EMERGING ISSUES IN FOOD SAFETY AND QUALITY
FOR THE NEXT DECADE

February, 1991

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, DC 20204

under
FDA Contract No. 223–88–2124
Task Order No. 3

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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) in accordance with the provisions of Task Order No. 3 of the FDA Contract No. 223–88–2124. It was edited by Elwood O. Titus, Ph.D., Senior Scientific Consultant, and John M. Talbot, M.D., Senior Medical Consultant, based on discussions of and materials evaluated by a group of consultants convened by LSRO. The individuals selected as consultants were chosen for their qualifications, experience, and judgment, with due consideration for balance and breadth in appropriate professional disciplines. The consultants and others who assisted in the preparation of this report are listed in Chapter IX.

This study was initiated in September 1988 and was to be completed in June 1989. For reasons beyond the control of FASEB and the FDA, the study was interrupted for a period of 15 months in 1989–1990. The consultant group met in early 1989 and again in October 1990 to obtain background information, identify pertinent issues, evaluate the relative importance of emerging issues, and develop drafts of the report. The consultants reviewed each draft and the final report and provided additional documentation and viewpoints for incorporation into the final report. However, the LSRO accepts responsibility for the study conclusions and accuracy of the report; and the listing of these individuals in Chapter IX does not imply that individual consultants specifically endorse all statements in the report.

The final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the FASEB Board. Upon completion of these review procedures, the report was approved and transmitted to the FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent societies.

February 28, 1991
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
EXECUTIVE SUMMARY

The important food safety and quality issues likely to emerge in the 1990s will stem in part from the increasing complexity of the marketplace as demographic changes and consumer preferences take effect. The most important issues are expected to arise from: (1) the impact of scientific and technological advances, (2) imports and the increasingly international character of food production and marketing, and (3) the requirement to implement a diversity of important functions in the face of inadequate resources.

New aspects of the perennial problem of microbiological safety of foods continually emerge. In recent years modern methods have made possible the recognition of several bacteria as foodborne vectors for gastrointestinal and other disorders. Current challenges to the FDA are to clarify the mechanisms governing the virulence of these "emerging pathogens" and to explain why certain populations are particularly vulnerable to foodborne illness.

The scientific advances that promise the greatest impact on the FDA are the modern techniques for genetic manipulation. In addition to the genetic engineering of food ingredients, foods, and food sources, these have provided DNA probes for pathogen detection and methodology for the genetic analysis of the mechanisms that govern microbial virulence. Greater application of these techniques will enhance the FDA's ability to deal with the ever growing problems of microbial safety. New variants of the polymerase chain reaction may be expected to extend these capabilities.

The anticipated impact of genetically altered microorganisms and plants on the food supply will challenge the capabilities and resources of the FDA in its efforts to ensure the safety of foods produced by the new techniques without compromising the opportunity for development of new technologies. Extension of existing regulations appears to be the most appropriate approach to ensuring the safety of these products. However, the variety of new products and processes and public concerns about biotechnology will require flexibility in review procedures. As new plasmids and innovative genetic engineering techniques are applied to food production, the FDA may need to scrutinize the production process as well as the composition of the product. In each case the Agency must define those scientific questions that need to be answered if these procedures are to provide reasonable certainty of no harm.

Other emerging areas of concern will be the proliferation of new packaging techniques, advances in food processing and the preparation of low-calorie or high-fiber macronutrient substitutes by alteration of the physical and chemical properties of natural substances. Opportunities for microbial growth in controlled-atmosphere and low-oxygen packaging and the possible migration of components from new microwave heat susceptors are of concern. The use of non-nutritive substitutes for major dietary ingredients is emerging as an issue. These will require long-term evaluation before the ultimate nutritional consequences of their use and need for appropriate regulatory measures become evident.

The internationalization of the food industry will require increasingly sophisticated sampling and data handling strategies as well as increased resources for surveillance as the volume of imports increases and packaged prepared products supplant bulk foods. Maintenance of a scientific staff with sophisticated capabilities in epidemiology and methodology for pathogen detection will be important as importation of food products grows. International cooperation and harmonization of world food regulations are essential in today's environment, but demand resources that are not yet available. Support for and resources necessary to the FDA as a key agency in these activities are required.
Currently, and increasingly in the next decade, prioritization of resource-limited functions is a concern of the CFSAN. Demands on the Agency include research, regulation of food labeling, provision of consumer information, and maintenance of surveillance and testing regimens. The role of hazard-analysis and critical control point (HACCP) procedures in an increasingly complex food industry will be a concern of the 1990s. For the near future implementation of the new Nutrition Labeling and Education Act will be among the most demanding of the Agency's responsibilities.

The FDA interacts in a variety of ways with other federal, state, and local regulatory Agencies as well as with industrial and consumer organizations. State inspection and enforcement activities are an important adjunct to the FDA's role in maintaining food safety. The Agency must have the resources and authority to assume leadership in these relationships if uniformity and coherence in food regulations are to be achieved.

Emerging trends in risk assessment include more sophisticated methods of hazard identification, shift of emphasis from chemical toxicants to naturally occurring dietary components and changing aspects of the relation between science and law. Further application of risk assessment as an approach will draw more widely on many facets of the FDA activity and will represent an increasingly important mechanism for monitoring food safety. Despite current suboptimal conditions, the FDA has achieved remarkable success in keeping the American food supply healthy and safe. However, greater resources and sustained commitment by the government, public, and private sectors will be required in the future.
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I. INTRODUCTION

The legislative mandate of the Food and Drug Administration (FDA) includes a responsibility to assure a safe and wholesome food supply. In order to plan future programs of food safety inspection, surveillance, analysis, research, and food regulation, the FDA must be aware of new issues that will affect food safety and quality and their probable impact on policies, programs, and regulations during the 1990s.

In keeping with these responsibilities the FDA requested the assistance of the Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) in identifying those areas from which some of the more important issues might be expected to emerge. The contract Scope of Work directed the LSRO to consult scientists with broad-based expertise in the life sciences, food science, and risk assessment and to take into account their comments and information in preparing a report for submission to the FDA.

The FDA requested that LSRO assemble pertinent information relating to emerging food safety issues, provide descriptions of the issues, and evaluate current knowledge and opinion on what the FDA will need to address the issues. Some areas were identified by the FDA as possibly appropriate for consideration. The list is not exhaustive and was not intended to exclude other subjects of potential interest.

- Future Public Health Issues (e.g., novel foods produced by biotechnology, medical foods, new food processes, and packaging).
- Policies and Programs for Microbial Safety of Foods (e.g., the implications of increasing ease and sensitivity of pathogen detection).
- Policies and Programs for Monitoring the Food Supply (e.g., proper balance of surveillance and inspectional activities).
- The Agency's Role in Educating the Public about Food Quality and Safety (e.g., issues related to food labeling, nutrition labeling, and dietary advice to high-risk groups).
- The Use of Appropriate Regulatory Tools (e.g., the application of food standards and food labeling to include warning labeling).

In addition to the above issues, the Scope of Work invited suggestions for measures that would help the FDA prepare for future challenges involving food safety and quality. These suggestions included possible in-house changes in procedures, staffing, or information exchange as well as possible roles for the private sector, consumer groups, the Congress and the Executive Branch in meeting future challenges. Measures to improve communication with or enhance the role of these institutions were also invited.
II. BACKGROUND

A. SOURCES OF FUTURE PUBLIC POLICY ISSUES AND CHALLENGES TO THE FDA

Demographic changes and societal pressures in the 1990s will influence various facets of food production, processing, distribution, and consumption. The anticipated diminution in household size and the increase in the number of single-parent families and working women (Siegel and Davidson, 1984; U.S. Bureau of the Census, 1983, 1987) will increase the demand for convenience foods, microwaveable products and longer shelf-life packaging. The increase in the mean age of the population and in the institutionalized elderly will affect the needs for specialized packaging and processing techniques. Ancillary factors will arise such as the need for greater education and training in microbiological safety as increased populations of food handlers intervene between production and consumption.

The marketplace will also respond to the demand for ethnic foods as the proportions of minorities in the population increase (Farley, 1988a). Consumer preferences, a significant factor in market volatility, will continue to reflect changes in life style and demographic trends but will be strongly influenced by other factors. Not the least of these will be a highly competitive food industry eager to exploit innovative marketing opportunities. During the current decade increased public perception of the diet-health relationships inferred in numerous recent epidemiological surveys can be expected to affect public acceptance of advertising and to increase the demand for specialized foods (U.S. Department of Health and Human Services, 1988; National Research Council, 1989).

In addition to this background of societal factors there are other major forces that affect the emergence of issues likely to concern the FDA. In this report, these have been differentiated into three general areas.

- The impact of recent scientific and technological advances. Modern biotechnology, for example, promises to provide a variety of new products from genetically altered organisms as well as sensitive DNA probes for the diagnosis of food contaminants. Modern materials science will find numerous applications in innovative packaging.

- The "globalization" of the marketplace as the quantity of imports grows larger and food production is increasingly in the international sector.

