Journal of Cellular Biochemistry 56:210–224 (1994)

VIEWPOINT

Prospects for Application of Biotechnology-Derived Biomaterials*

Kiki B. Hellman, Grace Lee Picciolo, and C. Fred Fox

Center for Devices and Radiological Health, U.S. Food and Drug Administration, Rockville, Maryland 20852 (K.B.H., G.L.P.) and Department of Microbiology and Molecular Genetics, University of California, Los Angeles, CA 90024-1484 (C.F.F.)

PROGRESS IN BIOTECHNOLOGY

Broadly defined, biotechnology is any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, to develop microorganisms for specific uses, or to develop materials that mimic molecular structures or functions of living systems [1]. Over the past 10 years, biotechnology has created new approaches for preventing and treating disease and is on the brink of providing approaches for increasing the efficiency of world food production, protecting the environment, and expanding the options for chemical and energy production.

A report from the United States (U.S.) National Academy of Sciences indicates that biotechnology is a rapidly expanding industry that analysts predict will play a prominent role in the U.S. economy, by the year 2000 [2]. According to the most recent report by Ernst and Young, global sales of biotechnology-derived products have grown from zero in 1980 to $5.9 billion in 1992 [3]. Sales are projected to be at least $50 billion by the end of the decade [4].

Industry analysts and academic scientists acknowledge and emphasize the importance of Federal government programs and policies to the future of U.S. biotechnology, particularly support for the basic and applied research, which is fundamental to the industry. The extraordinary success of biotechnology has been largely due to the creativity of U.S. scientists and to the foresight of the Federal government, which has supported basic research for over 30 years. These two factors have made the United States the global leader in biotechnology.

Biotechnology has had its greatest impact to date in human health, through the development of new pharmaceuticals, vaccines, diagnostics, and other medical products. More than 1,000 clinical trials are currently in progress using biotechnology-derived pharmaceuticals, and the Food and Drug Administration (FDA) has cleared or approved more than 700 biotechnology-derived diagnostic devices for clinical use [5].

Products currently approved or under evaluation by the FDA include new, safer, and more efficacious vaccines for infectious diseases, including the recently approved vaccines for hepatitis B and meningitis; therapeutic monoclonal antibodies; cytokines for bolstering the body's immune responses (interferon and interleukins); growth factors (e.g., human growth hormone for hereditary pituitary conditions); and anti-blood clot thrombolytic agents such as tissue plasminogen activator (TPA). Laboratory tests currently approved or under evaluation by the FDA include those for diagnosing infectious diseases, and cancer; for monitoring analytes and therapeutic drugs in body fluids and tissues; and for screening the blood supply. Products under development include vaccines for chronic conditions, such as allergies, inflammatory disorders (arthritis), and autoimmune diseases; tumor-specific immunotoxins; and new diagnostic assays, including those for genetic disorders and in vivo diagnostic imaging.

Certain advances represent fundamental breakthroughs in research and technology, and could be of great value in containing health care costs through new diagnostic, prevention, and treatment approaches. For example, the new field of molecular medicine, which seeks to un-

Received July 15, 1994.

The opinions and statements contained in this report are those of the authors and may not reflect the views of the Department of Health and Human Services (HHS) and/or the Food and Drug Administration.

Address reprint requests to Kiki B. Hellman, Center for Devices and Radiological Health, Food and Drug Administration, Rockville, MD 20852.

derstand the molecular basis of disease, offers the possibility of answering the fundamental questions surrounding disease etiology and, by implication, identifying the specific targets for early diagnosis and effective treatment. The therapeutic approaches offered by molecular medicine range from the large-scale ex vivo production of cloned blood clotting factors VIII and IX for more cost-effective and efficient treatment of hemophiliacs to the introduction of in vivo replacements for these defective genes through gene therapy.

By introducing normal genes into persons with genetic abnormalities, scientists hope to effectively treat and cure the affected individuals. Gene therapy trials have been approved in the United States for the treatment of adenosine deaminase (ADA) deficiency, cystic fibrosis and other inherited disorders, cancer, and acquired immunodeficiency disease syndrome (AIDS). The National Institutes of Health (NIH) have approved 42 protocols for clinical investigations using human gene transfer and gene therapy techniques [5]. Multifactorial disorders that are the result of complex interactions between one or more genes and the environment, such as heart disease, cancer, stroke, diabetes, schizophrenia, and hypertension, are likely targets for gene therapy intervention.

