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Food Drug Cosmetic Law JOURNAL

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

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REPORTS

TO THE READER

The JOURNAL's first article "Counseling Your Medical Client: Law—Business—Strategy" by *Philip Sperber*, states that counsel can be most effective by taking a step-by-step approach in advising clients on how to cope with new laws, regulations and norms of conduct. The step-by-step approach would involve taking the client through all considerations, decisions and actions that must be taken from a point at which a new product idea is formulated to its full-scale market introduction. Mr. Sperber is manager of the legal department of Cavitron Corp.; his paper was presented at the 32nd annual meeting of the Food, Drug and Cosmetic Law Section of the New York State Bar Association which was held on January 27, 1977 in New York. His article begins on page 148

In his article "Regulating Pharmaceutical Innovation: An Economist's View," *J. E. S. Parker, Ph.D.* states that governments, in their anxiety to protect the general public from the effects of bad drugs, may have a detrimental effect on the flow of innovations. Dr. Parker cites the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act in 1962 as a contributory factor to the lack of innovation in the American pharmaceutical industry. Dr. Parker is senior lecturer at Otago University, Economics Department, Dunedin, New Zealand. His article begins on page 160.

Robert W. Harkins, Ph.D., states that drugs, foods, cosmetics, toxic chemicals, consumer products, etc., all pose a risk of hazard to man and that society must set a priority for food safety evaluation within this broad context. He further states that in an effort to test those materials which may pose the greatest risk to man, we need an overall assessment before national commitments are made for food ingredient safety testing. Dr. Harkins is Vice President of Scientific Affairs of the Grocery Manufacturers of America, Inc. His article, "Food Additive Safety Evaluation" which was presented on behalf of the Grocery Manufacturers of America before the Senate Select Committee on Small Business on February 24, 1977, begins on page 182.

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Journal

Counseling Your Medical Client: Law—Business—Strategy

By PHILIP SPERBER

Mr. Sperber Is a Manager of the Legal Department of Cavitron Corp.

The New Medical Device

COUNSELING A MEDICAL DEVICE COMPANY has become a mind-boggling task over the past few years. The three major areas of concern have been the Bureau of Medical Devices & Diagnostic Products, the Bureau of Radiological Health and product liability. All three areas have undergone a rapidly changing transition. The Bureaus are in the middle of classifying products, promulgating standards and setting up procedures for premarket clearance and well-controlled investigations. In the product liability area, standards of conduct and care have become more strict.

Counsel can be most effective by taking a comprehensive step-by-step approach to advising his client or company on how to cope with the new laws, regulations and norms of conduct. This involves taking the company through all the considerations, decisions and actions that must be made from the point at which a new product idea is thought of—right through experimentation, testing, development, investigation, manufacturing and full scale market introduction.

Let us begin with a situation where a company has a new idea for a medical device that has commercial potential. The first thing the company needs to know is the expense of government compliance and the risk of not being able to obtain approval to market the device within a reasonable period of time.

If the proposed device is not within a type of device that has been classified in Class I (General Controls) or Class II (Performance Standards), the device will fall under Class III (Premarket Approval) pursuant Section 513(f)(1) unless it is substantially equivalent to a device that was on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. However, if sufficient information exists to establish controls or a performance standard to provide assurance of safety and effectiveness, the Secretary can be petitioned to remove the device from Class III pursuant Section 513(f)(2).

If insufficient information exists for establishing a performance standard to assure safety and effectiveness and if the device is to be used for supporting human life or preventing major impairment of human health or if it presents a potential unreasonable risk of illness or injury, then premarket approval will be necessary before the device can be marketed. In this situation, the company can expect market introduction of the product to be delayed beyond the normal timetable for product development in order to comply with formal testing protocols and premarket application submission requirements.

If the proposed device is substantially equivalent to a device that was on the market prior to May 28, 1976, the company can market the product before obtaining premarket approval. However, pursuant Section 501(f)(2)(B), premarket approval must be obtained within 90 days after the Secretary promulgates a premarket approval regulation for the device pursuant Section 515(b), but in no event earlier than 30 calendar months from the date that the device was classified into Class III pursuant Section 513(d).

The Medical Device Exploratory Phase

If the product idea gets the green light, the next stage is exploratory research and experimentation to determine feasibility. A breadboard is assembled and tested. At this preprototype stage, company personnel should take into consideration voluntary standards, government standards and product liability factors. The days of debugging a product after problems develop in the field are becoming a thing of the past. Recalls, corrective actions and product liability law suits make it essential that the safest and most effective design be selected as early in the product development process as possible.

Guidelines and standards established by organizations such as the American National Standards Institute, the American Society for

Testing and Materials, the American Standards Association, the Association for the Advancement of Medical Instrumentation, the Emergency Care Research Institute, the Institute of Electrical and Electronic Engineers, the International Electro-technical Commission, the International Standardization Organization, the National Electrical Manufacturers Association and the National Fire Protection Association carry much weight with juries as evidence of a level of care to be exercised by manufacturers. In addition to considering the accepted practices of industry, company technical personnel should explore all reasonable design alternatives and investigate the dangers involved with performance goals and the intended purpose of the device prior to detailed design work and prototype construction. It is also important to determine how a selected product design could be subject to misuse or abuse having nothing whatsoever to do with the intended function of the product. These product liability considerations should not be put off in the product development process to a point in time where, for budgetary and political reasons, personnel may be locked into the particular design selected.

If there are performance standards applicable to the medical device pursuant Section 514 or if there are applicable performance standards pursuant Part 1010 of the Radiation Control for Health and Safety Act regulations, these should be studied carefully before selecting a design for the prototype phase of product development. Not only must these standards be complied with prior to market introduction, but they also serve as *prima facie* proof of negligence if not complied with because they are circumstantial evidence of a standard of care established by our society.

The Nonclinical Device Study

Prototype design and construction, bench testing, field testing and animal investigations should be carried out in the most reasonable manner feasible for a device that does not need premarket clearance and which is not subject to promulgated standards. When there are applicable standards under the Medical Device Amendments or the Radiation Control Act, care must be taken to comply with test procedures outlined in such standards.

In the situation where the device is expected to be classified in Class III or is in Class III and is expected to stay there, the manner in which the company conducts its nonclinical investigations to determine safety and effectiveness takes on great importance in the

company's ability to obtain prompt premarket approval. On November 19, 1976, the FDA published proposed regulations for good laboratory practice (GLP) when making nonclinical laboratory studies that form part of the data to be submitted in the premarket approval application. Nonclinical laboratory studies must be done pursuant to an approved protocol under the supervision of a study director with adequate professional or scientific credentials. Strict adherence to personnel qualifications, GLPs, accurate recording of verified data, quality assurance personnel responsible for the integrity of the data obtained and adherence to protocols, written operating procedures setting forth in detail the methods, materials and schedules to be used in testing, the maintenance and calibration of testing equipment, retention of records, equipment and specimens, and the recording of statistical methods employed for analyzing the data.

Before the company commences with the nonclinical prototype testing phase, it should decide whether to file an application for approval of a product development protocol pursuant Section 515(f). The product development protocol route enables the company to develop the medical device simultaneously with the data necessary to demonstrate safety and effectiveness, in accordance with the requirements and objectives of the protocol. After the protocol has been carried out and the objectives are met, a notice of completion of the approved protocol is submitted to the Secretary. If the Secretary declares the protocol completed, such an order is equivalent to approval of an application for premarket approval for the device, and the company now has clearance to go ahead with market introduction.

If it is up in the air as to whether premarket approval will be needed for the device, the company may not want to bother with the onerous requirements of the product development protocol red tape. Also, if the company is in a rush to get the device out onto the market, in a situation where premarket approval is not needed for the 30-month period of Section 513(d), the company may not want to wait the 120 days for approval or denial of its proposed product development protocol.

The Clinical Device Investigation

After completion of testing, analysis and final prototype redesign, the company is ready to commence drafting design specifications, ordering materials, writing the bills of material and preproduction

prototype construction for brief lab and environmental tests and extensive clinical investigation if premarket approval is required for the device. The integrity, quality control, record keeping and protocol details of the human trials must be even more rigorous and exhaustive than the nonclinical laboratory studies.

If the device does not have the benefit of the 30-month grace period for being classified into Class III pursuant Section 513(d), then an application must be submitted for an exemption for investigational use pursuant Section 520(g) in order to start testing the device on human subjects. The proposed investigational device exemption regulations published by the FDA on August 20, 1976 indicate the voluminous things that have to be done by the sponsor of a clinical investigation which completely foreshadow in time and expense the requirements of the proposed nonclinical laboratory study regulations.

Medical Device Production

Upon completion of *in vitro* and any necessary *in vivo* testing and investigations, the final design of the medical device should be reviewed one last time for compliance with performance standards promulgated by the pertinent FDA bureaus and for product liability proofing prior to production release for a pilot run. Also, if the medical device needs premarket approval prior to sale, a notice of completion of the product development protocol or an application for premarket approval should have been submitted with sufficient lead time because the Secretary has four months within which to approve or reject product development protocol completion and six months within which to reject or approve the application for premarket approval

There are a number of ways to "liability proof" a new medical device. When the final design and method of manufacture has been decided on, a brainstorming session should take place to foresee what the ultimate user might do to the device without the benefit of any instructions on use and intended purpose. This exercise will bring out hidden defects, hazards and other problems associated with equipment usage by careless personnel. This session will also bring out the need for various labeling contraindications and warnings.

The company's quality control people should conduct and discuss with the designers, the manufacturing manager and project engineer a systems safety analysis and fault-free and failure mode

and effect analysis under the assumption that a newly designed and manufactured product will malfunction.[1] Each step of the manufacturing process should be analyzed and discussed to determine where human error or carelessness and assembly or machine fault may result in finished devices not meeting design and performance specifications. Critical components should be selected for 100% zero defect testing at various points during the production process. Inspection procedures should be established for vendor components, part tolerances and operating parameters that affect product safety and effectiveness. Vendors should be asked to sign agreements whereby they promise to maintain records related to critical materials, parameters and components and promise to notify the company whenever modifications are made.

Finally, good manufacturing practices (GMPs) promulgated by the FDA should be strictly adhered to. Proposed GMP regulations were published August 5, 1975 for inclusion in Subchapter H of Title 21 of the CFR and should be paid attention to as an indication of final GMPs to come. In light of these regulations, it would probably be a good idea for the company to make the quality control staff independent of production and reporting directly to the president or general manager. In-process, incoming and rejected or obsolete components and labeling should be separately handled and stored; quality control instrumentation should be calibrated per National Bureau of Standards prime standards and should be periodically inspected and maintained at least twice a year pursuant written procedures with records of each calibration being maintained; critical components should be identified with a control number with a record maintained of inspections performed; production records should be kept for critical operations identifying the operator, date and checking performed; changes in material, components purchased or any aspect of the design should be permitted only after a formal approval procedure has been completed; there should be a written master product record of all specifications and procedures for product design, quality control and labeling; at least one unit of each product model and prototype should be retained together with all associated documentation as part of the company's product history record and adequate distribution records should be provided for where feasible to facilitate corrective action or a recall.

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[1] *Chestnut v. Ford Motor Co.*, 445 F. 2d 967 (4th Cir. 1971).