- Severely constrained resources will require continual attention in addressing issues of accommodating multiple demands for surveillance, research, and education. Central concerns in setting priorities will be the need for a proactive stance in anticipating problems and the assumption of leadership in regulatory affairs.

B. ROLE OF THE FOOD AND DRUG ADMINISTRATION

The legal framework within which the above issues can be addressed is noted in "Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration" (Food and Drug Administration, 1985):

The mission of the Food and Drug Administration is to enforce laws enacted by the U.S. Congress and regulations promulgated by the Agency to protect the consumer's health, safety, and pocketbook.
These laws include:


(2) Sections of the Public Health Service Act relating to biological products for human use (42 U.S.C. 262–263) and control of communicable diseases (42 U.S.C. 264).

(3) The Radiation Control for Health and Safety Act, relating to electronic products which emit radiation, such as x-rays, lasers, microwave ovens, and TV sets (42 U.S.C. 263b–263n).

The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the United States. With numerous amendments, it is the most extensive law of its kind in the world. Many of the states in the United States have laws similar to the Federal law, and some have provisions to add automatically any new federal requirements.

The law is intended to assure the consumer that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; ... and that all labeling and packaging is truthful, informative, and not deceptive. Another law, the Fair Packaging and Labeling Act, affects the contents and placement of information required on the package.

Measures to deal with emerging issues must be considered with due regard for these laws. They clearly define the FDA's role in regulating food safety with respect to monitoring and surveillance, standards for food identity, the regulation of labeling and food additives, and the prevention of adulteration. Nevertheless, some important aspects of food safety are under the jurisdiction of other agencies (Hutt, 1984). For example, the Food Safety and Inspection Service of the Department of Agriculture covers inspection of the wholesomeness of meat and poultry; the Environmental Protection Agency sets pesticide tolerances; the Federal Trade Commission has a role in establishing standards for food advertising; and other agencies such as the Centers for Disease Control and the National Marine Fisheries Service have legally defined roles related to food safety. Certain of these agencies also have responsibilities to promote technology or industrial interests. Under the circumstances it is not surprising that jurisdictional complications can occasionally lead to disagreements on policy.

Critics of the federal food safety regulatory process, including a number of consumer groups, have complained of the lack of an integrated food safety and quality policy and inadequate enforcement of existing laws (Leonard and Turner, 1988). These critics have called for reform in food safety laws and establishment of a unified, effective federal agency to manage national nutrition issues including food safety and quality. If the current allotment of jurisdictions continues (Public Health Service, 1990a), many issues in food safety will require memoranda of understanding, joint committees, and a variety of ad hoc mechanisms to facilitate interagency collaboration.

In the early 1980s, intensive efforts were made to persuade Congress to reform the food safety laws (Roberts, 1983; Smith, 1987). The proposed changes included: (1) creation of a new regulatory category, comprising basic and traditional foods, with its own set of safety standards; (2) redefinition of "safety" to include the absence of significant risk or harm under conditions of use; (3) authorization of the gradual phaseout of certain banned foods or food additives; (4) streamlined procedures for setting tolerance limits for required or unavoidable substances in food and for reviewing petitions; (5) the mandatory use of risk assessment and of outside scientific peer review in certain circumstances; and (6) other provisions to modernize the law (Smith, 1987).
The bills introduced during the 97th and 99th Congresses died without legislative action, as did the Kennedy–Waxman bill (S. 722; HR. 1725) of 1989, which addressed the question of negligible risk. One major food bill, that mandated nutritional labeling was passed in 1990 (U.S. Congress, 1990a). However, consumer pressure for nutrition and food safety legislation has not abated in this period and is cited in recent press reports as a major reason for anticipating a renewal of Congressional interest (Sugarman, 1991).

Issues in need of legislative attention should emerge from the deliberations of the Advisory Committee on the Food and Drug Administration, established by the Department of Health and Human Services to examine the Agency's mission, responsibilities, and structure. In response to a request for public comment (Public Health Service, 1990b) a FASEB presentation to the Chairman of the Advisory Committee focused on: (1) the probable impact of rapid scientific and technical advances in drugs, vaccines, foods, and nutrition science on the FDA's ability to fulfill its future regulatory mission; (2) the inadequacies of the FDA's human and physical resources to meet its current and future responsibilities; (3) major impediments to an efficient, effective FDA; and (4) recommendations for improving the FDA's future capabilities (Edgington, 1990).

An interim report of the Advisory Committee (Public Health Service, 1990c) suggests that, although options for the FDA's placement within government will be addressed, the central question before the Committee will be how best to provide the Agency with sufficient authority and support so that it can function responsibly and promptly. Although some new legislation can be expected, the existing regulatory framework is fundamentally sound (Thompson et al., 1990) and has served the nation well with relatively few amendments. The remarkable flexibility made possible by appropriate interpretation of the food additive and adulteration amendments to the Food, Drug and Cosmetic Act has been noted by Thompson et al. (1990) and in comments on r-DNA regulation by Frank (1990). As in the past the inherent flexibility of the law should provide an effective framework for handling food safety issues emerging in the 1990s.
III. MICROBIOLOGICAL SAFETY, A RECURRENT ISSUE

A number of issues expected to confront the FDA are concerns of long standing. Microbiological safety is of primary importance. Recent cost estimates (including medical expenses and lost productivity) for all foodborne illness in the United States range from 7.7 to 23 billion dollars per year (Todd, 1990). Bacterial foodborne illnesses account for about 80 per cent of this total and salmonellosis is the major disease. Outbreaks due to bacteria currently far outnumber those caused by chemicals, parasites, or viral agents and are expected to do so in the future. Table 1 illustrates the distribution of bacterial pathogens responsible for outbreaks between 1983 and 1987 as tabulated by Zottola and Smith (1990) from data provided by the Centers for Disease Control (1990). Table 2 shows an estimate of percentages of total outbreaks for the same period ranked by causative organism. Despite some ominous possibilities, outbreaks of foodborne illness are rare and American consumers enjoy the safest and most wholesome food supply in the world (Archer, 1988).

Microbiological safety will continue to be a factor in most decisions related to food regulation. New aspects of the problem are continually appearing, especially the emergence of new pathogens as microorganisms adapt to changes in food production and processing and new populations of microorganisms are favored by these changes (Archer, 1988). Within the last decade, *Listeria monocytogenes*, *Campylobacter jejuni*, *Vibrio spp.* and *Escherichia coli* 0157:H7 have become recognized as foodborne pathogens (Zottola and Smith, 1990). Seasonal and geographic factors in pathogen distribution are increasingly recognized (Doyle, 1990).

The list of diseases linked to food vectors has grown longer in recent years as procedures for the identification of the causative agents have improved and some foodborne microorganisms now appear to cause disease in organ systems other than the gastrointestinal tract (e.g., reactive arthritis and peri- and myocarditis). In recent years outbreaks of microbial contamination such as the dramatic *Listeria monocytogenes* infection of 1985 (Donnelly, 1990) have exacerbated concerns about microbial safety. Consequently, a need for more research, including the development of increasingly sophisticated diagnostic methodology has been expressed (Young, 1988a). Much of the recent research on foodborne illness has been summarized in a series of reviews (Doyle, 1990; Jones, 1990; Lund, 1990; Skirrow, 1990; Tranter, 1990) that offer, among other items, useful surveys of the epidemiology, the immunological and biological properties, and the mechanisms of virulence of the major pathogens.

Measures to maintain a microbiologically safe food supply deserve the FDA's attention in the 1990s. Improper food handling is the most frequent cause in outbreaks of contamination (Archer, 1988), especially in food service establishments where food must be prepared well in advance of serving (Lund, 1990; Tranter, 1990). A survey of outbreaks in 1980–1985 revealed that three preventable practices, improper cooling, time lapse before serving, and infected personnel were responsible for 87% of the outbreaks (Zottola and Smith, 1990). Programs for consumer and worker education will need to be expanded. Sanitization to prevent environmental contamination of food processing areas remains especially important in *Listeria* control (Donnelly, 1990; Todd, 1990). Scientific questions still must be answered as to why certain immunocompromised or otherwise vulnerable individuals are at risk from particular organisms and what biochemical mechanisms govern the development of virulence in certain strains. For example, the virulence factors of *L. monocytogenes* (Jones, 1990) and the plasmids governing the virulence factors of *Yersinia enterocolitica* (Doyle, 1990), need to be further characterized in order to develop laboratory markers for the differentiation of virulent from non-virulent strains.
### Table 1. Foodborne Disease Outbreaks Caused by Pathogenic Bacteria, 1983–19871,2,3.

<table>
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<tbody>
<tr>
<td>Salmonella</td>
<td>72</td>
<td>78</td>
<td>79</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>13</td>
<td>11</td>
<td>17</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>14</td>
<td>11</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Shigella</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>8</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bacillus Cereus</td>
<td>-</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Streptococcus Group A</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus, other</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Excerpted from Centers for Disease Control, 1990
2 Reprinted with permission of Food and Nutrition Press, Inc.
3 Listeria not reported as foodborne during this period.