Progress being made in the development of molecular probes to identify the genetic defects known to cause disease in humans and gene therapy to correct such defects is due in large part to the Human Genome Project, which represents the largest biology research effort ever to be directed at a single goal. The project, supported by the NIH and the Department of Energy (DOE), seeks to identify and sequence the 100,000 genes that comprise the human genome. This project will create a database that will provide biologists and physicians with direct computer access to this information. Recent discoveries include a probable genetic link to hypertension, several genetic defects linked to Alzheimer's disease (a neurodegenerative disease that affects four million individuals in the United States alone), and the familial breast cancer and colorectal cancer genes. The vital research being conducted under the Human Genome Project promises to usher in a new age of medicine with a substantial impact on society. In fact, it has been predicted that by the year 2000, pharmaceutical companies will routinely use genomic data to create new drugs and diagnostic techniques.

New interdisciplinary research areas in biotechnology at the interface of biology and engineering, such as tissue engineering and biomaterials science, are having an impact on the development of novel health care products including biosensors, unique drug delivery systems and extracorporeal therapy devices, implants, and other prostheses. In addition, the knowledge gained through health-related biotechnology research contributes to the advancement of biotechnology research in non-health-related areas.

Newly developed delivery systems include transdermal patches and biocompatible polymers that carry a therapeutic drug and release it either at a constant or prescribed rate. New medical devices and systems for delivering large biomolecules and other biotechnology-derived materials to target sites within the body for therapeutic purposes are also being developed. The use of devices containing genetically modified cells is one such innovative approach to therapy. Recent preliminary results with an animal model suggest that diabetes can be effectively treated with a biohybrid device containing insulin-secreting cells. Cell and molecular biology approaches coupled with engineering principles have led to the development of engineered tissues to restore, maintain, and improve tissue function. This approach has been used to engineer skin for the treatment of wounds and sequelae of chronic diseases such as diabetes. Other engineered human tissues being developed include peripheral nerves, bone, cartilage, and blood vessels.

In order for the benefits of all these various new products to be fully realized, manufacturing and bioprocessing techniques must be developed to translate innovations at the research bench into commercially available products. Whether for manufacturing bulk products like artificial sweeteners and ethanol or few producing large quantities of biotechnology products such as insulin, bioprocessing offers a level of precision, specificity, and predictability that would not otherwise exist. Bioprocessing offers new production opportunities for a wide range of products from pesticides, flavoring agents, and pharmaceuticals, to environmentally benign biotechnology-based approaches for production of plastics, fibers, textiles, and a myriad of other chemical and consumer industry products.

A strong, coordinated Federal program for biotechnology research and development including manufacturing and bioprocessing will ensure that these advances are rapidly translated into commercial products which will play a pivotal role in the world's economic growth through the end of this decade [5,6]. Federal funding during this time must focus on the following key areas: (1) developing improved tissue engineering and cell culture techniques to produce, characterize, and demonstrate the potential of novel biomaterials for use in living systems; (2) developing stable biosensors that will work reliably in bioreactors, separation columns, and living tissues; and (3) developing methods for scale-up and process control and monitoring in order to foster a more rapid turnaround from product discovery, through process concept, and finally to pre-commercial pilot production.

BIOMATERIALS AND MEDICAL DEVICES

Biotechnology Applications

In general, a biomaterial can be considered as any material that is used in the body to achieve a diagnostic or therapeutic purpose. The definition of a biomaterial has changed over the years as new technologies have become available and as our knowledge of the body's functioning at a microscopic and macroscopic level has increased. For example, the former emphasis on the use of synthetic materials with the characteristics of inertness relative to host tissue has evolved to a desire for bioactive materials that respond to host tissues, such as being reabsorbed (as with bioabsorbable sutures). The incorporation of functionally specific molecules, such as growth factors and extracellular matrix components, furthers this concept of bioactivity by creating material surfaces that modify cellular responses to the implant.

Early clinical applications of medical implants range from the heart pacemaker, heart valve, and artificial hip replacement, to denture bridges and silicone implants. Other products currently available or under development include cardiovascular replacements such as vascular grafts, left ventricular assist devices, drug pumps, intraocular lenses, synthetic oxygen carriers, bone and joint replacements, and soft tissue augmentation materials.

