are polyunsaturated and 9 grams are saturated. The rest of the fat is monounsaturated. The Nutrition Label must list the total fat content of the product, but breaking it down into polyunsaturated and saturated fat and showing the percent of calories supplied by fat is optional.

If you have special dietary needs that involve cholesterol, fats, or sodium, be sure to look at the Nutrition Label.

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