### Table 2. Total Reported Confirmed Foodborne Disease Outbreaks (%) Caused by Pathogenic Bacteria, 1983–19871,2,3.

<table>
<thead>
<tr>
<th>PATHOGENIC BACTERIA</th>
<th>NO. OUTBREAKS</th>
<th>% TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>342</td>
<td>57.0</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>74</td>
<td>12.3</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>47</td>
<td>7.8</td>
</tr>
<tr>
<td>Shigella</td>
<td>44</td>
<td>7.3</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>28</td>
<td>4.7</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>24</td>
<td>4.0</td>
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<tr>
<td>Bacillus cereus</td>
<td>16</td>
<td>2.7</td>
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<tr>
<td>Escherichia coli</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>Streptococcus Group A</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptococcus, other</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1 Excerpted from Centers for Disease Control, 1990
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3 Listeria not reported as foodborne during this period.
Summary: New aspects of the perennial problem of microbiological safety of foods continually emerge. In recent years modern methods have made possible the recognition of several bacteria as foodborne vectors for gastrointestinal and other disorders. Current challenges to the FDA are to clarify the mechanisms governing the virulence of these "emerging pathogens" and to explain why certain populations are particularly vulnerable to foodborne illness.
IV. IMPACT OF SCIENTIFIC AND TECHNOLOGICAL ADVANCES

A. GENETIC ENGINEERING AND BIOTECHNOLOGY

1. DNA probes as diagnostic agents

Modern molecular biology has provided useful techniques with which to address the microbiological problems noted earlier. Labeled DNA probes can be used for specific identification of target micro-organisms by hybridization to the latter's DNA. Estimates of the potential use of these newly developed DNA probes (or gene probes) to increase the precision, speed, and convenience and decrease the cost of microbial safety testing of foods are highly optimistic (Young, 1988a). One hundred DNA probes have been identified by the FDA experts as technically feasible, and additional probes are being developed. According to Archer (1988), gene probes as used by the FDA can quantitatively differentiate microbes that possess virulence genes from those that are harmless but otherwise identical. The technique has been applied to Y. enterocolitica. The application of gene probe technology promises marked improvement in food safety monitoring.

Gene–probe technology can be made faster and more applicable to difficultly culturable viruses and bacteria by use of the polymerase chain reaction (PCR) (Saiki et al., 1985). In a short time small quantities of DNA can be amplified in vitro to levels sufficient for identification by blot techniques and interaction with probes. The technology is developing rapidly. PCR has been used to amplify genes for monoclonal antibodies, thus enhancing the immunoassay techniques already useful in pathogen identification (Wasserman, et al., 1987) and in the detection of chemical contaminants. PCR techniques have had wide forensic use and a recent review (Office of Technology Assessment, 1990) may offer some insights useful in regulatory applications. Other methods such as the ligase chain reaction, nucleic acid sequence–based amplification and Q beta replicase, which relies on RNA sequences rather than DNA, offer additional advantages in gene replication (Van Brunt, 1990).

Recent studies of virulence in Y. enterocolitica suggest that although invasion genes are involved, pathogenicity is complex and depends on other factors as well. DNA probes offer a means to gain insight into the mechanisms of microbiologic virulence and the pathogenesis of several diseases of unknown etiology (Archer, 1988).

2. New products and processes

Food biotechnology has been defined as the use of living organisms to make or modify foods and the use of genetic manipulations to improve microorganisms, plants, and animals. The benefits of these new techniques have been summarized by the former Commissioner of Food and Drugs (Young, 1988a). It is anticipated that new methods of biotechnology will provide foods that are more nutritious and abundant, less expensive than those from traditional sources, and perhaps inherently safer.

The first applications of the new techniques in the food industry have been gene transfer into microorganisms for production of enzymes useful in food processing. Chymosin prepared from E. coli by r-DNA techniques has been approved (Maryanski, 1990a) and a long list of useful enzymes potentially accessible by genetic manipulation has recently appeared (Whitaker, 1990). Because some of the useful enzymes of Lactococci are coded by plasmids that are easy to isolate, these organisms may be increasingly useful in biotechnology (Harlander, 1990).
The next wave of products will probably be food crops from transgenic plants (Maryanski, 1990a). A useful survey of gene transfer techniques used in plants has been offered by the Office of Technology Assessment (OTA) (1988). Tissue culture of plant protoplasts is useful in the introduction of new genes into plant tissue (Wasserman et al., 1987). Regeneration from protoplasts or protoplast fusion has the potential to transmit multigenic traits but is limited in applicability (International Food Biotechnology Council, 1990). Plant tissue culture for the biosynthesis of natural products such as flavors and colors is being investigated extensively.

Advances in the engineering of food plants by the transfer of foreign genes have already yielded varieties of crops that tolerate herbicides, resist viruses, and resist insect damage by producing natural insecticidal substances. Traits designed to improve food crops are being engineered into tomatoes, potatoes, and other food crops (Rogers, 1989). The number of plants susceptible to gene transfer by the currently best characterized vector, the Ti plasmid from Agrobacterium tumefaciens, is somewhat limited (International Food Biotechnology Council, 1990), but means to introduce DNA into a wider range of species are being developed (Office of Technology Assessment, 1988).

A recent survey of current and anticipated developments in food biotechnology predicted a relative rise in agricultural advances and in new or modified food ingredients and a decline or plateauing of efforts on new or improved foods and food processing techniques (Food and Drug Administration, 1988a). More than 400 items of potential interest were identified in the survey. An annual growth rate of at least five percent in the commercialization of herbicide- and pest-resistant plants is predicted by the Office of Technology Assessment (1988). Major proportions of both the genetically manipulated food plants examined by the OTA and the items surveyed by the FDA are expected to be available commercially between 1990 and 1992.

3. **Safety and regulatory issues with products of genetically altered organisms**

Technical issues that may face prospective users of food biotechnology include: (1) the need for product specification, (2) assurance of microbiological purity and stability of cultures, (3) possible exposure of consumers to foreign DNA, (4) possible introduction of metabolites including microbial toxins, and (5) prediction of possible levels of exposure as consumption of new products increases (Munro, 1989).

The impurities encountered in r-DNA-derived biologicals offer an example of some of the problems in the use of engineered microorganisms for production. Among these are endotoxins, host cell proteins, DNA, certain methionylated products, proteolytic clips, monoclonal antibodies, amino acid substitutes, and endogenous viruses (Garnick et al., 1988). Precise quality control to keep such adulterants to a minimum is achievable with modern technology. In reviewing possible approaches to the safety testing of biotechnology-derived food products, Anderson and Cuthbertson (1987) noted that the "most important problems are the impossibility of proving absence of harmful effects (whether known or not yet experienced) and our ignorance of many biological mechanisms and how they are affected by external factors." These authors suggested that any proposed regulations should provide a balance between protection of the consumer and environment and sufficient technologic freedom to promote innovation and the benefits that application could bring.

Regulatory policy as to whether products of genetic manipulation of microorganisms, yeasts, fungi, food plants, and food animals are new food additives for purposes of regulation even though the products may be chemically identical to the same products derived from "natural" sources is under development (Korwek, 1988; Maryanski, 1990b).
Theoretically, under the Coordinated Framework for the Regulation of Biotechnology the use of new manufacturing processes should not affect the legal status of previously cleared foods or food additives unless the method changes their identity or creates adulterating impurities (Office of Science and Technology Policy, 1986). The Coordinated Framework states that existing statutes are appropriate for regulating biotechnology-derived products. However, the Framework also recognizes that such products may require additional regulation, different types of analysis and review, and in some cases, different procedures for licensing or approval, primarily because such products may present different risks and because of the increased level of public concern about biotechnology (Mahinka and Sanzo, 1987).

Since 1986, the FDA has maintained that existing food safety statutes are adequate so that foods and ingredients produced by r-DNA methods can be reviewed in the light of the intended use of the product on a case-by-case basis (Office of Science and Technology Policy, 1986). Under this approach product applications review focuses on scientific questions that must be answered in each case to permit a conclusion of safety under the reasonable-certainty-of-no-harm standard.

The growing diversity of applications makes it likely that these questions will differ considerably as new products appear. More complex scientific questions can be expected with the appearance of food crops from transgenic plants. Concerns that expression of the transfected genes may produce unexpected, possibly allergenic compounds or changes in nutrient/toxicant ratios continue. Although products rather than processes are being regulated, Maryanski (1990b) has suggested that the FDA may consider scrutinizing the genetic engineering methodology when relatively new plasmids or genetic techniques are applied for the first time to food crops. The FDA may need to establish new administrative procedures to receive and evaluate information which will allow determination of whether a new application raises significant scientific questions and whether a petition should be required (Maryanski, 1990b).