Marketing the Medical Device

Regardless of whether premarket approval is required, no medical device can be marketed prior to 90 days notice to the FDA pursuant Section 510(k) if it is being introduced into commerce for the first time or if it is not substantially equivalent to a device in commercial distribution prior to May 28, 1976 or a device introduced after May 28, 1976 that has been put into Class I or II. As of December about 1000 510(K)s had been received by the FDA from manufacturers, and only six or seven had been classified by the FDA as devices requiring premarket approval pursuant Section 513(f)(1).

Before a new electronic medical device or model can be marketed on time, an initial or model change report must be submitted to the Bureau of Radiological Health pursuant Sections 1002.10 and 1002.12 of the Radiation Control Act Regulations. Furthermore, electronic medical devices that must comply with applicable standards promulgated by the Bureau of Radiological Health must have a certification of compliance permanently affixed to the device prior to distribution or delivery.

Prior to shipping a medical device for sale in another country, that country's health agency must approve importation and the Secretary must be notified of such approval if the medical device does not comply with that country's laws or does not comply with the requirements of the Medical Device Amendments of 1976 if the product were to be marketed in the United States, pursuant Section 801(d). Thus, a medical device will be deemed adulterated or misbranded by the FDA if it is being sold in Canada without the proper labeling pursuant Part I of the Canadian Medical Devices Regulations, if the device was not tested in Canada pursuant Section 13 of said Regulations, if distribution records of the device in Canada have not been maintained pursuant Section 21 of said Regulations, or if the detail notification statement is not submitted to the Director (of the Health Protection Branch of the Department of National Health and Welfare) within ten days of the date of first sale of the device in Canada pursuant Section 23 of said Regulations.

There are a number of continuing obligations to be complied with once a medical device is marketed by a company. Between November 15 and December 31 of each year, each medical device company must register every establishment it owns or operates engaged in the manufacture, preparation, propagation, compounding or processing of medical devices pursuant Section 510 of the Medical

Device Amendments and Subpart B of Part 807 of the Regulations pursuant thereto. Pursuant Section 510(j)(2) of the Medical Device Amendments, each medical device company must report to the Secretary during the months of June and December a list of devices newly introduced into commerce. Pursuant Section 1002.11 of the Radiation Control Act Regulations, medical device companies must submit an annual report between June 30 and September 1 of each year summarizing all quality control procedures, testing, complaints, tracing and other records for certain electronic products. If the company is exporting medical devices, annual notification must be given to the Secretary identifying the devices to be introduced over the next twelve (12) months and the countries to which they are to be exported pursuant Section 801 of the Medical Device Amendments.

Noncompliance of Medical Devices

Manufacturers of electronic medical devices must report accidental radiation occurrences, which are injurious or potentially injurious exposures, to the Director of the Bureau of Radiological Health immediately, pursuant Section 1002.20 of the Radiation Control Act Regulations. Any electronic medical device that has a defect or fails to comply with a federal performance standard must be brought to the Secretary's attention together with a statement of the measures to be taken to take corrective action in the form of repair, replacement or refund, pursuant Parts 1003 and 1004 of the Radiation Control Act Regulations. Defect or noncompliance notification must also be made to dealers or distributors and traceable purchasers pursuant Section 1003.10. Finally, medical device companies should be aware of the fact that in addition to a mandatory recall for devices not meeting promulgated standards or improper or no certification, companies are subject to a penalty of up to $300,000 pursuant Section 360C(a), (b)((1) of the Radiation and Control for Health and Safety Act.

The FDA on June 30, 1976 published proposed regulations on recall policy and procedures for medical devices that do not emit electronic product radiation. Once the final regulation is promulgated, medical device firms that voluntarily take corrective action or remove products from the market must notify the appropriate FDA district office with detailed information on the defect, hazard, products

produced and distributed and the recall strategy relating to the depth of recall, public warnings and effectiveness checks. It cannot be stressed too strongly that a product recall contingency plan should be established and carefully implemented whenever necessary. If notification is inadequate with respect to contents or spread or depth of parties being notified, the medical device company can expect the FDA to insist on a second notification program and further efforts until the FDA makes a final decision on termination of the recall action.[2] One of the most sensitive areas where a company has failed to use good judgment is depth of recall. A broadcast mailing to hospitals with respect to a defective product may not be sufficient if there is a likelihood that these institutions may not disseminate the information properly to surgeons and physicians using the equipment—likewise, with respect to a mailing to distributors or retailers.

The medical device company should also establish in advance an understanding with its vendors and distributors regarding the roles that each will play in a product recall, as well as who pays or shares in the expenses involved. Such agreement in advance will also assure that the distributor and retailers are meeting their obligations to keep adequate records for tracing the flow of products through the distribution channel to the ultimate users. Who bears the cost of the recall is of grave concern because a single MD notification can run up to $300,000.[3]

To avoid criminal prosecution, the chief executive officer of a medical device company must take measures ahead of time that are adequate to assure no violation occurs and must take measures to immediately remedy a violation when found.[4] The FDA brought 45 criminal proceedings against individual executives and firms in fiscal year 1975.[5] In the same period of time, the FDA recalled 266 devices, seized 36, obtained court injunctions with respect to three and sent about 1800 regulatory letters for less serious device violations.[6]

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[2] In the summer of 1976, the FDA requested the Cordis Corp. to send an additional letter to users with respect to its Kappa pacemakers.

[3] Cost estimation made by Jim Hulse, Esq. of Becton-Dickinson during a panel discussion at the September, 1976 annual meeting of the American Surgical Trade Association.

[4] *United States v. Park* Supreme Court decision.

[5] FDA Annual Report for 1975.

[6] The FDA Annual Report for 1975; Hoffman, Joel E., "Enforcement Trends under the Food, Drug, and Cosmetic Act—A View From Outside" The Food & Drug Law Institute Work Session on Enforcement, Washington, D. C., March 17, 1976.

It is clear that the breadth and complexity of complying with all the laws and regulations applicable to medical devices require the coordinated efforts of many individuals in any one company. The chief executive would be well advised to designate a key executive as the company compliance officer and liaison with the FDA. The chief executive should also make it mandatory that he be notified immediately of any suspected violations, complaints or injuries. Different people with pertinent specialized experience should be made responsible for the different areas of concern, such as standards development, device classification, GMPs, performance standards compliance, performance standards certification, nonclinical laboratory testing, clinical investigations, FDA application submissions for devices in the premarket approval class, Section 510(k) submissions prior to market introduction, equipment labeling, inspections, product recalls and initial and annual reports.

Medical Device Inspections

FDA inspectors and investigators showed up unannounced at 1621 device factories, warehouses and plants and took 688 devices for analysis and related documentation in fiscal year 1975.[7] These inspections lasted anywhere from a matter of hours to a duration of weeks.

A typical inspection involves following the raw materials from receiving right through production to warehousing. Typical questions that the investigator will ask are: who has responsibility for FDA compliance by a particular device being inspected? where are the complaint files kept? is there a formal routine complaint handling procedure? is quality control organizationally independent of production and what official does each unit report to? are there written equipment maintenance and calibration procedures? are there written records for each, batch, device or series produced? are reserve samples of finished devices retained and for what period of time? and are returned goods segregated, retested and redistributed or destroyed?

It is important that the company employee escorting the FDA inspector be knowledgeable in the overall operations and have access to vendor, production, quality control and product history information. The escort should also know the FDA's and company's rights with respect to disclosure of information. For instance, although the inspector can demand all documentation required under Section 519

[7] The FDA Annual Report for 1975.

and 520(g) of the Medical Device Amendments, the FDA has no authority to see the financial, sales, pricing, personnel and research data other than shipping information, personnel qualifications and information relating to nonclinical laboratory and clinical testing pursuant Section 704(a). It is a good idea to have top management represented when the inspector's report is completed and discussed. Not only will this clear up misunderstandings, but it will also facilitate immediate compliance by a company which subsequently receives a warning letter describing violating conditions or a regulatory letter, which must be responded to within ten days.

The Medical Device Overview

The increased expense of complying with ever increasing FDA regulations, of not being able to introduce new products on schedule or at all, of having to cope with recalls, of having to cope with more frequent product liability suits, or having to pay tremendously higher insurance premiums (if insurance can be obtained at all in the medical device area), and of persuading reluctant vendors of components and materials to supply the medical device company's needs, is surely putting a severe strain on two thirds of the 7.5 billion dollar medical device industry composed of small companies with annual sales less than ten million dollars.[8] Many of these small firms will need to strategically plan their future as to whether to continue in the medical device business, divest product lines representing the greatest risk (for instance, those for which premarket clearance is needed), or sell out to a larger company because of insufficient working capital to cope with the new regulatory and consumer activist environment.

The situation is quite different for larger device companies where the ratio of the cost of compliance to annual sales is quite small compared to what the ratio would be for a small instrumentation firm, whose profits after taxes might very well be less than the actual cost of compliance. The large device company not only has the financial, legal, regulatory and quality control resources to handle the additional burden of compliance, but can also integrate vertically to assure sources of supply for critical components. Also, larger device companies will no longer find competition from smaller firms as competitive because these small firms will no

[8] Jan. 4, 1977 press conference of the Ford Administration Interagency Task Force on Product Liability singled out the medical device industry as being one of the most severely affected by substantial hikes in product liability premiums between 1974 and 1976.

longer be introducing innovative products protected by patent rights as frequently as in the past. In the absence of this competition, larger firms should be able to capture larger market shares, raise prices in response to the added cost of government compliance, and extend the life cycle of existing products in the absence of pressure from smaller firms coming out with improvements and new generation devices.

The larger companies will want to reexamine their acquisition programs this year for a number of reasons. The small firms will be more amenable to selling out or merging than in the past. With an increased supply of acquisition candidates, the price tag for smaller firms should fall to more modest levels in comparison with past years. Third, the acquisition of new businesses and product lines in existence prior to May 28, 1976 is an attractive alternative to the expensive, slow and risky route of product development protocol and premarket approval ventures stemming from internal development of new products. **[The End]**

DEXTROPROPOXYPHENE LISTED AS SCHEDULE IV CONTROLLED SUBSTANCE

The drug dextropropoxyphene has been added to the Drug Enforcement Administration's list of Schedule IV controlled substances, effective March 14, 1977. The DEA has provided that all drug registrants have until August 14, 1977 to comply with the security, labeling, and packaging provisions of the order.

The main objection expressed to the proposed listing concerned the time allotted for the installation of new, or expansion of existing, security measures for the drug. Other comments opposed the listing on the ground that there is insufficient evidence to justify control. The principal manufacturer of the drug, Eli Lilly and Company, expressed no opposition to placing the drug in Schedule IV.

In the event that compliance with any of the requirements imposes special hardship, the DEA said it will consider justifiable requests for a time extension.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,841 and 80,864

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Regulating Pharmaceutical Innovation: An Economist's View

By J. E. S. PARKER, Ph.D.

Dr. Parker Is Senior Lecturer at Otago University, Economics Department, Dunedin, New Zealand.

GOVERNMENTS FACE A DILEMMA in regulating pharmaceutical innovation. In their anxiety to protect the general public from the effects of bad drugs, they may have a detrimental effect on the flow of innovations. Resolution of this dilemma calls for a nicety of judgment and a degree of sophistication that would seem difficult to attain. Certainly this is the conclusion to be drawn from the American experience during the last fourteen years. Since the passing of the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act in 1962, the regulatory climate in America has been tight. The consequences of unsympathetic attitudes have been considerable and this article will outline them. Comparisons will be drawn with the United Kingdom (U. K.). The purpose is constructive. Innovation in pharmaceuticals is complex. A review of the effects of a tight regulatory climate will help clarify the nature of the underlying mechanisms and provide a number of important lessons which may be relevant to official policy in the future.