The types of inorganic materials currently used in medical implants include metals, ceramics, polymers, and composites. Biologically derived materials include porcine heart valves, bovine carotid artery, reconstituted collagen and/or elastin, hyaluronic acid, and chondroitin sulfate.

Although many of the materials currently in use are functionally adequate, they are not optimal and have associated with them a number of chronic problems. Most of these problems involve issues of poor biocompatibility, with the present materials eliciting biodegradation, calcification, and cellular degradatory responses, as well as immune responses, thrombus formation, and hyperplasia. In addition, the materials can be subject to the leaching out of toxic agents and can increase susceptibility to infection.

Abundant clinical experience with implanted medical devices has demonstrated that natural materials which more closely resemble the human host may be more biocompatible. The use of processed natural tissue from different animal species as well as extracted and reprocessed animal tissue constituents has been successful to some extent in meeting this need. However, biotechnology-derived materials that achieve a high degree of homology with the host, as well as hybrid artificial organs, offer the possibility of resolving, to varying degrees, many of these biocompatibility issues.

Biotechnological approaches towards the creation of these replacement systems include the design and fabrication ex vivo of functional macromolecules, protein-lipid pores, membranes, and ECM constituents. These components can be isolated from cells, synthesized in vivo (e.g., by microorganisms), or synthesized chemically. The cloning and modification of genes encoding the monomers of biopolymer chains can produce entirely new types of biologically synthesized copolymers.

These developments are dependent upon significant contributions from the interdisciplinary field of biomolecular materials, which resides at the interface of biology and materials research and encompasses the biological fields of biochemistry, biophysics, molecular biology, cellular biology and chemistry, and the physical science fields of physics, engineering and materials science. Biomolecular materials include natural and synthetic substances with chemical, electrical, optical, structural, and interfacial properties that use or mimic biological phenomena.

Tissue Engineering

Tissue engineering has emerged over the past 10 years as a new technology that uses the

concepts and tools of biotechnology, cell biology, materials science, and engineering in understanding structure–function relationships in mammalian tissues [7,8] and in the development of biological substitutes to restore, maintain, or improve tissue function.

Human skin cells were the first differentiated cells to be maintained successfully as an engineered tissue. Scientists have since demonstrated the potential for growing virtually any tissue or organ in culture, including skin, blood vessels, bone, cartilage, nerve, oral mucosa, bone marrow, liver, and pancreatic cells. Growing cells in culture in two-dimensional monolayers enabled the study of cellular processes and allowed the possibility of genetic manipulation. Scientists have now begun to use three-dimensional cell culture techniques in which the extracellular environment of the cells can influence not only cellular products, but also cellular differentiation processes. Advances in the study of growth and tissue regeneration, at both the tissue and cellular levels, have added further information.

Engineered tissue consists of living cells in conjunction with a matrix material to provide scaffolding or support which can be integrated ultimately into the host as a hybrid artificial tissue or organ. The function of the material relies on its capacity to induce undifferentiated tissue stem cells to differentiate, to maintain the differentiated state, and to remain immobilized at the desired location. The matrix may be either biological or synthetic in origin. Natural materials can be remodeled or reabsorbed during host restructuring, while artificial ones can be synthesized that degrade into lower molecular weight components (synthetics based on chemical bonds such as esters and anhydride that are easily degraded by water). Both biocompatible biological and synthetic constituents can be engineered to induce specific interactions with host tissues. While no specific engineered tissue product has yet been approved by the FDA, products under development include interactive wound and burn dressings and artificial cartilage.

Encapsulated Cellular Implants

Encapsulated cell therapy is a method by which one replaces cells within the body that have been destroyed by disease in order to augment circulating or local levels of the deficient molecules. Possible uses include the implantation of islets of Langerhans cells to treat diabetes, of dopamine-secreting cells to treat Parkinson's disease, and of catecholamine- or enkephalin-secreting cells to treat chronic pain.