Similar questions are also addressed in a report by the International Food Biotechnology Council (1990), which has developed useful procedures for evaluating the safety-in-use of food products produced through genetic modification. The safety provisions of the report have been summarized by Lindemann (1990). It offers a flexible tiered-approach system that is guided by decision trees. Separate decision trees are proposed for each of three product categories: microorganisms and their products, single chemical substances and simple mixtures, and complex mixtures and whole foods. Each tree embodies a series of detailed questions concerning the genetic origin of the parent organism, the history of use of the relevant plasmids, and the composition and safety of the product.

At the culmination of this process questions concerning the suitability of the gene transfer techniques will have been dealt with and the assembled information can provide the basis for a decision to accept, reject, or subject the test material to further study. The report proposes that regulation of genetically modified food plants and food processing microorganisms be patterned on existing law and practice.

As new products increasingly appear, regulatory concerns will shift from the scientific and technical to the legal arena. While federal agencies have focused their regulatory actions on the end products, public concerns and litigation challenges have come largely from individuals and groups with serious concerns about possible adverse health effects of the processes and the negative effects on the environment of releasing products of biotechnology (Mahinka and Sanzo, 1987; Mellon, 1988). In view of these challenges, the proposals of Miller et al. (1990) may be of interest. These authors have devised a scientifically defensible algorithm from which the levels of necessary oversight of field trials and release of genetically altered organisms can be defined when circumstances require such action. Oversight regimens for trials in the environment are not at present a function of the FDA. However, the logic of using risk assessment to provide a credible defense of the process so that the product can be regulated on its own merits may be relevant.
The use of genetically altered organisms promises to provide a diversity of products that consists largely at first of enzymes and food components produced by fermentation and then progresses to foods from transgenic plants. Current regulatory proposals recognize that an important first step in safety evaluation is to determine which basic scientific questions are relevant. It will be important to ensure the safety of these products without discouraging new applications of technology. Frank (1990) has observed that a scheme of regulation based on sound scientific principles can alleviate the concerns of commercial innovators about inhibitory over-regulation.

The anticipated volume and variety of new products will place significant demands on the FDA resources. The Agency will need expanded research capabilities to strengthen its science base and its commitment to fermentation research at the National Center for Food Science and Technology, Illinois Institute of Technology, Chicago, IL. Personnel for technical support and petition processing will be needed.

B. INTERPRETATION OF SCIENTIFIC DATA

Scientific advances influence significantly the manner in which scientific data relative to food safety are interpreted and translated into regulatory action. In recent years methods of chemical and biochemical analysis have made commonplace the detection of substances at levels so low that their mere presence cannot reasonably constitute evidence of risk. The regulatory process has been similarly complicated as such sensitive microbiological techniques as DNA probes or enzyme linked immunosorbent assays (ELISA) have become able to detect widespread biological contamination at very low levels. For ubiquitous contaminants such as V. vulnificus, which is present in commercially harvested oysters (Madden, 1988) decisions based solely on the determination of their presence may be inappropriate. In such situations the technical question of how to find the organism becomes secondary to the many other health and economic factors to be considered in the risk analysis.

A complication in such analyses is the variability of risk in different segments of the population. L. monocytogenes, for example, is a risk to pregnant women (Gellin and Broome, 1989) and V. vulnificus causes severe disease in persons with cirrhosis and hemochromatosis (Blake et al., 1979). Framing rules to protect persons at high risk without restricting access to the product by individuals with little risk of illness may well present difficult decisions to federal regulators.

Currently decisions about the levels of food contaminants must be made on a broad scale with concern as to the applicability of the Delaney Clause and with regard to issues raised in the recent discussions about "zero risk," "negligible risk," and potential benefits of new or existing food products (Anonymous, 1990a). The consultants concluded that there is a recurrent need for the development of criteria for the interpretation of analytical and microbiological data so that concepts such as "safety," "acceptable risk," and so forth may be applied uniformly and effectively.

C. CHANGES IN PACKAGING TECHNOLOGY

Modern materials and technical advances, such as multilaminar films, have led to considerable improvement in packaging technology for promoting high-quality, shelf-stable, fresher tasting, and safer foods. The rapid proliferation of technical innovations is expected to continue through the 1990s and may include changes made in response to environmental concerns.

Current techniques include aseptic, controlled or modified atmosphere, and vacuum packaging (Shank and Carson, 1987). In the United States, aseptic packaging is used mainly for homogeneous, low-acid, liquid foods and starch-based, viscous products such as puddings; it has been extended to include low-acid foods containing particulate matter such as chowders and stews (Smith et al., 1990a). The principal safety issue is control of microbial contamination and growth in such foods.
Optimizing ultra-high-temperature, short-time process systems to preserve taste and other food quality characteristics while simultaneously providing an ample margin for microbial safety represents a series of technical issues that are being investigated by food industry research and development (Chandarana et al. 1987; Lund, 1987).

Controlled or modified atmosphere packaging extends the shelf-life of bakery products, fresh meats, poultry, fish, and fresh fruits and vegetables. Nitrogen, oxygen, and carbon dioxide are used to modify the packaging atmospheres. For example, carbon dioxide combines with moisture in the package to form carbonic acid, which is bacteriostatic and fungistatic. Vacuum packaging is a form of modified atmosphere packaging in that carbon dioxide is released by continuing metabolic activity of the packaged fresh food product. Smith et al. (1990b) have reviewed the numerous factors that must be taken into account to determine optimal gas compositions, which differ considerably for different fresh foods. Control of minor products of metabolism such as carbon monoxide, ethylene, ethanol, and nitrogen oxide, further reduces product degradation in fresh meats, vegetables and fruits, but presents a challenge to the designers of packaging materials. The use of gas-absorbing or gas-releasing sachets for this purpose is rapidly developing. Sachets to scavenge oxygen, control carbon dioxide levels, and to release ethanol as a mold inhibitor are available or being developed (Smith et al., 1990b). Sachets to adsorb and oxidize the maturation-promoting hormone, ethylene, have extended the shelf life of fruits by 50 percent (Labuza, 1990). Although these sachets are used extensively in Europe and Japan, their use in North America has been limited. However, as their economic advantages are appreciated they are expected to emerge as an important technology in the 1990s (Smith et al., 1990b).

An important issue associated with controlled and modified atmosphere packaging is whether the process retards growth of spoilage organisms, which produce recognizable degradative effects, while allowing the unrecognized growth of pathogenic anaerobic organisms. For example, packaging materials with low oxygen permeability may create anaerobic conditions within the package, that favor growth of C. botulinum or other pathogenic microorganisms (Shank and Carson, 1987).

These risks apply as well to La cuisine sous vide, a recently developed food processing technique whose products are popular in Europe. Meal components, vacuum packed in heat-resistant plastic containers, are cooked slowly at low temperatures to preserve flavor, chilled, and kept in refrigerated storage for as long as 21 days (Smith, 1988). However, some potential pathogens grow at low temperatures (Segal, 1988) and contamination may arise during the increased handling necessary for repackaging (Anonymous, 1988). Special equipment and precise temperature-time control are critical to the microbial safety of sous vide foods. Because of the danger of mishandling they must be manufactured and distributed under Hazard Analysis and Critical Control Point (HACCP) procedures. As the sous vide distribution chain acquires sufficient technology to handle vacuum-chill techniques on a large scale, the process can be expected to spread in the United States (Baird, 1990). It will need careful monitoring for microbial contamination (Anonymous, 1988, 1989; Lioutas, 1988).

Some aspects of earlier packaging issues that are likely to persist into the early 1990s are the migration of substances into foods, the generation of pyrolytic products by ultra-high-temperature processing, and the use of heat susceptors for microwaving. The FDA evaluates packaging materials in its Packaging Integrity Laboratory and regulates packaging materials and components as indirect food additives (Shank and Carson, 1987). An example of food packaging migrants is bis(2-ethylhexyl)phthalate, a plasticizing agent used to soften plastic films. The Joint FAO/WHO Expert Committee on Food Additives has recommended that human exposure to this compound as a result of its migration from food-contact materials be reduced to the lowest technically feasible levels because it is considered to be a hepatocarcinogen in mice and rats (World Health Organization, 1989). However, for many packaging materials the level of dietary exposure and the intrinsic toxicity of components migrating into food are low. The Agency has proposed rules that would permit it to establish levels of migration below which a manufacturer would not have to petition for approval of a packaging material (Food and Drug Administration, 1990a).
Heat susceptors, which are increasingly used for the browning of foods in the microwave oven, will present some technical issues to the FDA in the 1990s. These packaging materials contain aluminum finely dispersed on a plastic food contact layer, an adhesive, and a paperboard substrate. High local temperatures (350–400° C) are generated as the aluminum absorbs the electrical component of the microwave energy. These temperatures can on occasion lead to disruption of the plastic food contact layer and release of pyrolysis products. The FDA has accordingly proposed rules that identify the data required to establish limits for the safe use of these products (Shank, 1990a). New susceptor technologies currently being developed will achieve higher temperatures and more controllable heat fluxes by substitution of ferritic metals for aluminum. One problem with these is that doping with nickel is a key method for setting the temperature limits. The consequences in terms of possible food contact with the metal mixtures will have to be considered (Labuza, 1988). The higher susceptor temperatures can be expected to result in the development of new plasticizers and more stable packaging components to prevent their leaching into food (Smith et al., 1990b).