An economist, when asked to predict the effects of a regulatory agency whose purpose is to monitor pharmaceutical innovation, would compile a mental check list. Included in this would be a knowledge of the following: the folklore and political environment of the agency's operations, the terms of reference, the type and character of the administrative structure, means of access to scientific knowledge, methods of communication with applicants, working protocols and rules of evidence,

the incentive structure, attitudes to risk and the underlying model of innovation. Comment on this list will follow under the subheadings below, and a summary of the effects of regulatory tightness in the U. S. A. post 1962 will also be included.

Folklore and Political Environment

The folklore and political environment underlying the enabling legislation of a regulatory agency, may provide some useful insights into operating attitudes. If the laws have been framed in an atmosphere of mistrust, the agency's role may then be interpreted as a brief to protect the general public and not as a supervisory joint venture to promote and foster innovation. The atmosphere underlying the 1962 Kefauver-Harris Amendments represented a political groundswell that was essentially critical and mistrustful of the U. S. pharmaceutical industry. In such an atmosphere, delays in approving innovations caused by the regulatory process become a benefit and not a cost in the eyes of those responsible for operating the agency. It is clear that this mistrust continues today. Drugs, the drug industry and the Food and Drug Administration (FDA) are considered fair game by politicians. The average number of formal Congressional hearings relating to the FDA is between 35 and 40 per annum.[1] The Congressional criticism in 1974 of the FDA's final approval of beta blockers for angina underlines the persistence of this mistrust.[2] As one commentator observed, this case ". . . is destined to become a classic in the history of *political pharmacology*, with very wide implications for the legislation and regulation of drugs."[3] (Stress added). In most other countries, such ill-informed criticism would never have been voiced. America is thus saddled with a regulatory system where sound medical judgment may not be the sole criterion guiding decisions. The FDA is involved in an atmosphere that requires political as well as medical caution. This is a pressure that can do little to improve the quality of operations.

The contrast with the British system in basic attitudes has been very considerable. In Britain, the emphasis has been on trust and the regulatory attitude has centered on cooperation. The political

[1] *New Drugs;* pending legislation. Legislative Analysis No. 13, 94th Congress, July 8, 1976. American Enterprise Institute.

[2] Wardell, William M. and Lasagna, Louis, *Regulation & Drug Development,* American Enterprise Institute 1975.

[3] *Ibid.*, p. 122.

environment has also been much more wholesome. The activity of the regulatory agency is not considered fair game for parliamentary comment. As a result, delays in approval have been minimal. Unfortunately, there are signs that things are changing for the worse. With the implementation of the Medicines Act of 1968, the indications are not encouraging. More will be said on this later.

Terms of Reference

The terms of reference of a regulatory agency may have a considerable impact on the process of innovation. For example, the 1962 Amendments laid down a new series of guidelines for the FDA. The major changes related to the need for manufacturers to prove efficacy (in addition to safety) and control was extended over the clinical stages of investigation. Prior to the Amendments, approval was not required to test drugs in humans. After 1962, a sponsor had to comply with the Investigational New Drug (IND) procedure and receive FDA approval before a new pharmaceutical could be used in man. Preclinical data has to be submitted for review and supervision extends through the clinical stages of drug investigation. Thus, the FDA terms of reference cover safety and efficacy and include control over clinical research.

Unfortunately, safety and efficacy requirements are easy to prescribe by legislation, but extraordinarily difficult to implement. Safety is a relative and not an absolute concept, and efficacy is often patient, specific and frequently only assessable after widespread general usage of a pharmaceutical. Any institution charged with this dual responsibility will have a built-in cautionary bias which is likely to result in delay. Legislation requiring that efficacy, as well as safety, be determined prior to marketing, is in effect requiring that user conditions be simulated by an extensive series of tests. Monitored release and post-marketing surveillance procedures are shunned as major assessment techniques. Thus, the burden of proof falls on clinical trials. Because it is seeking a substitute for the final market, the regulatory agency will press for these to be as large and as long run as possible. The applicant on whom the cost burden falls, finds itself involved in a simulation exercise—where the pressure is for absolute proof, and where the regulatory authority has a bias towards a sample size and duration period much greater than is practicable. The result of this conflict is likly to be delay.

Structure

The type and character of the administrative structure may be highly relevant to the operations of a regulatory authority. Types of arrangements vary from an organization which is a fully integrated department of government, to a quasi-independent body which meets sporadically and which functions on an *ad hoc* basis. An authority that is a "full blown" department of government has many advantages. It will have the full panoply of supportive services, will tend to have a continuity of experience and operate on well-defined procedural lines. These virtues may not, however, be appropriate for the job in hand. It is too easy to unleash prejudice by the use of the word bureaucracy, but under the circumstances it is perhaps appropriate. A large, slow-moving, relatively inflexible organization, which is an almost inevitable characteristic of a civil service type of structure, may be highly undesirable for the task in question. In the treatment of submissions, it is plausible to argue that a faster moving, more flexible type of organization is required. Frequently, these are the virtues that are associated with small organizations which have an administrative structure that confers a degree of independence.

The differences in the U. S. A. and the U. K. regulatory authorities are instructive here. The FDA is a full blown department of State whereas in the U. K., prior to the Medicines Act of 1968, the Committee on Safety of Drugs (CSD) was a small, quasi-independent, flexible organization. With the Act, the operating methods of the CSD have been incorporated into law and its name changed to the Committee on Safety of Medicine (CSM). Registration procedures have become mandatory. They are no longer voluntary. These changes are more than nominal. There is now a much more formal organizational structure and its character is veering towards that of the FDA. This is beginning to show in terms of the numbers employed and in concern at the speed of response to submissions.[4] Another indication of

[4] Concern became so acute that the Association of the British Pharmaceutical Industry conducted a study to determine the delays associated with the processing of all types of submissions to the CSM—*A Three Year Review of Submissions to the Committee on Safety of Medicines* July 1970—September 1973. ABPI 1974. No comparable data exists for the period when the CSD was the regulatory authority. The commentator, therefore, has to speculate on the contrast between the two regimes. Three factors suggest a worsening performance. One, the anxiety expressed by industry members leading to the ABPI study. Two, some companies were beginning to concentrate their early development activities abroad, because of CTC approval delays. Three, comment on the deteriorating regulatory climate by knowledgeable independent observers. See footnotes (20) and (23).

the effects of formalizing the existing system is to be found in the License of Right Procedure and the restrospective review of existing products.[5] Pharmaceutical manufacturers have been given the right to apply for a "product license of right" for products already on the market before September 1, 1971, and approximately 36,000 licenses have been granted. By this means, existing drugs have been given the opportunity to become legal within the new system.

Retrospective review is more worrying. Pharmaceuticals that have been granted a product license of right are to be reviewed for their efficacy. Apparently, past experience in use is no longer adequate. The judgment of the CSM's predecessor and the market is not to be trusted. A panel review procedure is to be used to screen existing products. Notice that the acceptance criterion requires a demonstration of efficiency. "No hazard" will not be sufficient. Drug companies will be required to provide data to establish the effectiveness of products on which the market has already passed judgment. Many thousands of man hours of research personnel time will be absorbed in providing review data, whose purpose is merely to formalize information which is already known to users of the drugs. In effect, therefore, the British system would appear to be changing in emphasis away from practical experience in use as the best guide to safety, quality and efficiency. In this sense, the British regulatory system has become less trusting; a development that does not augur well for future regulatory performance.

Incentive Structure

An important element in the operational character of any organization is the incentive or reward structure. Regulatory authorities normally interpret their role as a screen to defend the public from "bad" drugs. This perception is to some extent determined by the way in which sanctions and rewards are levied on them. In such organizations, there is usually no penalty for delay and no reward for prompt decisions. Put another way, all the sanctions tend to be lined up for the occasion when a bad drug is passed. When this happens there is public arraignment, opprobrium and heads roll. Under such an incentive structure it is inevitable that there will be a predisposi-

[5] For a description of the procedure see Marriott, J. V. R., "Safety, Efficacy & Quality Review in the United Kingdom." FOOD DRUG COSMETIC LAW JOURNAL 495 (Aug., 1957), also Reekie, W. Duncan, *The Economics of the Pharmaceutical Industry;* Macmillan 1975, p. 106.

tion towards caution. The balance of the incentives is negative.[6] There is no positive encouragement to foster prompt decisions. Delay is therefore favoured. It gives the appearance that certainty is being established. A cynic may also say that given a long enough delay, a submission will be self solving. Experience from less timorous regulatory systems in other countries may clear the way for a safe decision. The overall effect of such a "consumer protection" attitude is that the patient is protected from drug hazard and not from disease and discomfort.[7] This is an indictment of stunning force and one which is particularly relevant to America. In fact, Commissioner Schmidt of the FDA has stated that to his knowledge there has not been a single Congressional Committee to investigate the failure of the FDA to approve a new drug. Investigations have been entirely on approvals.[8] It has probably applied with less force in Britain. The means of access to scientific knowledge and, at least until recently, a more trusting regulatory atmosphere have offered an escape from such a myopic attitude.

Scientific Expertise

Access to scientific expertise and staffing practice has a very considerable bearing on the character of the operations of a regulatory agency. Submissions must be approved and, therefore, expert scientific opinion is required. How this expertise is supplied is important. It may come from "in house" personnel or may come from outside the organization. The distinction in the source of advice is highly relevant. It is tempting for a regulatory authority to employ its own scientists. There are, however, disadvantages. These relate to the quality of personnel and their independence of judgment. The nature of the job militates somewhat against attracting really top quality men. The primary role of a scientist employed in such an agency is to appraise the research work of others. Employment in such a role offers neither the glamour of independent research, nor the prospects for eminence that are associated with other avenues of scientific employment. It is, therefore, likely that the staff attracted to such a job will be of less than top quality. This would not matter so much if their task was

[6] Peltzman, S., on p. 278 of *Regulation, Economics and Pharmaceutical Innovation;* Proceedings of the second seminar on the economics of pharmaceutical innovation edited by Cooper, Joseph D., American University, Washington, D. C. 1976.

[7] Wardell, William M. and Lasagna, Louis. *Regulation & Drug Development,* American Enterprise Institute 1975, p. 163.

[8] Schmidt, A. M., "The FDA Today: Critics, Congress, & Consumerism." Paper presented to the National Press Club, Washington, D. C., Oct. 1974. (Mimeo.)

less onerous. Unfortunately, the quality requirements are very demanding. Such men are required to vet pharmaceutical innovations and must therefore be of a calibre that they themselves are near the frontiers of current knowledge. When they are not in this class, the result is antipathy from submitting companies, and delay.[9]

Allied to the problem of the quality of "in house" personnel, is that of independence of judgment. Using outside personnel has two major advantages. The first arises from choosing consultants who are acknowledged experts in their field. The second relates to the independence of judgment of such experts. An assessment of safety and efficacy of a new pharmaceutical at the premarket stage is very rarely a simple matter. As indicated earlier, these concepts are probability based, and it is in such situations that an outside opinion may be of the greatest value. The consultant is able to exercise judgment which is independent in a number of important ways. As an acknowledged expert, he may sustain and carry an opinion which is contrary to "departmental" judgment. As an outsider, he will probably be free of the unconscious opinion forming process that occurs within any organization. Furthermore, because his major source of income is not derived from the regulatory authority, there is less economic pressure to conform to the prevailing opinion. He is likely to be free from the negative incentive structure described above, and may well be less timorous in his attitude. As a result, the risk/benefit tradeoff in assessing new pharmaceuticals may be shifted away from the short-sighted consumer protection viewpoint. A consultant is, therefore, in a position of strength which goes beyond his status as an expert. He may be able to orientate the regulatory decision process towards patient benefit, and away from drug hazard.