An encapsulated cell implant consists of cells that secrete the desired hormones, enzymes, or neurotransmitters, enclosed within a polymer capsule implanted into a targeted site within the host. The capsule wall is designed to allow passage of small molecules (glucose and other nutrients, as well as the therapeutic molecules) and to retard the passage of large molecules (e.g., elements of the immune system). Data from animal studies suggest that the functional activity of secretory cells is maintained in vivo (Lysaght et al., page 196, this issue). In vivo animal data suggest that the transplanted cells are protected from destruction by the host's immune system, allowing the use of unmatched allogeneic, or even xenogeneic, tissue without systemic immunosuppression of the recipient. The limited supply of donor human tissue and the toxic effects of immunosuppressive drugs required to prevent rejection of conventional transplants are two of the difficulties that preclude widespread transplantation into humans. Both limitations may be overcome by the use of the encapsulation method.

Developing this technology for human use requires careful selection of each of the three major components of the implant: the capsules or membrane material, the intracapsular milieu, and the cells themselves. Prototypical implants may then be tested in animal models of the disease and in humans. The FDA has recently published a Points to Consider document on cell therapy, which alludes to the use of a variety of animal sources for tissue transplantation [9]. This and genetically engineered human cells offer new possibilities for treating disease by cell therapy [10,11].

Impact on Public Health and Medical Practice

Biomaterials have already had an impact on public health by correcting some of the physical problems associated with aging, chronic diseases, autoimmune disorders, and traumatic injury. Current research in biotechnology and biomaterials is likely to lead to the development of products that could return hundreds of thousands of individuals to productive, satisfying lives while saving billions of dollars in annual medical costs, and at the same time fueling economic growth in the biotechnology sector.

Parkinson's disease is a familiar example of a chronic condition for which present therapies are inadequate. Current drugs seldom restore full function, provide only temporary respite, and produce detrimental side effects due to their nonspecific delivery. Encapsulation technology (Lysaght et al., this issue, p. 196) may enable the simultaneous delivery of several different dopaminergic agents to their desired site(s) of action. In addition, the ability to use xenogeneic cells or tissue in an encapsulated cell implant may overcome the limitations imposed by inadequate amounts of human tissue, especially of fetal cells.

Similar benefits are also likely to be realized with diabetics. Recent studies with insulin-responsive diabetes have shown that more frequent dosage with lower amounts of insulin produces fewer serious side effects. A more desirable insulin administration protocol could be achieved by using biomaterial-incorporated controlled-release forms of insulin, or by the use of transplanted or encapsulated islet cells. Furthermore, diabetics frequently develop nonhealing ulcerations. The article by Pierschbacher (this issue, p. 150) describes the use of extracellular matrix proteins or their derivatives for inducing wound healing.

Improved healing of bone fractures and increased biocompatibility of implanted artificial joints may also be addressed through advances in biotechnology and biomaterials. The article by Reddi (this issue, p. 192) presents the possibility of using biotechnology-derived factors to stimulate differentiation leading to cartilage and/or bone formation. An article by Ducheyne outlines the possibility of administering nonbiological materials that will have a synergistic effect with factors inducing differentiation. These methods may aid the healing of fractures by reducing the rate of nonunion. In addition, bone-inducing factors can be delivered with a supporting artificial matrix in order to foster the healing of joint implants.

Finally, the article by Ziegler and Nerem (this issue, p. 204) describes progress in the development of tissue engineered blood vessels. In patients requiring multiple bypass surgeries, autologous blood vessels are frequently unavailable, and existing artificial materials are limited by such factors as vessel diameter.

KEY ISSUES RAISED BY BIOTECHNOLOGY APPLICATIONS IN BIOMATERIALS

Scientific and Clinical Issues

Given the complex nature of biomaterials, which may be composites of biotechnology-derived components of human and/or animal origin and synthetic materials, evaluation of preclinical models for biomolecular materials is probably best treated on a case-by-case basis. This allows individualized consideration of the unique risks posed by a potential product. Such an assessment in turn facilitates the proper design of testing protocols, including the best choice of an animal model, where appropriate.

Since the increased biocompatibility of these new materials will derive in part from their mimicking of human tissues, it is unclear whether animal modeling prior to initial human trials is appropriate. Animal models may not be appropriate for the evaluation of humanized biomaterials and, with the possible exception of primates, may not provide meaningful information regarding their effectiveness. Furthermore, the increased effort to create analogous products solely for the purposes of animal testing could introduce additional costs and delay or render unfeasible the development of new biomaterial therapies.