Related issues that will require the FDA’s attention in the 1990s will be the European Community’s efforts to harmonize standards for testing food contact materials and the improvement of methodology to measure the migration of plastic components into foods at high temperatures (Castle et al., 1990).

In summarizing packaging issues, the LSRO consultants noted that the major impact on the FDA will come from the volume of new introductions and the concern for microbiological safety as reduced oxygen techniques and other changes in gaseous atmosphere expand. As packaging methods evolve to extend the shelf life of both refrigerated and unrefrigerated foods, the issue of microbial contamination will require sustained vigilance by the food industry and the FDA (Anonymous, 1987, 1988; Hintlian and Hotchkiss, 1986; Hotchkiss, 1988; Shank and Carson, 1987).

D. FOOD PROCESSING

Ultra-high-pressure food processing is a novel experimental approach that may prove feasible as a food protection/processing technique during the current decade. Tenderization of meats, retardation of microbial growth, and extended shelf life are some anticipated benefits that result from volume changes induced by high hydrostatic pressures. Microbial safety, possible adverse biomedical reactions to the products, and the effects on migration of packaging materials into the products are some of the questions that need to be answered for these procedures (Farkas, 1987).

Irradiation is a food protection technology that has not achieved its potential in the United States. Currently the treatment of foods by exposure to various forms of ionizing radiation is limited in this country to the control of insects and microbes in dried spices, herbs, and other dehydrated foods from plants and the control of Trichinella spiralis in fresh pork (Engel et al., 1988). Radiation is also used for retarding growth and maturation of fresh fruits and vegetables and for preventing sprouting in potatoes (Newsome, 1987; Shank and Carson, 1987). Extensive research and testing of food irradiation since the early 1950s have established the safety of irradiated foods, (including bulk meats) exposed to doses of radiation as high as 1 Mrad (one million rads = 10 kilograys*) of gamma or high-energy x-irradiation. The process induces no radioactivity in the foods, and the radiolytic products do not include chemicals alien to those produced by conventional thermal food processing methods (Newsome, 1987). Consumer anxiety over perceived hazards of irradiated foods is an issue that has resurfaced and will grow as new initiatives are undertaken to test the marketability of a wider choice of such products. There is some question as to whether the FDA by itself can fully address this dichotomy between scientific criteria for food irradiation and public perception of risk. International agreement on control and inspection, careful development of federal regulations, research, and consumer education are all important in establishing that the process is both safe and acceptable.

* 1 gray = 1 joule/kg = 100 rads.
Other techniques that are providing either novel foods or new approaches to producing traditional foods or food ingredients include supercritical liquid extraction of spice extracts, oleoresins, and oils; alkaline peroxide bleaching of certain dietary fibers, and microparticulation of egg and milk proteins to produce fat substitutes (Drewnowski, 1990; Shank and Carson, 1988). A processed mycoprotein, already approved in the United Kingdom as a meat substitute in pot pies, is being evaluated by the FDA (Shank and Carson, 1988). A biotechnology company in New York that was experimenting with bacteriosins announced a formulation that is reportedly effective against at least one strain of Salmonella. The company estimates the product will be valuable for combatting Salmonella in poultry (Cowley, 1988).

E. MACRONUTRIENT-SUBSTITUTED FOOD INGREDIENTS

New issues related to the safety of food additives can be expected from the increasing appearance of low-fat, low-calorie, low-cholesterol and high-fiber substitutes for macronutrients. These so-called "designer foods" (Shank, 1990a) are likely to be consumed in large quantities and the potential for considerable human exposure to these substitutes will be a concern in safety evaluation.

Fluffy cellulose, unabsorbable fat substitutes ("fat-free fats"), spreadable low-fat "butter" which has less fat by virtue of a higher water content, and meat protein substitutes are among developmental or recently introduced food products that permit substitution of conventional macronutrients in foods (Sugarman, 1988). Fluffy cellulose is described as a no-calorie fiber made from sources such as straw, citrus pulp, or sugar beets, that can be used for major dilution of wheat flour without affecting taste and other quality characteristics of baked goods.

Cholesterol-free eggs, meat, and dairy products; meatless meat pies, high-fiber bakery products, and reduced calorie sweeteners are also being developed by the food industries in the United States and abroad (Sugarman, 1988).

Because of the major role of fat in the pleasurable sensory response to food (Drewnowski, 1990) and the increasing public emphasis on dietary fat reduction, the food industry's emphasis on low-fat products can be expected to continue. Two new fat replacements have recently appeared. Simplesse®, a product prepared by microparticulation of egg and milk proteins, has been approved for frozen desserts by the FDA. Olestra®, a nonabsorbable sucrose polyester fat substitute developed by The Procter & Gamble Company, contributes no fat, cholesterol, or calories to the consumer and behaves like conventional fats in food processing. It is being evaluated by the FDA for use in snack foods and as a partial substitute in cooking oils (Harrigan and Breene, 1989).

As noted by Miller et al. (1987), the nutritional implications of substituting synthetic, nontraditional materials such as sucrose polyester and carboxymethylcellulose for natural food ingredients are unknown. For example, the effects of highly lipophilic nonabsorbable substances on absorption of fat-soluble vitamins are unclear. The long-term effects of consuming foods of high organoleptic quality and little nutritive value are a matter of concern. Possible changes in appetite or taste perception require study. If macronutrient substitutes become ubiquitous in the food supply, it will be imperative to assess the impact of these food substitutes on dietary adequacy and nutritional status in all segments of the population.

Summary: The scientific advances that promise the greatest impact on the FDA are the modern techniques for genetic manipulation. In addition to the genetic engineering of food ingredients, foods, and food sources these have provided DNA probes for pathogen detection and methodology for the genetic analysis of the mechanisms that govern microbial virulence. Greater application of these techniques will enhance the FDA's ability to deal with the ever growing problems of microbial safety. New variants of the polymerase chain reaction may be expected to extend these capabilities.
The anticipated impact of genetically altered microorganisms and plants on the food supply will challenge the capabilities and resources of the FDA in its efforts to ensure the safety of foods produced by the new techniques without compromising the opportunity for development of new technologies. Extension of existing regulations appears to be the most appropriate approach to ensuring the safety of these products. However, the variety of new products and processes and public concerns about biotechnology will require flexibility in review procedures. As new plasmids and innovative genetic engineering techniques are applied to food production, the FDA may need to scrutinize the production process as well as the composition of the product. In each case the Agency must define those scientific questions that need to be answered if these procedures are to provide reasonable certainty of no harm.

Other emerging areas of concern will be the proliferation of new packaging techniques, advances in food processing, and the preparation of low-calorie or high-fiber macronutrient-substitutes by alteration of the physical and chemical properties of natural substances. Opportunities for microbial growth in controlled-atmosphere and low-oxygen packaging and the possible migration of components from new microwave heat susceptors are of concern. The use of non-nutritive substitutes for major dietary ingredients is emerging as an issue. These will require long-term evaluation before the ultimate nutritional consequences of their use and need for appropriate regulatory measures become evident.
V. FOOD SAFETY ISSUES RELATED TO IMPORTS AND THE GLOBALIZATION OF THE FOOD INDUSTRY

With the rapid internationalization of the food industry and the growing public taste for exotic foods, the volume and variety of foods imported into the United States are increasing dramatically. Food import entries tabulated by the U.S. Census Bureau have approximately doubled in a ten–year period and were projected to reach about 1.2 million entries in 1990. This translates into about 16 million tons of imported food entering the United States annually (Farley, 1988b). The diversity of foreign food sources will also increase, especially as eastern European countries seek to enter the global market, and the anticipated extensions of trade with Mexico and Latin America materialize. Emerging international trade agreements will impinge on many aspects of the FDA activity. Although details will depend on the outcome of current negotiations, the General Agreement on Trades and Tariffs (GATT) will affect the distribution of agricultural products in import and export markets. Completion of the economic union of the European Community in 1992 will require enormous effort to harmonize the food standards and regulations of the nations involved.

The FDA is concerned about the safety of imported foods, the evaluation of which requires knowledge of the manufacturing processes at the point of origin and a sustained analytical testing effort at the ports of entry. In recent years as food imports have increased, they have also largely changed from bulk materials to finished products, thus depriving the FDA of its former opportunities to monitor the final stages of production under Good Manufacturing Practice (GMP) requirements (Office of the Federal Register, 1990). Under the circumstances adequacy of sampling becomes a concern, but the increased use of multi–product containerized shipping has made this difficult to achieve. Long–term planning to establish sophisticated and efficient sampling strategies and expanded facilities for automated data handling are needed.

Sources of many imported new foods vary widely in their populations of latent pathogens. In view of this and the differences among countries in public health regulatory practices, greater emphasis on microbial contamination and the possible emergence of unexpected pathogens will be necessary. Thus, the FDA will need to employ staff skilled in modern methods of pathogen identification and to maintain institutional expertise in epidemiology.