In America, the FDA relies almost entirely on the opinion of its own "in house" scientific personnel. In Britain, there is a much greater emphasis on the advice of outside consultants.[10] This contrast in access to scientific opinion at the decision-taking stage, may have been an important factor explaining faster appraisal times in Britain. Thus, in a sample of 43 chemical entities introduced into America between 1965 and 1969, the average lead time of Britain over America was 2.1 years.[11] The independence of judgment and the positive attitude of outside scientific experts towards pharmaceutical innova-

[9] See footnote 1.

[10] Dunlop, Sir Derrick, "The British System of Drug Regulation" in Landau, Richard L., (editor) *Regulating New Drugs*, Chicago University 1973.

[11] See footnote 7.

tion may well have been a major influence predisposing the system against delay, and in favour of prompt decisions.

Procedures

Contrast in working procedures yield interesting insights into the nature of the regulation process. In the U. S. A., submissions to the FDA and subsequent communications are almost always in documentary form. While not prohibited, person-to-person contact between the Administration and applicant company is not encouraged. All oral communications are documented and there is a marked formality surrounding these exchanges. As a result, this type of interchange tends to be little used and in practice, contact is almost exclusively via exchange of documents. In the U. K., means of communication are less formal. Documentation is readily supplemented by person-to-person contact. Company R and D men and members of the CSM meet, to iron out problems. Telephone contact is not unusual between registration managers and CSM staff. In effect, the system has a degree of flexibility that can help sidestep the delay which is inevitable, when the written word is, in effect, the only medium of communication. Referring back to folklore, a system which has arisen and evolved in a trusting atmosphere is unlikely to be overconcerned with devising procedures to protect agency personnel from "undue influence." Where the atmosphere is less trusting the situation is likely to be different. Working protocols will be devised to insulate the regulatory agency from pressure. Formal methods of communication will be preferred. An inevitable casualty will be person-to-person contact. The cost of debarring the most effective means of communication is likely to be delay.[12]

Impact on Project Selection

Basic attitudes, means of communication and the quality and independence of the scientists assessing submissions can have a serious feedback effect on innovation. Imagine a company research manager at the planning stage appraising projects put to him by his staff. A major factor in the decision process will be the attitude of the regulatory authorities. Where the scientists employed in the agency are of ordinary quality, where attitudes are not trusting, where the incen-

[12] To sample the negative attitude towards informal contact see Review Panel Drafts Guidelines for Industry—FDA Relations, in the Pharmaceutical Manufacturers Association Newsletter Sept. 6, 1976.

tive structure is negative and where communications are restricted to written submissions, there is likely to be a "small-step" bias. In order to avoid the frustration and delay that will be a virtual certainty with a major innovation, companies are likely to opt for developments that are more modest. The logic underlying such a preference for the "small-step" is persuasive. A submission which involves a considerable departure from accepted technology faces a number of difficulties. The written form of submission is a poor medium of communication where it is not reinforced by personal contact between the instigators of the research and the assessors. Large departures from existing knowledge induce a natural caution in those who have to be persuaded. Often a new principle is involved and the innovating company may find itself as a mentor with a truncated means of educating the regulatory agency. Under the circumstances, it is reasonable to assert that companies will shun developments which are large. In effect, the psychology of project selection will be affected by a basic decision rule which can be baldly stated as "the bigger the step forward, the bigger the delay."

Those familiar with the processes underlying innovation in all types of industry will know that progress is usually achieved by a gradual and painstaking accumulation of minor changes. This process is known as "technology building on technology" and refers to a situation where innovations arise out of a process of a cumulative synthesis of past knowledge.[13] Particular innovations tend to be modest and come from and tend to be based on the technology that has preceded them. This does not imply that the rate of advance will be slow. When aggregated, these minor improvements may well represent a brisk rate of technological change. For most industries this process of cumulative synthesis is accepted as normal. Pharmaceuticals, however, are often singled out for different treatment, and the denigrating and highly emotive term "molecular manipulation" is frequently employed. It is important to realise that all industries have their version of molecular manipulation. It is even more important to appreciate that the quite normal emphasis on minor achievement in pharmaceuticals may be reinforced by regulatory procedures. Mistrustful and long-delayed official appraisal may add to the natural caution of research managers, and induce a "small step" bias which is greater than if regulation were more sympathetic. In other words, it is being argued that the emotive

[13] Langrish, J., Gibbons, M., Evans, W. G., & Jevons, F. R., *Wealth from Knowledge*, Macmillan 1972.

term "molecular manipulation" should be defused by use of the more accurate description "technology building on technology," and the possibility is being advanced that the particular flavour of pharmaceutical regulation, may be a contributory factor to a preference for modest innovation.

The Implied Model of Innovation

The American system of pharmaceutical regulation implies a model of innovation that is deficient in a number of respects. The emphasis on premarket testing procedures, the rare use of monitored release and the weakness of post-marketing surveillance procedures, indicates too high a degree of faith in simulation. It is effectively being assumed that premarket testing procedures provide a reliable guide to behaviour in final use. This attitude is carried as far back as the preclinical stage. The IND procedure before a drug may be tested in healthy human volunteers, implies a strong belief that animal testing provides a valid base for predicting effects in humans. A checkpoint is, therefore, introduced in the process of pharmaceutical development so that the FDA may appraise and verify results before giving permission for use in man. In a recent paper, the underlying assumptions or rubrics of the FDA are examined and the author concludes ". . . that their logical and factual base is usually precarious and often fallacious and that alternative and equally tenable assumptions might make the drug development process more effective for society as a whole."[14] It is well argued that animal testing is likely to be an unreliable predictor for use in man. The rubric that the earliest stages in clinical investigation are the most hazardous is refuted. Exhaustive premarketing evaluation is challenged in its assumption that it protects the public from widespread hazard, and it is concluded that premarketing observation, no matter how intense can never be an adequate substitute for surveillance of a drug in general use.[15]

The implied model underlying the U. K. system would appear less fallible. Trials on healthy human volunteers are permitted without permission of the CSM. It is only at the stage of use in patients that permission in the form of a Clinical Trial Certificate (CTC) is required. Less emphasis is placed on premarket evaluation in the sense that there are well organized post-marketing surveillance and adverse drug reaction procedures. Monitored release of selected preparations is also

[14] Wardell, W., in "Regulatory Assessment Models Reassessed," of Cooper (editor) p. 240.

[15] *Ibid.*

used. In effect, there is some shift of emphasis towards the market and a degree of reliance placed on the judgment of the physician as the arbiter in the risk/benefit tradeoff for patients.

A major advantage of the U. K. system is that control is only introduced at the stage when a new drug is to be used in patients. Permission is not required for use in healthy human volunteers. Not only does this mean that regulation occurs at a later stage than in the U. S. A., it also implies a much more sophisticated model of the innovation process. It implies an appreciation that pharmaceutical development is more complex than the "disease specific potential drug" model. It allows for the fact that some drugs do not follow the conventional discovery pathway where a compound is identified as having possible therapeutic value for a specific disease, and a highly directed routine is then followed from testing in animals through to evaluation in man. Some compounds have a very different discovery pathway. They may form the basis of an experimental hypothesis, where no specific disease is under consideration and where their therapeutic value will not become clear until they have been evaluated in man. Examples are Propranolol, Methyldopa and Chlorproniazine. A discovery pathway of this nature implies an appreciation of two fundamental points. First, that there are some areas where animal models offer limited or no indications for man. Second, that the discovery and development process can and does extend beyond the introduction of a drug into man. The FDA model of innovation does not seem to recognise that some pharmaceuticals may have more complex pathways. The effect of basing regulation on a model of innovation that is too simplistic may be considerable. It may go beyond merely delaying the introduction of a drug. It may actually decrease the possibility of discovery. Where the discovery pathway is dependent on use in humans to clarify the nature of the hypothesis under investigation and to define the therapeutic area, the IND procedure may actually prevent their investigation.[16]

Attitudes to Risk

Regulatory authorities' attitude to risk may be classified as absolute or relative. An absolute approach to the risks associated with new pharmaceuticals refers to a situation where the major emphasis in the appraisal procedure is to protect eventual consumers from harm. The concern is on securing "risk free" drugs. Interpretation of the

[16] Coates, J. A., in comments on pages 185-190 of Helms, R. (editor) *Drug Development & Marketing* American Enterprise Institute 1975.

meaning of the term "risk free" is of course fraught with difficulty, but it does imply that in the assessment of the tradeoff between risk and benefit, the major focus of attention of the authorities will be on the possible harm that may arise. Under a relative risk approach the emphasis is different. There is less of a consumer protection attitude, and the anxiety is more towards the progress of medicine and the relief of illness. With such a regime, the thrust of regulatory performance is towards securing pharmaceutical innovation. Thus, in the trade off between risk and benefit, greater weight is assigned to the positive aspects of a new drug's performance. Relatively less emphasis is placed on risk in the appraisal arithmetic. There will tend to be prompt appraisal and with this will go a well developed post-release information collection procedure. In effect, because the emphasis under a relative risk system is on securing consumer benefit, the procedures are oriented to give the prescribing physician a greater say in the appraisal arithmetic. New pharmaceuticals tend to be made available earlier, but for this to be acceptable there has to be a sophisticated and sensitive post-release reporting system. With this, adverse reactions and unforeseen indications may be rapidly identified and harm, thus, contained.

The contrast in the logic between the two attitudes is as follows. Under the absolute approach the intention is to screen out "bad" drugs, so that those which eventually emerge are deemed safe. Given that this job is done thoroughly, there will be little need for feedback mechanisms to keep the authorities informed once a drug is in general use. Under the relative approach, the market is effectively being asked to partake in the risk/benefit arithmetic and, thus, a strong feedback of information is required so that the nature of the tradeoff may be continuously monitored. It is not unreasonable to represent the CSM as operating a relative risk system and the FDA an absolute risk system. Evidence from the "drug lag" studies suggests that Britain tends to be more prompt and positive in its appraisal of new drugs. There is also a sophisticated and multi-layered feedback mechanism permitting continuous monitoring of pharmaceuticals as they enter and are established in general usage. In America, slow appraisal times and poorly developed post-market reporting procedures suggest that safety has a greater degree of emphasis in the regulatory mind. This is consistent with the absolute risk approach. Later in this paper, when reforms are under discussion it is suggested that information feedback systems in America should be improved. But such improvements will only make sense if there is also a shift in attitude towards

that of the relative approach. The addition and sophistication of post-marketing procedures will only add to delay, unless the regulatory attitude changes in emphasis so that more prompt appraisal is "purchased" via improved market feedback.

Evidence of the Effects

Studies by economists and others of regulation in pharmaceuticals now indicate a range of effects. Nearly all of these are based on American experience and the majority relate to the influence of the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act. The demanding nature of the amendments and the way in which they have been interpreted by the FDA provide a case study in unsympathetic regulation and yield lessons of considerable importance. Academic conventions require that the conclusions be expressed in a conditional fashion and be hedged with the appropriate caveats. However, it would not be unfair to state that the weight and quality of evidence that has now been amassed makes it difficult to deny the findings with any degree of conviction.