Regulatory Issues

More than a dozen companies responding to a survey conducted specifically for this Workshop expressed a unanimous desire for guidance from the FDA concerning various issues raised by biomaterial implants (to be reported in a future issue of the Journal). While applauding the FDA's efforts to produce such guidance documents as "Points to Consider," these companies also noted the inadequacy of these documents in clearly specifying what experimental evidence constitutes compliance. This concern suggests that there must be improved communication between companies and the FDA, possibly through joint scientific workshops.

RECOMMENDATIONS

Participants in the Workshop on Biotechnology Applications in Biomaterials, together with the Organizing Committee (see Biotechnology Applications in Biomaterials, this issue, p. 143), summarized the topics of the Workshop and developed the following informal recommenda-

tions to address the issues raised by biotechnology-derived materials and to guide follow-up activities. These recommendations cover those areas, including research directions, funding and resources, and regulatory and coordination initiatives, that participants believe to be necessary for continued progress.

Research

There are several areas of research relating to biomaterials where emphasis in both the public and private sectors may speed the development of health care products. In addition, while this field is highly interdisciplinary in nature, there as yet exist no formal lines of communication between materials scientists and cell biologists to facilitate the determination of research needs in the various contributing sciences.

One such area that should be a high priority for the biomaterials community is the determination of all the major and minor extracellular matrix components and their interactions which lead to the assembly of supramolecular complexes. The existence of the amino acid RGD motif, elucidated by Pierschbacher and Rouslahti and important in molecular recognition in the matrix (Pierschbacher, this issue, p. 150), underscores the need to discover the remaining recognition motifs of the matrix constituents. Substantial interaction between scientists in several fields and with various federal agencies will be required to coordinate progress in this area. In addition, there should be a similar initiative to aid the development of large animal models to support preclinical testing of human matrix materials as a prelude to human trials.

Stem cell research is a second major area that should be emphasized by the biomaterials research community. The ultimate goal of creating organs and tissues ex vivo will require the production of stem cells in industrial quantities. Progress has been limited to date to hematological/immunological stem cells. It is likely that optimal homeostatic interactions between implant cell and the host for certain conditions will occur only with human-derived cells, despite advances with encapsulated, xenogeneic cells. Such efforts will require input from cytokine and matrix research as well.

Another essential research area involves the determination of those molecules involved in cell homing and cell–cell contact, which could be important in the delivery of replacement cells. These interactions might be particularly critical in cell replacement therapy for the nervous system for the treatment of neurodegenerative disease.

Regulatory Initiatives

In order for new developments in biotechnology applications in biomaterials to be rapidly transferred into commercial products, good communication both within the FDA and between the FDA and industry are essential for the timely assessment of these products' safety and effectiveness. The pace of change is so dramatic that cooperation between the various funding agencies, the FDA, and industry is critical for facilitating regulatory compliance. Early interaction with the FDA in the process of evaluating a new medical device can help to resolve problematic issues before they become impediments to approval. The burden of responsibility for a product's design, manufacture, and quality control, lies with the product's sponsor who must adhere to the principles of Good Manufacturing Practices, and perform the proper laboratory and clinical testing.

The FDA evaluates products on a case-by-case basis and decisions are based on the validity and reliability of the scientific evidence. As biotechnology progresses and new technologies emerge, the FDA must determine (1) the type of information needed for developing regulatory guidance, and (2) the specific type of guidance most useful both to manufacturers and to the FDA reviewers. The following initiatives are suggested as potential approaches to addressing these issues.

Standards Setting and Regulatory Guidance

The FDA develops different types of guidance for the regulated industry. Historically, Points to Consider documents, such as the FDA Points to Consider for Monoclonal Antibodies, have been helpful in providing general guidance to the industry for products using a particular approach or technology. Such guidance, which can be updated as improvements in the technology require, contains a description of elements important for consideration in product development and, as such, would be important for the continued development of biotechnology-derived biomaterial applications. These elements include the manufacturing procedure, characterization of the product, performance evaluation, and tests of safety and effectiveness.