As imports increase, demands for increased testing and surveillance will intensify. This will require sophistication in the interpretation of surveillance data as well as expansion of field staff, analytical facilities and data bases within CFSAN. The FDA lacks the necessary resources to expand the current analytical testing program to include a statistically valid sample of the domestic and imported food supply (Shank and Carson, 1988). Increased emphasis is needed on analytical testing of imported foods for compliance with all the FDA food quality and safety standards including whether low– and high–acid foods meet specifications.

A development related to the increase in imports and the public concern over pesticides is the mandate by the Pesticide Monitoring Improvements Act of 1988 (U.S. Congress, 1988) for the FDA to establish cooperative agreements to obtain pesticide usage data from countries exporting foods to the United States. These data, if available, would supplement those now obtained from the Battelle World Agrochemical Bank (Food and Drug Administration, 1990b) and enhance the Agency's ability to target surveillance plans.

The FDA has noted the advisability of encouraging brokers, importers, foreign governments, and foreign producers to assume a greater role in assuring that imported foods are in statutory compliance (Young and Benson, 1989) and has included in the CFSAN needs assessments a modest program to assist in the training of foreign workers.
Efforts in international communication and cooperation on issues of food safety and quality can be very demanding of time and personnel resources. Memoranda of understanding are now in place with over 40 nations (Modeland, 1988); other negotiations in connection with international harmonization of regulations and standards will continue. The Codex Alimentarius Commission is emerging as the most suitable multinational scientific body for harmonizing food, health, and sanitary regulations worldwide (Lyng, 1988). The FDA will have to enhance its participation in the development of food standards, a major activity of the Codex. Preparation of Certificates of Free Trade will make increasing demands. It will be particularly important if the FDA is to provide leadership in international affairs that the Agency be provided with personnel and resources to adequately represent the United States in international deliberations.

Summary: The internationalization of the food industry will require increasingly sophisticated sampling and data handling strategies as well as increased resources for surveillance as the volume of imports increases and packaged prepared products supplant bulk foods. Maintenance of a scientific staff with sophisticated capabilities in epidemiology and methodology for pathogen detection will be important as importation of food products grows. International cooperation and harmonization of world food regulations are essential in today’s environment, but demand resources that are not yet available. Support for and resources necessary to the FDA as a key agency in these activities are required.
VI. RESOURCE ALLOCATIONS

A. PRIORITIZATION

Resource limitations will be a deterrent to the full implementation of a number of CFSAN activities that are likely to be of concern in the 1990s and that are regarded as important by the FDA advisors (Food and Drug Administration, 1990c). Prioritization of functions competing for resources that will probably always be less than sufficient is an issue that the FDA must address frequently. It is noteworthy that CFSAN's personnel roster has fallen from 861 in 1974 to a current 821 while the FDA as a whole has grown from 6324 to 7722 (Shank, 1990b). A Comprehensive Needs Assessment report that documents the resources required for full implementation by 1997 of each of the Center's many responsibilities will be published in early 1991. It offers an in-house source that will be useful in priority considerations.

Shank (1990b) has noted that in prioritizing suggestions emerging through its Project Management System, CFSAN must consider the extent of the FDA's legal authority as well as public health and safety issues. Some otherwise high priority projects may not be supported because there is insufficient fundamental scientific information. To an extent these considerations apply to establishing generic criteria for resource allocation to major areas. The LSRO consultants were of the opinion that such criteria might include:

- The urgency, not just the importance, of the activity.
- The extent to which competing functions specifically target food safety.
- The appropriateness of the FDA as the agency best qualified to do the job.

It is inherent in the FDA's role that unforeseen crises will frequently override the most rational of priorities and that pressure from special groups or legislative mandates will necessitate realignment of scarce resources.

Resource limitations include not only dollars and people, but time. The LSRO consultants noted that trends in regulatory needs may develop faster than the Agency's response time. The requirement to maximize flexibility so as to decrease reaction time is a factor to consider in priority questions.

The LSRO consultants felt that it is highly desirable, as noted also by Shank (1990b), for the FDA to adopt a proactive stance, thereby anticipating potential food safety problems rather than primarily responding to unforeseen emergencies.

B. RESEARCH

Research is regarded as an important component of CFSAN activity and an aid in maintaining a proactive, scientifically credible position (Shank, 1990b). The need for the FDA to continue in-house research in an agency with restricted resources is occasionally challenged but has recently been defended by Taylor (Anonymous, 1990b) and Scheuplein (Anonymous, 1990c) in presentations before the Advisory Committee on the Food and Drug Administration. Both authors noted that timeliness of response in developing analytical methods or in providing scientific support for decision making is an important benefit of maintaining a seasoned research staff. A research program devoted half to development of sensitive analytical procedures and half to a variety of studies including among others food microbiology and development of genetic probes has been described by Young (1988b).
Significant new demands on research resources can be expected as the products of biotechnology increasingly enter the market. Because the first wave of these developments will be primarily fermentation products, research problems will need to be focused on large scale fermentation technology. The completion of an industry–academia–government consortium, the new National Center for Food Safety and Technology, in Chicago is apparently expected to deal with this problem (Shank, 1990b) as well as other issues related to packaging and preparation technologies.

C. CONSUMER EDUCATION

The FDA has been engaged for some time in the preparation and promulgation of major revisions in food labeling regulations which, when implemented, should improve the amount and quality of nutrition information available to consumers (Food and Drug Administration, 1990d). Recently the Institute of Medicine of the National Academy of Sciences published an exhaustive review of food labeling issues and provided sweeping recommendations for the extension of nutritional labeling to most foods (Institute of Medicine, 1990). The report has been useful in the formulation of the FDA's labeling regulations to implement the recently passed Nutrition Labeling and Education Act of 1990 (U.S. Congress, 1990a). This legislation will extend considerably the FDA's role in bringing nutritional information to public attention. Among its numerous provisions the new law requires most processed foods to be labeled with amounts and types of fat and carbohydrates and the amounts of cholesterol, sodium, dietary fiber and protein. It requires the Secretary of Health and Human Services to determine whether there is sufficient scientific evidence to support disease-related health claims about a variety of foods. The law sets forth detailed time frames for several specific accomplishments. Although a number of provisions for labeling are similar to those proposed earlier, the FDA's role in implementation of the new law will require the preparation of numerous documents and a major commitment of resources and time.

With respect to activities other than labeling, Mayer (1990) has noted that it is not clear who in the government is responsible for public education in health and nutrition. Primary federal responsibility for nutrition and food safety education is shared by other agencies of the Department of Health and Human Services and the Department of Agriculture. The Federal Trade Commission also has a role in regard to standards for food advertising. An education function for the FDA appears implicit in the Federal Food, Drug and Cosmetic Act, whose intention is, "... to assure the consumer that foods are pure and wholesome, safe to eat, and produced under sanitary conditions" (Food and Drug Administration, 1985).

The FDA's programs in food safety and quality, including its research, testing, monitoring, and special investigations generate valuable data and information, much of which needs to be disseminated to users such as other federal and state agencies, the food industry, and U.S. consumers. The U.S. Department of Agriculture's Extension Service and the FDA have prepared a Memorandum of Understanding committing the two agencies to coordinate and communicate on matters relating to developing, exchanging, and sharing educational materials, information pieces, and other major agency activities in the areas of food safety, nutrition, and veterinary medicine (U.S. Department of Agriculture, 1989).

The FDA publications containing information on food safety, quality, and nutrition include the monthly FDA Consumer, the FDA Drug Bulletin (which contains information for physicians and other health care specialists on food safety and nutrition), informal "Backgrounders" and, as part of an industry assistance program, Information Materials for the Food and Cosmetics Industries. The latter lists publications and audiovisual materials and their sources on numerous topics relating to food safety and quality. They are available from the FDA and other federal as well as nongovernmental sources (Food and Drug Administration, 1988b). Information is also disseminated by press conferences and congressional hearings.
The FDA provides resource material consistent with its charge and is concerned with nutrition information at the consumer level as part of its mandated role in food labeling. The LSRO consultants felt that the FDA should not be expected to assume demanding educational programs in addition to these responsibilities and to its regulatory burdens. The Agency, however, is a repository of valuable scientific information and should continue to be an important contributor of scientific input to those institutions generating educational programs in diet and health.

Because of the inescapable demand for up-to-date food safety information by a variety of audiences, including journalists and consumers, there is pressure for the FDA to have an educational role that extends beyond food labeling issues. It will be critically important for the FDA to communicate the results of risk assessment studies and the basis for its safety decisions in language intelligible to the layman if public misconceptions of risk are to be avoided. There is an additional responsibility to make available information concerning risks to sensitive populations such as pregnant women, the immunocompromised, and the elderly.

Resources will be needed for these important activities. At a minimum, the FDA must have two things: first, a sufficiently large expert staff and research facilities to respond to public demands for facts to deal with real or perceived food safety issues; and second, sufficient resources to compile and transfer information about food safety and quality to other government and private agencies with programs in consumer education.