The Drug Lag

Regulatory tightness in the U.S.A. has been such that important pharmaceuticals have been available in other countries and not in America. Importation and use without FDA clearance is not permitted and so the armory of drugs available to the American physician has suffered a relative decline. The contrast in availability has been most marked in cardiovascular, diuretic, respiratory and gastrionentinal areas compared with Britain.[17] In wider and numerical terms ". . . up to the end of 1971 the overall British lead for mutually available drugs was, in terms of drug-years of prior availability, double that of the United States. In terms of exclusively available drugs, Britain has nearly four times as many as the United States."[18]

There is little doubt that the FDA has acted as a dissemination bar and slowed the adoption rate of pharmaceuticals developed in the U. S. A. and abroad. In a survey of 216 physicians associated with the University of Rochester School of Medicine and Dentistry, the respondents were asked about their knowledge of and desire for 12 major drugs

[17] Wardell, W. M., "The Drug Lag: An International Comparison." *Proceedings of the Fifth International Pharmacological Congress*, July 1972.

[18] Wardell, William M. and Lasagna Louis. *Regulation & Drug Development*, American Enterprise Institute 1975, p. 77.

available abroad but not in the U. S. A. The low level of awareness was signified by the average respondent indicating that he had heard of only 1.6 of them. However, where drugs were known of in detail, approximately 78 percent of them were thought to be sufficiently good, to be wanted in America.[19] Thus, awareness was low, but where the drugs were known, there was usually a desire to have them made available. Pharmaceuticals judged by other countries to be of major importance have been delayed or withheld from the American market. The lag in approval would seem least justifiable when widespread foreign usage has already established clinical parameters. Under these circumstances, delays imposed by FDA procedures which deliberately ignore this evidence would not seem warranted. However, it was not until 1973 that criteria were proposed by which foreign clinical data on a drug would be accepted as evidence for an NDA. Even now, however, such data may only be a supplementary character. The primary data has to be generated in the U. S. A.

Since 1972, there have been improvements and some of the marked differences in availability of pharmaceuticals have been reduced. In a number of major areas, the discrepancies compared with Britain have been reduced or eliminated. Exceptions are in the treatment of hypertension and the problem of potassium balance in diuretic therapy.[20] The U. S. A. is still noticeably behind Britain in these areas. Explanations for the improvements include a more enlightened regulatory approach in the U. S. A. and the onset of a more conservative trend in Britain. Hopes that the FDA's attitude has come in line with a medically sound approach to regulation should not however rise too high. The object lesson from 1974 of the criticisms of the approval of beta blockers for angina should be a reminder of the limited scope for change.[21]

The Costs of R and D

Submission procedures have imposed considerable cost increases on pharmaceutical companies. There are the direct costs incurred by the requirements of regulatory agencies. In addition, there are the more important, but less obvious, costs associated with raising the level of uncertainty, lengthening the development period and inter-

[19] *Ibid.*

[20] Wardell, William M., Developments in the introduction of new drugs in the United States & Britain 1971-74, in Helms (editor).

[21] *Ibid.*, p. 171, footnote (9).

rupting the feedback mechanisms. The natural progression in the development of a pharmaceutical from a new chemical entity (NCE) to a marketable product is now, to a large extent, determined by the requirements of the regulatory authorities. When considerable delays are involved and when procedural barriers are imposed, the continuity of the process may be destroyed. This may create very considerable problems for the morale of research personnel, and may adversely influence the knowledge generation process whereby experience feedback is used to reappraise and redirect. Flexibility may be lost and the whole R and D process suffer. One study suggests that between 1962 and 1972 development costs per NCE in America rose from $1.2 million to $11.5 million.[22] Another estimates that the impact of the 1962 Amendments has been to raise the cost per NCE by a factor of 2.3.[23] Cost increases are almost bound to have a direct influence on the productivity per unit of research expenditure. In fact, productivity in the U. S. A. per dollar of R and D expenditure fell from an index number of 593 in 1960-1 to 100 in 1966. Similar figures for the U. K. are 293 and 100 respectively.[24]

Discovery Rate

When total development and clearance times in the U. S. A. change from approximately 2.5 years in 1962, to 7.5 to 10 years in 1972, there is likely to be a direct impact on the discovery rate.[25] Companies might compensate for regulatory tardiness by increasing R and D. To maintain a constant flow of new products in the post-Amendment period it has been estimated that an increase by a factor of 2.35 would have been required.[26] In practice, however, this does not appear to have happened. R and D spending has increased but this has not maintained the rate of innovation. Since the 1962 Amendments, the flow of NCEs in the U. S. A. has been more than halved. Furthermore, in the opinion of one authority, this reduction can be wholly attributed to the Amendments.[27] The U. S. A. has changed

[22] Sarett, L. H., "F. D. A. Regulations and Their Influence on Future R. & D." *Research Management*, March 1974.

[23] Grabowski, Henry G., Vernon, John M. and Thomas, Lacy Glenn, "The Effects of Regulatory Policy on the Incentives to Innovate," in *Impact of Public Policy on Drug Innovation & Pricing*, edited by Mitchell, Samuel A. and Link, Emery A., American University 1976.

[24] *Ibid.*

[25] See footnote 22.

[26] Bailey, Martin N., "Research & Development Costs & Returns: The U. S. Pharmaceutical Industry," *Journal of Political Economy*, Jan./Feb. 1972.

[27] Peltzman, S., *Regulation of Pharmaceutical Innovation*, American Enterprise Institute, 1974.

from a situation where it was responsible for the majority of the world's discoveries, to one where the number of new products introduced reaching sales of $1 million per year between 1968-72 was 26, compared with 44 for Britain.[28] For such an alteration to have occurred, there must have been a very dramatic change in the scientific and business environment in America. There has been, and the most plausible culprit is the FDA in the post 1962 era.

Research Depletion

One consideration that may exonerate the American regulatory authorities from a degree of blame may be the increasing difficulty in achieving innovations. It may be that earlier pharmaceutical discoveries have exhausted the obvious routes to innovation, and that subsequent changes require more scientific talent and a greater expenditure of resources.[29] There is some evidence to support this point of view. R and D expenditure both in the U. K. and U. S. A. has risen very fast during the 1960's and research output has fallen, both in unit expenditure terms, and as a rate per unit time. Even in the U. K. where regulatory tightness has not been so evident, R and D productivity has been falling.[30] It may, therefore, be true that there has been some research depletion, with a plateau being reached, which is unrelated to the regulatory climate.

Evidence on the influence of depletion of the stock of research opportunities is limited and not easy to interpret. One study covering the period 1954 to 1969 finds that "depletion" had the postulated negative effect and was statistically significant. However, it did not have anything like as large a quantitative impact as the regulatory variable in accounting for the decline in NCEs per R and D in the U. S. A.[31] Furthermore, when these results are re-estimated with a longer run of data (1954-74) by different authors, the coefficient of the depletion variable becomes statistically insignificant, but it does continue to have the expected sign.[32] Using different measures of the depletion variable, and adopting the U. K. as a comparative control, these same authors then go on to find that there is some evidence of research depletion. But again, this effect is not revealed to be as impor-

[28] Clymer, Harold A., The Economics & Regulatory Climate: U. S. & Overseas Trends, in Helms (editor).

[29] Schmidt, Alexander, testimony before U. S. Senate Subcommittee on Health of the Committee on Labor & Public Welfare, Hearings on Legislation Amending the Public Health Service Act & Food, Drug, and Cosmetic Act, 93 Congress, Aug. 1974 p. 30-47.

[30] See footnote 23.

[31] Bailey, Journal of Political Economy.

[32] See footnote 23.

tant as regulation.[33] In effect, the overall conclusion stands: regulation has reduced the discovery rate and increased costs. Research depletion may be considered only of minor importance.

Concentration of Innovational Output

The delays and costs associated with regulatory tightness may consolidate the position of established companies. By lengthening the time a pharmaceutical takes to get to the market, and increasing the attrition rate of product candidates, the FDA adds to the uncertainties associated with R and D. This may have the effect of deterring the entry of firms into pharmaceutical research, and thus, make the position of existing firms more secure. In addition, the premium on size implied by the high costs and risks of research may mean that only the largest companies are able to continue and, therefore, innovational output may gradually become more and more concentrated. The argument has been somewhat overstated for purposes of clarity. In practice, entry by firms is not so much a question of newcomers being attracted into pharmaceuticals, but rather existing firms redirecting their efforts into other markets within the industry. A successful innovation puts competitive pressure on the products of other firms. These firms may respond by further innovation and companies not in that particular submarket, may be attracted there by its success. Evidence suggests that the pharmaceutical industry in the U. S. A. is competitive in the sense that there are considerable rank changes over time of the sales of leading companies within submarkets. This impression is backed up by indices of market instability.[34] In effect, it is being argued that R and D is a crucial factor determining competition between drug firms, but that regulatory tightness has a detrimental effect on the productivity of R and D and, therefore, damps the force of innovative competition. Increased concentration of innovational output results, with the brunt of the adjustments falling on the smaller company.[35]

Evidence for increases in concentration is impressive. The four firm concentration ratios of *innovational* output in the U. S. A. have risen from 0.462 for the period 1957-61 to 0.610 for 1967-71. Innovational

[33] See footnote 23.

[34] Cocks, Douglas L., Product Innovation and the Dynamic Elements of Competition in the Ethical Pharmaceutical Industry, in Helms (editor).

[35] Jadlow, Joseph M., "Price Competition and the Efficacy of Prescription Drugs: Conflicting Objectives," *Nebraska Journal of Economics and Business*, Autumn 1972. See also Pharmaceutical Manufacturers Association yearly figures on research and development by the smaller firm reproduced on page 49 of *New Drugs;* pending legislation.

output for each firm is measured by its numbers of NCE introductions, where these are weighted by their sales over the first three years of product life. Sales are used to give a quality weighting. When firms are ranked by their size as indicated by their total sales of ethical drug products, then the four largest firms accounted for approximately 24% of total innovational output during 1957-61 and nearly 49% in 1967-71.[36] This is a dramatic shift and illustrates a strong movement towards greater concentration of innovational output in the U. S. A. amongst the very largest ethical pharmaceutical companies. Surprisingly, a countertrend seems to apply in the U. K. The explanation is to be found in the performance of American companies in Britain and this will be made clear below.

Influence on Other Economies

Regulatory tightness has had an influence on the performance of American companies abroad. In 1962, firms in the U. K. accounted for 47% of ethical drug sales. By 1971, this market share had declined to 38%. New product innovation shows a much more dramatic decline. In the 1962-66 period, American firms in Britain accounted for 48% of new product innovations, but only 15% in the 1967-71 period.[37] It is highly plausible to argue that the flow of new products available for introduction into the U. K. was affected by the tightening of the regulatory climate in America, post 1962. As the number of discoveries in the U. S. A. declined, the stock of new products available for introduction into Britain suffered. A decline in innovation performance at home induced a lagged response or "echo effect" abroad.