In addition, there is a need for specific guidance for particular types of products such as the 1993 FDA Draft Guidance for the Preparation of an IDE Submission for an Interactive Wound and Burn Dressing. Guidance documents are made available readily to those who contact the FDA's Center for Devices and Radiological Health (CDRH) Electronic Docket (1-800-252-1366). There is a need for continued development of such guidance as, for example, the use of recombinant DNA technology in the manufacture of biomolecular materials and the use of human cells with synthetic or naturally derived matrices for the manufacture of tissue substitutes. To ensure that the industry collects pertinent data in support of product submissions, the application of ongoing FDA guidance to the specific design and analysis of appropriate in vitro, in vivo, and in situ studies is important. Guidance on clinical study design, as described in the 1993 FDA Final Report of the Committee for Clinical Review [12] and in the Draft Clinical Trial Guidance for the Diagnostic Class III Medical Devices, and the application to novel biomaterial product applications, would include information on appropriate control groups, sample sizes, characterization of individuals in the study, comparability of treatment and control groups, and the definition and blinded evaluation of end points.

In order to assist regulatory, academic, and material scientists with regard to appropriate tests on materials relevant for various applications, a prototype biomaterials compendium is being developed. This FDA Biomaterials Compendium is envisioned as a series of linked databases that will provide a single source of information for implantable devices with various related characteristics. The manufacturing processes, materials used in the manufacturing of a device, the properties of the materials used, clinical performance, and biological performance are samples of the information that will be available. The project is being developed in phases, where the first phase is a materials/devices identification table.

Additionally, a national initiative for Implant Retrieval and Analysis responds to the public perception of data deficiency for reporting information from implant usage. A preliminary organizational meeting[1] on the design criteria for such a system, termed the National Implant Data System, highlighted the need for interaction among the seven key parties involved, i.e., patient, physician, manufacturer, treating institution, insurer, regulatory agency, and society-at-large. The information would be interactive with such databases as the Biomaterials Compendium and would emphasize the interplay among the device materials and clinical outcome.

Standards for biotechnology-derived biomaterials should be developed through cooperation with the appropriate existing standards and industrial organizations, such as the American National Standards Institute (ANSI), American Society for Testing and Materials (ASTM), and International Standards Organization (ISO). The appropriateness and necessary modifications of existing standards, related to the special properties of these materials, will be considered, relative to the degree to which they impact safety and effectiveness of the resultant products.

It is also recommended that federal agencies (e.g., NIST, NSF, and NIH), industry, and research and development groups cooperate to propose and develop performance evaluation criteria and standards with sufficient flexibility for the FDA and industry to apply to products emerging from the rapidly changing biotechnology–biomaterials field. Continued development of documents guiding the FDA staff in reviewing these products is also essential.

Finally, established, ongoing FDA post-market surveillance programs should be applied to novel biomaterial device applications. These would include, among others, safety conferences for concerns in certain device areas, safety alerts, and public health advisories for the health care community. A centralized, easily accessible repository of information to adequately identify problems associated with biomaterial applications is needed. The information would include any adverse reactions noted during preclinical and clinical trials as well as post-market. Information on failed products could also be important for problem solving and technology improvement.

Evaluation of Novel Biotechnology–Biomaterials Products Data and Information Monitoring

It is recommended that FDA incorporate materials and their biological constituents into established Agency databases in order to monitor research and development activity, product submission by type and clinical indication, and any

[1]Notebook from "Planning Conference on Management Requirements for a National Implant Data System," April 9–12, 1994. Hyannis, MA, Society for Biomaterials, Minneapolis, MN.

adverse reactions throughout a product's development and marketing. Such a database would provide important information in such areas as (1) current and developing biotechnology methods, (2) present and future clinical indications, (3) product volume and industry growth, (4) general economic and market data, and (5) safety and effectiveness evaluation criteria. This information would serve as a resource for the development of guidance documents and for guiding regulatory strategy and decision making.

Safety and Effectiveness Criteria

In order to continue the development of appropriate regulatory evaluation paradigms for novel biotechnology-derived biomaterial products, criteria for safety and effectiveness must be established. It is recommended that these be prepared and developed through a consensus approach between the public and private sector with appropriate representation and involvement by FDA, other Federal agency staff, regulated industry, and advisory groups.

To guide the development of appropriate safety and effectiveness criteria and risk–benefit analysis, the following parameters should be considered: (1) host cell–biomaterial interactions, (2) overall biocompatibility, (3) metabolic disposition, (4) inflammatory and immunological responses, (5) toxicity, (6) mutagenicity, (7) carcinogenicity, (8) susceptibility to infection, (9) transmission of adventitious agents (including the spongiform encephalopathy agents), and (10) sterilization procedures. Test methods for these parameters should also be agreed upon and verified.