D. SURVEILLANCE AND INSPECTION

Inspection of food processing plants and imported foods and laboratory testing of foods for adulterants, and microbial and chemical contaminants are key activities of the FDA. The Agency's routine sanitation inspections are considered the cornerstone of its food safety checks (Thompson et al., 1990). The United States General Accounting Office (1989) has noted that of the total time the FDA spent on inspection activities in fiscal 1988 about 18 percent was spent on tasks related to imported foods and the remainder on tasks related to domestic products.

The LSRO consultants recognize the desirability of maintaining a proactive stance to anticipate necessary changes in the functions noted above. Inclusion of surveillance as an integral part of risk assessment would contribute to this end. Up-to-date epidemiological data, coupled with information on the appearance of contaminants or potential pathogens in major food sources may reveal areas that require regulatory guidelines or inspection regimens to monitor compliance.

Postmarket surveillance can be a timely way to discover potential food safety problems that may have slipped through the regulatory network. It can also be used in supplementary ways. The modest postmarket surveillance system of the FDA, for example, includes a data monitoring system designed to identify subgroups of the population that experience unique problems with food components.

Short term ad hoc surveillance programs for special situations are often useful. Characteristically these operations involve testing a class of products by standardized methods to determine whether there is an incidence of violative samples sufficient to warrant initiating inspection, compliance testing, more research or some other response. Surveillance programs may indicate that no problem exists in the population examined, or they may indicate that a particular type of inspection is required. In such instances they can be quite cost-effective.

Surveillance requirements will place demands on FDA resources. Compliance with the Pesticides Monitoring and Improvement Act (PMIA) (U.S. Congress, 1988) (for which no resources were provided by Congress) will require significant expansion of field personnel and resources for data handling and storage. Meaningful surveillance is strongly dependent on the validity of available
microbiological and analytical techniques and provision of these can also be demanding. The PMIA, for example, requires the development of methods to improve food monitoring. It will be necessary for the Agency to keep abreast of new pesticides as they enter the market. In this connection Shank (1990b) has pointed out the need for research to develop sensitive single sample, multi-residue methods for pesticide residues.

In general comments LSRO consultants noted that overlong commitment to a surveillance project that repeatedly yields the same indications of minimal problems can result in information overload. The consultants felt that surveillance programs may be most valuable when they are used to test a particular hypothesis. An example might be to test the effectiveness of a HACCP system by surveillance conducted before and after imposition of the program.

The ongoing, two-year study of the Department of Agriculture's Food Safety and Inspection Service on the HACCP system for preventing foodborne contamination (Adams, 1990; Food Safety and Inspection Service, 1990) could be a model for the FDA evaluation of its food safety programs. This system is designed to impose controls at all points in an entire manufacturing process where a hazardous or critical situation might occur. It offers the advantage of optimizing the efficacy of each step in a rationalized control system. When operating correctly its provisions for rigorous control should minimize the testing of finished packaged products except for monitoring. HACCP-based systems have been used for some years on a voluntary basis as a supplement to the FDA's GMP regulations, which relate largely to sanitation. It is mandatory for low-acid canned foods (Thompson et al., 1990). It is implemented by industry and monitored by the regulatory agency and thus appropriately places much of the burden for testing on the manufacturer.

As the food industry grows, the criteria for further implementation of HACCP systems will be issues in the 1990s. As Baird (1990) has pointed out in the case of sous vide processing, HACCP is essential in high-risk, large-scale, highly centralized food processing operations where human error could be an important risk factor. Waites and Arbuthnot (1990) stress the importance of extending the HACCP system over the whole food chain so that sites of production and raw materials are monitored as well as processes since it is difficult to remove pathogens or toxins once they have entered the food chain. The LSRO consultants noted that some projections of HACCP in this direction might have complications. If seafood from occasionally contaminated waters became subject to HACCP, pre-harvesting tests of the environment might become a critical control point. If so, additional innovations in methodology and legal authorization would be necessary. In any case the application of HACCP to an increasingly complex food industry will require ingenuity and flexibility of approach. An interesting test is a trial of HACCP procedures in fish inspection, which has been initiated in collaboration with the National Marine Fisheries Service in response to a Congressional mandate (Food and Drug Administration, 1990e).

The FDA is not alone in its concern for monitoring of food safety. Progress is being made in securing international cooperation in such areas as food product inspection, certification, and quality assurance. Domestic food processors are expanding efforts to meet standards of food safety and quality. The FDA will have to remain alert to these developments as it pursues its own efforts for the improvement of food safety and quality inspection procedures through the current decade.

E. COOPERATIVE AGREEMENTS WITH PUBLIC AND PRIVATE AGENCIES

Some issues in food safety and quality are not only subject to resource and legal limitations, but are inherently complex and difficult to resolve; responsible authorities in government acknowledge, "We can not do it all." Therefore the FDA has proposed increased cooperation and collaboration among government, food industry, and academic organizations to marshal scientific and technical expertise to solve problems in food safety, quality, and consumer education (Shank and Carson, 1988). The
importance of such cooperation has been described by McNutt (1988) who considers it a professional obligation for the public and private sectors to learn to work together. Mechanisms to foster this cooperation and collaboration include such initiatives as federally and state-sponsored workshops and symposia, participation in meetings of scientific and technological organizations, and contracts and grants for studies of issues involving specialists in government, academia, industry, the medical and legal professions, and consumer groups. An example of a cooperative agreement is the two-year study by the FDA and Giant Foods, Inc., on the effects of experimental food labeling on consumer purchasing behavior in supermarkets in Washington, DC, and Baltimore (Levy et al., 1984).

Temporary exchange of research and other professional personnel with universities, private institutions, and industry can help revitalize key staff and keep the agency attuned to major new developments. A sabbatical program has been proposed in the FDA's action plan (Young and Benson, 1989). The LSRO consultants observed that a lack of communication between scientists at the FDA and those in regulated industry works to the detriment of the public as well as the parties involved. Formal exchange programs could bring scientific knowledge and increased scientific skills to the FDA while at the same time developing support for industry compliance with the FDA objectives.

Summary: Currently, and increasingly in the next decade, prioritization of resource-limited functions is a concern of the CFSAN. Demands on the Agency include research, regulation of food labeling, provision of consumer information, and maintenance of surveillance and testing regimens. The role of hazard analysis and critical control point (HACCP) procedures in an increasingly complex food industry will be a concern of the 1990s. For the near future implementation of the new Nutrition Labeling and Education Act will be among the most demanding of the Agency's responsibilities.
VII. OTHER CONSIDERATIONS

A. ROLE OF OTHER SEGMENTS OF SOCIETY

Improving and maintaining optimal safety and quality of the nation's food supply represent extremely complex and challenging tasks that involve many components of U.S. society (federal agencies, the Congress, state and local governments, professional groups, industry, academe, and consumers). The official roles of the several responsible federal agencies have been noted earlier in section II B.

The FDA described the roles of state and local governments in food safety and quality as: "States inspect restaurants, retail food establishments, dairies, grain mills, and other food establishments within their borders. In many instances, they can embargo illegal food products, which the FDA cannot do. States 'own' fishing waters within their jurisdictions, which gives them authority over fish, including shellfish, taken from those waters. The FDA provides guidelines to the states for this regulation. Twenty-eight states have their own fish inspection programs. The FDA also provides guidelines for state and local governments for regulation of dairy products and restaurant foods" (Modeland, 1988). State inspection and enforcement resources are thus important to the success of the FDA's mission.

State and local government agencies cooperate with the federal government to ensure the safety and quality of foods produced within their jurisdictions. The FDA and other federal agencies help states and local governments develop uniform food safety standards and regulations and assist them with research and information. However, under the Commerce and Supremacy Clauses of the Constitution, the federal government has broad powers to prevent state regulatory activity. In terms of the commerce clause, federal courts will invalidate state regulatory actions if they lead to discrimination against interstate commerce to protect local economic interests from outside competition (as reviewed by Caswell, 1988).

Thus, the FDA is increasingly thrust into a dual role, on the one hand advisory and on the other adversarial, as issues arise over federal preemption of states' rights with regard to food safety and quality. Proposition 65 is an example of a state's initiative that has generated such issues as which food safety standards should prevail in California — federal or state? The FDA's role in protecting a national food market from state regulation of interstate-shipped foods will probably raise legal policy issues during the next decade.

The important concern in the resolution of these issues will be to achieve uniformity in food regulations when required by national policy considerations. In some instances preemption of state laws will be necessary and preemption is, in fact, provided for in certain applications of the new Nutrition Labeling and Education Act. When considering the alternatives it will be important to ask whether preemption will alleviate or exacerbate burdens on consumers and industry. It will also be desirable to consider whether preemption is likely to compromise the innovativeness and creativity that permit states to make their contributions to the regulatory process.