Export of Resources

One escape route for American companies to by-pass their home regulatory climate is to shift R and D effort into economies with more understanding pharmaceutical vetting procedures. There is some evidence that this has occurred. In 1961, foreign research of U. S. drug companies was approximately 5.3% of their total domestic R and D. By 1973, this had risen to 16.9%[38] American drug companies have increased their investment in manufacturing capacity abroad, and are also performing more development and clinical trials overseas. It is reasonable to assume that the trend to foreign investment has been encouraged by regulatory tightness, but the shift appears to have

[36] See footnote 23.
[37] See footnote 23.
[38] See footnote 23.

been fairly modest. If American companies had been wholehearted in their diversion of resources, it would seem reasonable to assume that the U. K. would have been a natural expansion base. The "echo effect" referred to earlier suggests, however, that the expansion of overseas facilities has been tentative. The unexpected decline in concentration in the U. K. was explained by the reduced performance of American companies in Britain. If the export of resources had been more vigorous, there may well have been an improvement and not a deterioration. Reasons for the tentative nature of the shift are to be found in the size of the American market, and the long term nature of this type of decision. The American market for pharmaceuticals is the largest in the world. Investment in new drugs may persist in spite of regulatory tightness because of the commercial attractiveness associated with success, even if it may be long delayed. In addition, the pull of overseas investment in research and development is modified by the FDA's attitude towards foreign clinical evidence. As already explained, it is only recently that such data has been permitted as "supportive" by the Administration. Furthermore, a shift in R and D resources is likely to take the form of a marginal change. In other words, overseas locations for research are likely to receive relatively more emphasis. It is most unlikely that existing research laboratories will be moved. This would be desperately bad for morale and very disruptive of work in progress. The long-term nature of the decision emphasizes a need to be very confident of the forces indicating that a change is necessary. R and D is basically an investment process in human capital. Changes in the location emphasis of such expenditure have to be achieved gradually and with considerable tact.

There is some very tentative evidence gathered by the present author, that British-owned companies are also beginning to respond to the less favourable climate now evident in Britain. As already indicated, since the implementation of the Medicines Act, the speed of response of the regulatory authority would appear to have deteriorated. It is not uncommon for approval in the form of a letter of intent for a CTC relating to an NCE to take over six months, and delays of over a year have occurred.[39] A delay of this length, at this particular stage in a drug's development is most disruptive. Continuity of effort suffers, and also the morale of the research personnel. In response to the deterioration in approval time, more clinical trials are now being conducted abroad. When questioned

[39] A three year review of submissions to the Committee on Safety of Medicines, July 1970—Sept. 1973, ABPI, 1974.

on this late in 1975 by the present author, senior executives in all the major British-owned pharmaceutical companies agreed that they now find themselves obliged to undertake trials abroad to avoid the CTC approval lag. The Scandinavian countries were the most frequently cited locations. The logic of this procedure is as follows. In Britain, foreign clinical data may be used as a substitute. The emphasis of the CSM is on the quality of the work done, not on its location.[40] Thus, there is no need to replicate work that has been done abroad, provided that it complies with the quality requirements. This "international" attitude has proved important in a most practical way. British pharmaceutical companies have been able to mitigate the delay in acquiring a CTC. Clinical trials can be conducted in other countries where approval is not required, or is more prompt. The data generated is then used to support applications to the CSM for a product license. If this procedure had been disallowed it is reasonable to assert that there would have been a much more marked shift by British companies of resources from the U. K. The wisdom of allowing quality and not nationality to be the criterion has probably damped what would otherwise have been a much stronger reaction to regultory delay. The ability of the CSM to take an "international" view has, thus, been a modifying influence, in a situation of deteriorating regulatory performance.

Object Lessons

By world standards, innovation in the American pharmaceutical industry would appear to have been overregulated. This is the blunt message to be inferred from the evidence of the "drug lag." The reasons explaining the poor regulatory performance are complex but would seem to be associated with:

(1) the demanding requirements imposed by legislation;

(2) the caution bias induced by the way in which decision-taking is structured;

(3) the degree to which the activities of the FDA are subject to political pressures.

By influencing the type and character of innovations permitted on to the market, regulatory authorities are the arbiters on society's behalf

[40] For a review of regulatory requirements see: *The International Regulation of Pharmaceutical Drugs*, A Report to the National Science Foundation on the Application of International Regulatory Techniques to Scientific/Technical Problems. Research carried out under N. S. F. Grant G1 41472. Principal investigator Kay, David A., March 1, 1975.

of the risk/benefit tradeoff of pharmaceutical innovation. The signs are, at least in America, that the line has been drawn too far back in favour of caution and safety. Changes and reforms are required that shift the emphasis away from an overconcern with drug hazard and towards the relief of suffering and disease. A decision-making climate is required so that medical judgment achieves greater influence. Somehow resolve must be stiffened away from temerity and towards innovation. The area in which reforms are most pressing would seem to be:

(1) in removing the FDA from political pressures;

(2) in upgrading the quality of FDA scientists;

(3) in the full acceptance of foreign clinical data, provided it is of a qualifying standard;

(4) in placing a greater emphasis on the market as the final arbiter. (Monitored release, post-marketing surveillance and adverse drug reaction procedures would appear the best instruments here.)

Monitored release is essentially a risk-reducing sampling device. Conditions of use and distribution are tightly defined and the numbers of prescribers limited. A new pharmaceutical can, thus, be approved under conditions nearer to those of general usage, but with reasonably tight scrutiny maintained. In this way, gradual release can be arranged as experience and confidence grow. The character of the licensing decision can, thus, be changed. There is less simulation of final market conditions. An additional tranche of evidence becomes available to substantiate the impression gained from clinical trials. Permission to market a drug, thus, becomes less of an act of faith. If post-marketing surveillance and adverse reaction reporting procedures are also well developed, the feedback mechanism should be sensitive enough to give early warning of unforeseen indications. The purpose behind gradual release and improved market feedback is to institute a tradeoff. In exchange for more information on drugs' behaviour in final use, the regulatory authorities should become less timorous. Delays in appraising and approving should be reduced. It is not intended that monitored release should merely be added to existing procedures and become yet another source of delay. The conditional acceptance implied by monitored release is specifically intended to speed the approval process. With this very important proviso, gradual release and improved market feedback should offer the final user a stronger voice in the risk/benefit

calculations, and this should lighten the decision-taking burden of the regulatory agency.[41]

Caveat

The reforms suggested above are all intended to allow a change in the regulatory approach. They are specifically tailored to foster a movement towards a relative attitude to risk. The intention is to shift emphasis on to the positive aspects of pharmaceutical innovation. Less political pressure, higher quality scientific personnel, a more international attitude towards foreign data and improved market feedback are all changes that are intended to alter the balance of the regulatory approach towards the relief of suffering and disease and away from drug hazard. But such a movement away from a consumer protectionist viewpoint and towards the innovation orientated relative approach will be extremely difficult to achieve. Opponents of such a change can cite actual examples of harmful drugs that have been prevented from reaching the market in America by the FDA. Proponents have to use much less persuasive opportunity cost arguments. Reference to lost benefits and the relative decline in the availability of drugs in America, is nebulous and carries little emotional impact. Even if the necessary legislative changes are achieved, translating the enactment into reality will require time and a strong will for change. Confidence, trust and scientific excellence require careful nurturing. Furthermore, specific items on the list of reforms may actually worsen regulatory performance. Thus, the introduction of monitored release may lengthen the appraisal period and become yet another hurdle for new drugs to cross. No speedup may occur and the pharmaceuticals concerned may never be freed from conditional release status. In effect, therefore, regulation may reach even further into the market and involve greater delay. It is clear, therefore, that change will not be easily achieved, and that reform may carry its own risks. **[The End]**

[41] For a detailed discussion see Wardell, William M., Monitored Release and Post Marketing Surveillance: Foreign & Proposed U. S. Systems in Mitchell & Link (editors). Also for a review of pending legislation see *New Drugs:* pending legislation.

Food Additive Safety Evaluation

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Overview

IT IS IMPORTANT, at the outset, to understand the statutory provisions of the Federal Food, Drug, and Cosmetic Act under which the Food and Drug Administration (FDA) regulates the various components of our food supply. For purposes of regulation under the statute, there are basically two types of food: (1) unprocessed agricultural products and (2) processed food.

An unprocessed agricultural product—such as raw milk, fruits and vegetables which are washed but otherwise not processed—is subject only to the safety provisions in Section 402(a)(1) of the Act, under which it may lawfully be marketed unless it contains a "poisonous or deleterious substance which may render it injurious to health." If such a substance is not an added substance, the food is not considered adulterated if the quantity of the substance does not "ordinarily" render it injurious to health. As long as raw agricultural produce remains unprocessed, it is not subject to any of the statutory provisions relating to food additives. Thus, unprocessed agricultural products are required to meet a relatively low statutory standard for safety.

In contrast, once any agricultural produce is processed in any way or is incorporated in any processed food—for example, when raw milk is pasteurized or homogenized or dried or made into butter, or when apples are made into applesauce, or when any fruit or vegetable is canned—far more complex and stringent statutory provisions apply. The status of each component of the resulting processed food must then be analyzed to determine compliance with Sections 402 (adulterated food), 406 (tolerances for poisonous ingredients in food), and 409 (food additives) of the Act. Of major importance, each com-

ponent of the food must be analyzed to determine compliance with the food additive requirements. The agricultural produce component of the processed food is subject to analysis under the food additive requirements to the same extent as any chemically synthesized component.

In order to be included lawfully in any processed food, every component must meet the statutory requirement of: (1) being generally recognized as safe (GRAS), or (2) being subject to a sanction or approval for use in food granted by the FDA or the United States Department of Agriculture (USDA) prior to September 6, 1958, or (3) being subject to a food additive regulation promulgated by the FDA, or (4) if used for color purposes, being approved by the FDA for provisional or permanent use by a color additive regulation. This statutory requirement does not distinguish between natural and synthetic components. And since most of the food that we eat today (except fresh meat, fruit, and vegetables) is processed in one way or another, it means that virtually all components of our food supply, whether produced by nature or synthetically, are subject to the same legal standards for safety.

The present legal requirements are undoubtedly not well understood. Many people believe that components of our food supply that are derived from agricultural produce are in some way exempt from compliance with the food additive requirements of the law. This simply is not true. Although an apple is not subject to the food additive requirements when sold as fresh fruit, it is fully subject to analysis under the food additive provisions of the law the minute that it is processed in any way; for example, when it is made into applesauce.

In discussing food safety, it is important that the term "food additive" be used properly, in the way that it has been defined by Congress in Section 201(s) of the Federal Food, Drug, and Cosmetic Act. A "food additive" is any food ingredient—including, as we have already noted, any food ingredient derived solely from natural origin as part of agricultural produce—which is not either GRAS or subject to a prior sanction. A food additive may be either natural or synthetic in origin, just as other food ingredients which are not food additives may be either natural or synthetic in origin. The term simply encompasses all those components of the food supply which have not achieved the status of general recognition of safety or were not approved by the FDA or the USDA for food use prior to 1958. Many synthetic chemicals used as food ingredients are, of course, not food

additives; and a number of natural components of our food supply are regulated as food additives.

Indeed, it is a paradox that we have less knowledge about the safety of food components that are not food additives than we do about the safety of food additives, because the statute requires specific testing of food additives before they may be approved for use in food whereas specific testing of other food components is not required. Every food is composed of hundreds of individual chemical substances. The composition of each complex chemical mixture which we call a "food" is imprecisely known, and the toxicological manifestations of these individual chemicals, let alone the combination, are simply not available for most food components. The common conception that food components which are not food additives are somehow "better" or "safer" than food additives is, therefore, demonstrably false.

The popular belief that chemically synthesized food ingredients are inherently less safe than those of agricultural origin is equally false. The list of natural poisons is impressively long, and many synthesized chemicals have been proved to be entirely safe for food use.

Modern chemistry has permitted the food industry to produce by synthesis many chemicals that are also produced in nature. Perhaps the best examples are the vitamins that are so commonly consumed today. Virtually all vitamins added to food or consumed as pills are chemically synthesized, but are equally effective and no less safe than their natural counterparts. It is likely that well over 99 percent of all chemically synthesized food components are identical to chemicals that are also found in food of agricultural origin. Man adds only a relatively few substances directly to food which are not also found in nature.

The "GRAS" List

Particular emphasis has been placed, in recent years, on the so-called "GRAS" list published in the *Code of Federal Regulations* by the FDA in 1959 and 1960. This is an extremely limited list of GRAS food components, as the FDA has itself acknowledged. Section 121.-101(a) of the FDA regulations states:

> "It is impracticable to list all substances that are generally recognized as safe for their intended use. However, by way of illustration, the Commissioner regards such common food ingredients as salt, pepper, sugar, vinegar, baking powder, and monosodium glutamate as safe for their intended use."

The regulation then goes on to state that the GRAS list includes some, but obviously not all, GRAS ingredients.

In April 1958, in testimony before the House of Representatives during consideration of the legislation that later became the Food Additive Amendments of 1958, the then Commissioner of Food and Drugs included in a list of "chemical food additives" the following substances which the FDA would regard as GRAS for use in food:[1]

Brandy	Lemon Juice
Butter	Margarine
Coffee	Molasses
Corn Oil	Mustard
Cream	Olive Oil
Dry Skim Milk	Wine
Lard	

None of these illustrative GRAS food ingredients appears on the FDA GRAS list or in any other list of GRAS substances. Similarly, peas, carrots, potatoes, apples, beef, and other common food ingredients of agricultural origin that are also GRAS do not appear on the FDA GRAS list. It is impossible to determine exactly how long a GRAS list would be if it were to contain all of these GRAS food components.

Beginning in 1969, the FDA undertook to review the safety of the food ingredients on its published GRAS list. Since there are so many GRAS food ingredients, this decision reflected the practical conclusion that any review of GRAS substances must begin somewhere, and the published GRAS list was as good a place to begin as anywhere else. As part of its review, the FDA contracted with the National Academy of Sciences to survey the industry for use levels of the substances on the published GRAS list.

Continuing Support for the Orderly Review of Food Ingredients

Grocery Manufacturers of America, Inc. (GMA) and other major food-based trade associations have given vigorous support to the review of the safety of food ingredients on the published FDA GRAS list. In May 1971, twenty-one trade associations joined together to promote and sponsor a briefing session at which the Na-

[1] Larrick, George P., Commissioner of Food and Drugs, Hearings on Food Additives before the Subcommittee on Health and Science of the House Committee on Interstate and Foreign Commerce. 85th Congress, April 15, 1958. p. 461.

tional Academy of Sciences launched a user and producer survey of GRAS substances. Mr. William O. Beers, President of Kraftco Corporation, said at that time:[2]

"We need a comprehensive, orderly review of GRAS substances not only to assure the continued safety of food ingredients, but especially, to forestall conditions which could lead to a loss of public confidence in our food supply.

"Therefore, we all have something to gain by assisting in this review. We will not only benefit by an accurate, scientific assessment of the safety of food ingredients, but we will also reassure the public that both industry and government are working toward a common objective—that of continuing protection of the well being of the American consumer."

Industry remains fully supportive of an orderly, systematic review of the safety of food ingredients. In preparation for the survey currently being undertaken by the National Academy of Sciences on the use of food ingredients (Phase III of the GRAS list survey), GMA participated in a briefing program in December 1975. The text of this presentation was published[3] under the title "Incentives for Further Industry Cooperation and Participation." The first reason invoked for participation in the survey was "a deep sense of corporate responsibility." While there are other significant reasons for participation in the survey, the continued protection of the public is far and away the most imortant justification for this activity.

Number of Food Ingredients Used in Food Production

For many years, questions have been raised about the number of food ingredients that comprise the food supply. To the best of our knowledge, a single, comprehensive listing of all of the individual food ingredients does not exist. In the *Code of Federal Regulations*, the FDA lists the following numbers of GRAS food ingredients, food additives and color additives for direct use in food production:

GRAS Food Ingredients

251	nonflavor substances[4]
223	natural flavorings and spices[5]
26	synthetic flavorings[6]
500	total GRAS Food Ingredients

[2] Beers, William O., The Need for an Orderly Review of GRAS Substances. Unpublished remarks delivered at the Industry Briefing on the GRAS Questionnaire. May 21, 1971.

[3] Harkins, Robert W., 31 FOOD DRUG COSMETIC LAW JOURNAL, 132 (March, 1976).

[4] 21 *Code of Federal Regulations* 121.101(d); 121.104(g)(23); 121.104(g)(24).

[5] 21 *Code of Federal Regulations* 121.101(e); 121.104(g)(25).

[6] 21 *Code of Federal Regulations* 121.101(g).

Food Additives

187	nonflavor substances[7]
3	nonflavor substances (interim basis)[8]
190	total Nonflavor Additives
131	natural flavorings[9]
728	synthetic flavorings[10]
859	total Flavoring Additives

Color Additives

31	permanently approved color additives[11]
3	provisionally listed color additives[12]
3	provisionally listed color lakes[12]
37	total Color Additives

The *Code of Federal Regulations* also lists some, but not all, ingredients that are indirectly added to food, that is, those substances permitted in food packaging materials, food contact surfaces and other applications where they may become a component of food. The FDA has referred to an estimated 10,000 indirect additives,[13] but this appears to be largely speculative and the number could actually be much larger.

Thus, the number of substances which comprise the food supply is quite large—more than 1000 agricultural products, approximately 2000 food components and 10,000-plus indirect additives. It would be a formidable task indeed to subject each of these 13,000-plus substances to detailed toxicological testing and analysis at this time.

[7] 21 *Code of Federal Regulations* 121.1001-121.1162; 121.1165-121.1257; 121.1259-121.1267.

[8] 21 *Code of Federal Regulations* 121.4001; 121.4004; 121.4005.

[9] 21 *Code of Federal Regulations* 121.1163.

[10] 21 *Code of Federal Regulations* 121.1164.

[11] 21 *Code of Federal Regulations* Section 8, Subparts C and D.

[12] 21 *Code of Federal Regulations* 8.501 (a).

[13] Gardner, Sherwin, Statement delivered before the Senate Select Committee on Small Business, Jan. 13, 1977.

Level of Use of Food Ingredients in Food Production

According to figures from the USDA, the U. S. per capita consumption of food totaled 1297 pounds per year—or 3.6 pounds or 56.9 ounces per day—in 1973.[14] Recent data permit the following approximate breakdown of this daily food consumption:[15]

	Per Capita Use (ounces/day)	Percentage of Diet (%)
Major food components of natural or agricultural origin, including the following categories:	56.42	99.2
Apples, potatoes, meat, eggs, etc.	50.72	89.2
Sugar	4.47	7.9
Salt	0.66	1.1
Corn syrup and dextrose	0.57	1.0
32 common food ingredients[16]	0.40	0.7
All other functional ingredients of natural and synthetic origin added at low levels	0.04	0.1
Total	56.86	100.0

Although flavoring agents are the most numerous ingredients used in food production, such substances are used in very small quantities. Many are, of course, of natural agricultural origin, and others are chemically identical to natural flavors. Results from a 1971 survey conducted by the Flavor and Extract Manufacturers Association on over 1400 flavors indicated that 71 percent of these flavorings were used in food processing at levels less than 1000 pounds annually, or less than 2.7 pounds per day.[17] This national use level corresponds to 0.000000013 pounds or less per capita per day.

Increased Complexity of Toxicological Testing Requirements

Over the past several decades, the requirements for toxicological evaluation of food chemicals have become more complex and elabo-

[14] U. S. Department of Agriculture, *National Food Situation*, May 1976, p. 15.

[15] Hall, Richard L., Food Additives, Nutrition Today, 8: 20, 1973; Panel on Chemicals and Health, President's Science Advisory Committee. *Chemicals and Health*. National Science Foundation. Sept. 1973.

[16] These ingredients and their functions are listed in Appendix A.

[17] Ford, Richard A. (Consultant to the Flavor and Extract Manufacturers Association). Private communication, 1977.

rate. In 1940, it was not uncommon to call a study of 30 days' duration a chronic toxicity study. Total testing of safety of food chemicals and drugs was commonly conducted in a few rats, a few rabbits and a few mice, was considered an adequate toxicological data base at that time.[18]

By the late 1950's, safety testing of food chemicals had become more elaborate and more formalized. A 1958 World Health Organization (WHO) report[19] distinguished between three types of toxicity studies: acute, short-term and long-term (chronic). Acute toxicity studies included testing both sexes in three species of animals (one a nonrodent species). Numbers of animals required were relatively small and were based on the statistical precision desired in the estimated LD_{50} for the substance tested. Short-term toxicity studies required two species of animals (one a nonrodent), 10-20 animals of each sex at each dosage level in the test, and usually a 90-day observation period. Chronic toxicity testing was usually conducted in the rat, with 25 or more animals of each sex at each dosage level in the test. The total period of observation was usually 12 to 18 months.

In 1959, the staff of the FDA Division of Pharmacology published a major review of the then existing requirements for toxicological testing of chemicals.[20] This review incorporated the principles of the WHO report of the prior year and provided additional information on the techniques used in the interpretation of toxicologic findings in animals. It was a major milestone in toxicologic testing in the United States and served as a guideline for such testing for a number of years.

Throughout the 1960's and 1970's further elaboration of toxicologic testing has taken place. Chronic toxicity testing sometimes included both rodent and nonrodent species, and the period of observation in nonrodents frequently extended for half a decade or more. Further attention was directed toward appraisal of teratogenicity, mutagenicity, and embryotoxicity.[21] A National Academy of Sciences

[18] Coulston, Frederick, 21 FOOD DRUG COSMETIC LAW JOURNAL 336, (June, 1966).

[19] Joint FAO/WHO Expert Committee on Food Additives. Procedures for the Testing of Intentional Food Additives to Establish Their Safety for Use. Second Report. WHO Technical Report Series No. 144. 1958.

[20] Food and Drug Administration. *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics.* The Association of Food and Drug Officials of the United States. 1959.

[21] Joint FAO/WHO Expert Committee on Food Additives. Toxicological Evaluation of Certain Food Additives with a Review of General Principles and of Specifications, Seventeenth Report. WHO Technical Report Series No. 539. 1974.

report gives a good summary of the status of the general requirements for toxicologic testing of food chemicals as of 1970.[22] Because of the complexity of this type of testing, increasing emphasis is being placed on the development of rapid, *in vitro* screening tests, particularly in the testing for carcinogenesis.[23]

It is clear that the past 35 years have seen a major change in the accepted requirements for toxicologic testing of food ingredients, from relatively simple testing to a very complex battery of testing procedures. These current procedures are designed to elicit not only the conventional adverse reactions that can occur to a chemical or drug but also the more subtle and complex expressions of toxicity that may only be observed over the entire life span of the animal, for example, in carcinogenicity testing or in the multigeneration reproduction studies. We anticipate that the next 35 years will produce similar improvements in toxicity testing. Toxicology is, of course, a very dynamic field, and we doubt that new types of testing will ever cease to be discovered.