Since diverse state requirements are more likely to be adopted if the FDA is seen as ineffective or unable to address the major concerns of consumers, the FDA's effectiveness in establishing reasonable and uniform regulations will depend on its credibility as a leader. It will be important that the Agency be backed by adequate scientific and legal resources. In a recent discussion of these questions before the Food and Drug Law Institute the Commissioner identified Agency credibility and a rigorous enforcement policy as major priorities of his incoming administration (Anonymous, 1990d).
The FDA is not defined in law as a "protector of the people," or as a "protector of the food supply," or as a nutritional decision maker. Nevertheless, the FDA is obligated to act in these, as well as in all the other areas that are stipulated by law. The LSRO consultants were greatly concerned over the imbalances between the FDA's work load in food safety and quality and the shrinking fiscal and human resources it has to do the job. A major gulf exists between what all segments of American society expect the Agency to do and the available means to accomplish its mission.

Congress develops legislation, oversees government operations, and approves the federal budget. Congress thus shares responsibility with the Executive Branch for providing adequate funding to assure a safe and wholesome food supply. According to the Subcommittee on Foods, Cosmetics and Veterinary Medicine some of the items most in need of authorization and adequate appropriations are a streamlined plan to provide the CFSAN with integrated office and laboratory facilities to replace the hopelessly inadequate current facilities and enhanced resources for surveillance and monitoring activities related to enforcement (Public Health Service, 1990a). The Food and Drug Administration Revitalization Act signed in 1990 will facilitate some of the internal activities of the FDA (U.S. Congress, 1990b). The Nutrition Labeling and Education Act of 1990 will have significant impact on the agency's resources (U.S. Congress, 1990a).

The American food industry recognizes that to remain competitive it must do all in its power to provide foods that are safe and of high quality. Consequently, the food industry invests part of its resources in research, testing, and analysis of its products, distribution systems, and storage systems.

Consumers who are the final arbiters of food quality and safety, have a strong influence on what appears and survives in the marketplace and consumer groups increasingly participate in legislative and rule-making activities at federal and local levels. Consumer groups monitor food safety and quality and call attention to problems which they consider important to the general public. Such concerns may be publicized regardless of whether scientific documentation supports the perception of the problem. Thus, issues sometimes arise that may be of greater priority to the public at large than to the scientific community. To the extent that good two-way communications can be maintained with consumers and the media, these groups may be helpful in increasing support of the FDA's programs, overcoming consumer concerns about food safety and encouraging needed legislation.

B. RISK ASSESSMENT

Risk assessment is a major mechanism by which the FDA monitors the safety of the food supply. A number of the activities noted in this report contribute importantly to this process. Despite the fact that many of these functions are under-supported and the FDA must operate under suboptimal conditions, the Agency has achieved a remarkable record and the American food supply remains healthy and safe.

Risk assessment provides both essential support for the FDA regulatory decisions and reassurance to a public concerned with food safety. Although expert opinion would place microbiological contamination as the greater hazard (Morgan and Fenwick, 1990), public concern has largely focused on possible toxicity and carcinogenicity of chemical residues, especially pesticides, in foods. Some emerging philosophic changes in evaluating risks associated with foods, food additives, and pesticides in foods are reflected in recent comments of FDA officials (Anonymous, 1990b; Scheuplein, 1990) and others (Ames, 1983; Byers, 1988a,b; Zeckhauser and Viscusi, 1990). For example, most scientists agree that the zero exposure to carcinogenic additives established by the Delaney Clause is illusory in view of modern analytical capabilities and should be ultimately replaced. Shank has suggested application of a more realistic concept of "negligible risk" (Anonymous, 1990a). Modern research has also brought changes to the hazard identification techniques that are classically an
early part of the risk assessment procedure. Paustenbach (1989), in reviewing these changes, has observed that in recent years significant strides have been made in our understanding of how to identify chemicals likely to pose a significant carcinogenic, developmental, or reproductive hazard to humans. Thus the straightforward approach to identification of carcinogens by two-year or lifetime studies of rodents at high doses has been supplemented by studies taking into account the genotoxicity of chemicals at low levels of exposure, the multiple biochemical mechanisms of action involved in tumor formation in treated animals, and epidemiological evidence. Paustenbach has further noted that "the more enlightened approaches to interpreting the significance of animal bioassay data should provide much more defensible hazard identifications."

While not all investigators would agree, Ames and Gold (1990) have suggested that the significance of conventional tests for carcinogenicity in rodents should be reexamined. Chemicals tested at near toxic (maximum tolerated) doses can cause chronic mitogenesis, irrespective of whether they are themselves mutagens. Ames and Gold (1990) proposed that the resulting enhanced risk of mutation by endogenous damage to DNA would account for the observation that about half of all compounds tested, whether of natural or synthetic origin, were carcinogens. This does not necessarily mean that induced mitogenesis is the major rate limiting factor in cancer, but the observation suggests that detailed studies of mechanisms are critically important in interpreting evidence of carcinogenicity, and extrapolation from high to low doses should be based on an understanding of these mechanisms.

An important aspect of risk characterization is the question of how the risk in question ranks against the risks of alternative hazards that are generally regarded as acceptable and to which the general public is more able to relate (Paustenbach, 1989; Morgan and Fenwick, 1990). In line with this concept, Ames et al. (1987) proposed to compare the risks posed by low level industrial carcinogens to those posed by naturally occurring toxins in the diet. In order to provide appropriate reference material they have most recently studied the wide variety of naturally occurring pesticides that occur in plants (Ames et al., 1990a,b). The authors estimated that Americans eat about 1.5 g of natural pesticides per day, which is about 10,000 times more than the synthetic pesticide residues eaten. However, the potency of these pesticides may be different so that weight alone is not the only consideration. At the doses of most human exposures the synthetic pesticides thus add only a trivial risk to the existing burden. Ames and his co-workers felt that priority in further investigation should go to testing of natural pesticides and pyrolysis products from cooking rather than to studies of hypothetical risks that are low with respect to background risks.

Similar considerations have led Scheuplein (1990) to observe that instead of food additives and residual pesticides in foods, most of the cancer risk in today's diets comes from traditional foods, certain traditional methods of food preservation, and the pyrolytic products of cooking. He suggested that acquisition of systematic, comprehensive data on the carcinogenic potential of all traditional foods would contribute much more to the protection of public health than regulatory efforts to eliminate all traces of contaminants from the food supply. In an appraisal of overall risks to human health and welfare, Zeckhauser and Viscusi (1990) call for the development and implementation of a science-based system of risk assessment and risk management to replace what they describe as the current muddled, ad hoc, unrealistic approach.

The ultimate impact of risk assessments will frequently be felt in court, where, as Barnard (1990) has pointed out, legal decisions will require accommodation between law and science. He examined two recent court decisions in which the principles underlying legal definitions of "safe," "significant risk," and "acceptable risk" were set forth. These definitions have emerged in large part in response to the vast increase in scientific data and new biological insights. The legal criteria involved in the courts' interpretation of these terms are stated to be essentially judgmental and involve a case-by-case approach. "Safe," for example, does not mean risk-free, and "acceptable risk" involves a judgmental determination based on three factors: the statutory basis, the scientific data, and the "risks
that are acceptable in the world in which we live." In Barnard's view, the legal principles underlying the definitions are dynamic and sufficiently flexible to encourage the incorporation of new scientific findings. Barnard (1990) also included a summary of recent discussions of the application of de minimis principles to the Delaney Clause and a review of the historical basis for the concept of "negligible risk."

An important observation stemming from these considerations is that "the distinction between sufficiency of the evidence of carcinogenic activity in animals and the judgmental weight-of-the-evidence evaluation of all the data in relation to human risk is becoming increasingly recognized as scientific understanding of the biological processes involved in carcinogenesis advances." This survey of the emerging relationships between law and science ends on a hopeful note particularly relevant to the FDA. "The legal principles and the scientific precepts are not only consistent with, but encourage, achievement of the goal of improving the adequacy of the science base to provide the best understanding of the true magnitude and character of human risk" (Barnard, 1990). In this connection it is important to remember that risk assessment, however well based in science and law, must be accompanied by clarity in risk communication if it is to be truly effective, and if the public is to have a realistic view of the risk:benefit questions in food safety.

Summary: The FDA interacts in a variety of ways with other federal, state and local regulatory agencies as well as with industrial and consumer organizations. State inspection and enforcement activities are an important adjunct to the FDA's role in maintaining food safety. The Agency must have the resources and authority to assume leadership in these relationships if uniformity and coherence in food regulations are to be achieved.

Emerging trends in risk assessment include more sophisticated methods of hazard identification, shift of emphasis from chemical toxicants to naturally occurring dietary components and changing aspects of the relation between science and law. Further application of risk assessment as an approach will draw more widely on many facets of the FDA activity and will represent an increasingly important mechanism for monitoring food safety. Despite current suboptimal conditions, the FDA has been remarkably successful in keeping the American food supply healthy and safe. However, greater resources and sustained commitment by the government, and public and private sectors will be required in the future.
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The Life Sciences Research Office (LSRO) would like to express its appreciation to the following persons and organizations for comments and information submitted in connection with this review. Copies of their submissions are available at the FDA Dockets Management Branch (Docket No. 88N–0401) and in the Open Files of the Life Sciences Research Office.

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