The battery of testing procedures currently utilized in the testing of food ingredients requires both a considerable period of time (minimum of three years) and substantial funding (approximately $500,000) to complete. It is for these reasons that rapid and less costly *in vitro* screening procedures are receiving so much attention at the present time, not just in an effort to reduce the time and cost of testing, but also to utilize the available testing facilities of the country most effectively. The screening tests, however, are *not* now capable of replacing *in vivo* studies in animals. Their use in regulatory decision making should be as a supplement to, not replacement for, conventional studies.

National Constraints on Safety Evaluation

There are several limitations on our country's capability to undertake safety studies on all food ingredients. The major limitations are:

[22] Food Protection Committee, Food and Nutrition Board, *Evaluating the Safety of Food Chemicals*, National Academy of Sciences, 1970.

[23] Chemical and Engineering News, 54: 18, 1976; Health and Welfare Canada, *The Testing of Chemicals for Carcinogenicity, Mutagenicity, and Teratogenicity*, Sept. 1973; Kirschman, John C., Safety Evaluation is a Risky Business, Unpublished remarks delivered at The Nutrition Foundation Food and Nutrition Liaison Committee meeting, Jan. 12, 1977; Kolata, Gina B., Chemical Carcinogens: Industry Adopts Controversial "Quick" Tests, Science, 192: 1215, 1976.

(1) limited number of qualified scientists, particularly pathologists;[24]

(2) limited number of qualified laboratories, both inside and outside government;

(3) competing priorities for testing other substances; and

(4) economic burden.

An examination of the limitations on cosmetic safety testing, which are analogous to those affecting food ingredient safety evaluations, is illustrative. Arthur D. Little, Inc., conducted a study[24] to evaluate the impact of legislation pending in 1974 that would have required safety testing of all cosmetics and ingredients used in cosmetics—a much smaller number of ingredients than are used in food. Based upon the estimated 1340 qualified pathologists practicing in the United States in 1974, Arthur D. Little, Inc. concluded that safety testing of the more than 25,000 cosmetic products and ingredients on the market would take at least 30 years at an estimated cost of $6.5 billion. This proposed legislation would have resulted in a staggering use of laboratory animals—a minimum of 60 million mice, 38 million rats, 6 million rabbits, and 0.5 million dogs. The report concluded that this proposed cosmetic safety testing

"would thus almost certainly have a serious adverse impact on other major research activities, such as the cancer and heart programs, new drug and food additive testing, etc., which compete for the same relatively limited number of qualified scientific personnel and facilities."

The severe limitations imposed by shortages of trained scientists and facilities, which can only be slowly corrected, are reasons why the impracticality of testing every food ingredient in every possible toxicological test protocol poses a major societal dilemma. Safety judgments can be based on experience with common food use and on known toxicity information without requiring repeated, periodic studies of good ingredients with the newest toxicological testing procedures.

Cost is also a significant factor. The FDA has estimated that the total cost of the GRAS list review program has been approximately $18 million to date.[25] For this expenditure, the FDA has been able to reach, in its judgment, the half-way point in the review of 439 non-flavor GRAS substances, a program initiated in 1969. One needs to

[24] Little, A. D., Inc., Report to the Legislative Planning Group of CTFA (Cosmetic, Toiletry, and Fragrance Association, Inc.), Feb. 15, 1974.

[25] See footnote 13.

compare the $18 million expenditure, the seven years and roughly 220 compounds reviewed with the total number of food ingredients already discussed above. If the FDA could complete the review process for the remaining compounds in half the time that it took for the review of the first half of the GRAS list, and at the same rate of economic cost, it would require more than our lifetime and hundreds of millions of dollars.

By and large, the work done to date by government and industry in reviewing the safety of existing food ingredients is based on a compilation of available data. The generation of new laboratory data —for example, chronic feeding studies in rats, dogs or other species— will add significantly to the costs of the review of the safety of food ingredients. Recently, the FDA outlined a comprehensive program to resolve the status of provisionally listed color additives.[26] Appropriate scientific investigations must be undertaken on about 30 color additives and data must be submitted to the FDA according to a prescribed schedule before final decisions will be made on the status of these colors. It is estimated that it will take four years and $3.2 million to conduct chronic toxicity feeding studies on just eight of these colors, each of which has already been evaluated in at least two species during earlier tests.

The "Food Lag"

According to the President's Science Advisory Committee report, there has been an overall decline in the number of new chemical entities introduced each year as intentional food additives.[27] The reason for this "food lag" is the increased regulatory requirements (that is, the Food Additive Amendments to the Federal Food, Drug, and Cosmetic Act) that must be met for approval of a new food ingredient.[28] Few companies are willing or able to spend upwards of $500.000 per compound to conduct, over a period of three to ten years, the required series of toxicological tests needed to support a food additive petition.[29] Unless a company receives a patent on a particular chemical, once the substance meets FDA approval any company is free to manufacture it. Furthermore, once a company makes such a financial investment on toxicological testing, there is

[26] *Federal Register*, 41 : 41860, 1976.

[27] Panel on Chemicals and Health, President's Science Advisory Committee. *Chemicals and Health*, National Science Foundation, Sept. 1973.

[28] Oser, Bernard. 21 Food Drug Cosmetic Law Journal, 616, (Nov. 1966).

[29] Muul, Illar et al., Science, 193 : 834, 1976.

still the possibility that the FDA will delay acceptance for months or years or reject the food additive petition.

At a time when the world is deeply concerned about its ability to feed an ever-growing population, we should be very concerned indeed about national policies that discourage innovation in food technology. This is the time when new methods of food production and processing should be advanced as a national priority.

Essentiality of Setting Priorities

When setting priorities for safety evaluation of food ingredients, two broad overlapping areas of concern must be recognized: (1) the total universe of chemicals in man's environment of which food ingredients are a small and relatively well-defined segment, and (2) the relative potential hazard of the individual food ingredients.

Foods, drugs, cosmetics, medical devices, toxic chemicals, pesticides, environmental contaminants and an enormous number of consumer products all pose a risk of hazard to man. Society must set a priority for food safety evaluation within this broad context, taking into consideration the available resources for toxicological evaluation —qualified scientists testing facilities and funds. Unfortunately, there is today no organized effort within government or society at large to rank these hazards in order to set priorities for toxicological testing and evaluation. In an effort to test first those materials which may pose the greatest risk to man, we need an overall assessment *before* national commitments are made for food ingredient safety testing.

Achieving a comprehensive, orderly review of the safety of food ingredients and reassuring the public that both industry and government are working together toward a common objective are mutual goals to which the Congress and the food industry need to strive. We appreciate this opportunity to submit comments to the Committee on the use, regulation, and safety evaluation of food ingredients.

APPENDIX A
Functions of 32 Commonly Used Food Ingredients

Flavoring Agent/Flavor Enhancer
- Monosodium glutamate
- Mustard
- Black pepper
- Hydrolyzed vegetable protein

Stabilizer/Thickener — imparts or maintains the desired texture, consistency and thickness in foods
- Sodium caseinate
- Acacia
- Modified starch

Leavening Agent—produces a gas that lightens dough or batter
- Yeasts
- Monocalcium phosphate
- Sodium aluminum phosphate
- Sodium acid phosphate

pH Control Agents—controls the acid-alkaline balance in foods
- *Sodium carbonate
- *Calcium carbonate
- *Dicalcium phosphate
- *Disodium phosphate
- Sodium bicarbonate
- Hydrogen chloride
- Citric acid
- Sulfuric acid
- Sodium citrate
- Sodium hydroxide
- Acetic acid
- Phosphoric acid
- Calcium oxide

Emulsifier—permits dispersion of tiny particles or globules of one liquid in another liquid
- Lecithin
- Mono- and diglycerides

Preservative—inhibits bacteriological spoilage of foods
- Sulfur dioxide

Firming Agent—produces desirable crispness or texture in foods
- Calcium chloride

Processing Aid—assists in filtering or removing unwanted color
- Calcium sulfate

Effervescent—causes bubbles when escaping from a liquid
- Carbon dioxide

Humectant—retains moisture in foods
- Sodium tripolyphosphate

Coloring Agent
- Caramel

[The End]

* Also acts as leaving agent

OTC PANEL ON TOPICAL ANTIBIOTIC PRODUCTS REPORTS FINDINGS

The Advisory Review Panel on OTC Antimicrobial Drug Products has advised the Food and Drug Administration that five antibiotics used in over-the-counter first-aid ointments are safe and effective for shielding minor cuts from bacteria and foreign substances. The panel noted, however, that there is no proof that these antibiotics cause infected wounds to heal faster by killing bacteria, and that further study would be needed to prove the usefulness of first-aid ointments for this purpose. The FDA has issued a proposed monograph for OTC topical antibiotics based on the panel's recommendations.

Safe and Effective Antibiotics

The five antibiotics judged safe and effective in protecting skin wounds were bacitracin, polymixin B sulfate (when combined with another antibiotic), and three varieties of tetracycline (chlortetracycline hydrochloride, oxytetracycline hydrochloride, and tetracycline hydrochloride). The panel found there was insufficient data to conclude that three other antibiotics—gramacidin, neomycin sulfate, and polymixin B sulfate used alone—are safe and effective in protecting skin wounds. Special attention was given neomycin sulfate because of a number of reported rashes resulting from its use. Further studies were suggested by the panel to determine the extent of skin rash before a final decision is made on its suitability for continued OTC use.

Labeling

The advisory panel recommended that the labels on all OTC first-aid ointments warn against use longer than one week, on eyes and for treating long-standing skin conditions. It also recommended that the label advise the user to seek a physician's care in the case of deep or puncture wounds or serious burns, or if itching, redness, swelling, or pain develop or increase during use.

Comments

Comments on the panel's recommendations and the FDA's proposal must be received by the FDA no later than June 30. Submissions will be available at the FDA's Hearing Clerk's Office, and additional comments replying to those on file may be submitted until August 1, 1977. After evaluating the comments, the agency will issue a monograph of safe and effective ingredients and acceptable labeling claims for all OTC first-aid ointments.

Antibiotic FDA Proposal, ¶ 45,451

PROPOSAL DEFINES ROLE OF INACTIVE INGREDIENTS IN OTC DRUGS

Each inactive ingredient in an over-the-counter drug would have to perform a specific function, in addition to meeting existing safety standards, under a recent proposal by the Food and Drug Administration. The intent of the requirement is to prevent an active ingredient found to be not generally recognized as safe and effective or to be in need of more testing from being retained and redesignated as an inactive ingredient if it does not perform an acceptable function as such. Although inactive ingredients need not appear on the labeling, the proposal requires that if one such ingredient is declared, then all must be declared. Two exceptions exempt the declaration of colors, fragrances, flavors, and identifiers from disclosure of their components and limit the disclosure rule to voluntary declaration of inactive ingredients.

Conditions an inactive ingredient would have to fulfill to meet the FDA's requirement for safety and suitability include being listed in an official compendium as a pharmaceutical aid, being used at no higher level than reasonably required for its purpose, and not interfering with the effectiveness of the product or with tests that determine whether the product meets its professed standards. The proposal lists acceptable categories for use of inactive ingredients, such as air displacement agents, emulsifiers, and stiffening agents and defines incidental ingredients to which the requirements would not apply.

Comments on the proposal will be accepted until June 13, 1977.

FDA COMPLETES RECODIFICATION PROGRAM

Recodified and reorganized regulations relating to enforcement, administrative practices and procedures, delegations of authority, and color additives have been issued by the Food and Drug Administration. The reissuance of the general regulations marks the end of the FDA's program, begun several years ago, of recodifying and republishing its regulations to make them easier to find and understand.

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