The selection of the criteria of a product's effectiveness is to some degree dictated by the individual product, the manufacturer's claim, and its intended use. However, the appropriate design of in vitro, in vivo, and clinical studies—including the rationale for study selection, end points, measurement, and analysis [12]—is fundamental to product assessment.

Training and Education

The field of biotechnology-derived biomaterials is highly interdisciplinary, and training programs should continue to be developed for FDA staff through Agency staff colleges or other means that reflect this complexity, including specific training in immunology and materials science technology. Since the technology will affect at least three different FDA Centers, either in the form of regulated products or in processes for use in the manufacture of regulated products, Agency-wide training efforts related to the technology and product applications should be strengthened. In addition, the mechanism developed for multidisciplinary review of these cross-discipline products should continue to be refined and updated as needed. Workshops, conferences, and/or tutorials should continue to be sponsored with the participation of FDA, other relevant Federal agencies, industry, academia, and professional societies, in order to share information on research and development, product safety and effectiveness issues, and regulatory requirements.

Funding and Human Resources

During the past 15 years, reports from both the public and private sector have articulated the critical elements in fostering the biotechnology industry's growth while successfully translating biotechnology research into products for improving public health. It is clear that biotechnology's contributions to the health care field in the United States during the 1980s would not have been possible without Federal funding through the prior three decades of investigator-initiated research in such fields as molecular and cell biology, bioengineering, and other disciplines. Much of this research was supported by the NIH and, to some extent, by the National Science Foundation (NSF).

The Federal government now needs to support interdisciplinary research as the nature of problems and ideas becomes more complex. Such enterprises as the newly formed National Institute of Science and Technology (NIST) Consortium on Advanced Biosensors and the NSF-sponsored bioengineering centers, which address problems of product scale-up and bioprocessing, are examples of the focus needed to assure continued progress. Industry is just beginning to apply biotechnology to a wide spectrum of manufacturing processes including the manufacture of pharmaceuticals, and biomolecular materials for health care, such as the biosynthesis of fibers (silk and cellulose), adhesives from acquatic environments, and bioceramics.

While there has been a general improvement in the transfer of technology from the bench to industry, further improvements are needed. A number of Federal programs have been developed for facilitating technology transfer, including: (1) the Small Business Innovation Research

(SBIR) program, which each agency has in place for supporting proposals according to its particular mission; (2) the Cooperative Research and Development Agreement (CRADA), which is being used increasingly between government agencies and industry to explore research projects with commercial potential, with the latter providing part of the support; and (3) the Advanced Technology Program (ATP), operated by NIST, which supports proposals that have commercial possibility. There are also a number of academic, industry, and state government cooperative programs in at least twenty or more states.

Because of the recognized technological importance of biotechnology, and the need to maintain and strengthen the leadership role of the United States in this field [5,6], the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), as part of a Budget and Planning Crosscut Initiative in biotechnology in 1991 and 1992, convened the 12 different federal agencies that fund biotechnology programs in order to categorize, analyze, and coordinate their support of basic science research, research into the social impact of biotechnology, and their infrastructure. The areas of focus included those of agriculture, energy, environment, health, and manufacturing/bioprocessing, and the general scientific foundations of biotechnology.

This initiative accomplished the following: (1) the generation of the first comprehensive description of biotechnology research across the 12 federal agencies involved, (2) the formulation of national goals, objectives, and strategies in biotechnology; (3) the construction of a framework for categorizing biotechnology research programs; (4) the creation of an inventory of existing biotechnology programs; (5) the development of preliminary recommendations for implementation of the proposed strategies; and (6) the projection of budgets based upon various funding options. The strategic framework and priorities of this initiative will guide the continuing Federal effort to ensure a solid base of science and engineering research in this critical technology.

In 1993, the FCCSET Biotechnology Research Initiative concentrated on biotechnology programs in human health and the environment, seeking to direct a more focused and selective multiagency emphasis in a few key areas of biotechnology. In-depth review and planning are specifically addressing problems and opportunities in the areas of manufacturing/bioprocessing, energy, and agriculture [13]. It also addresses goals listed in "Technology for America's Growth" released by the U.S. administrative branch [14].

The FY 1993 Federal budget supported manufacturing/bioprocessing research programs in eight Federal agencies. For example, the varied manufacturing and bioprocessing research programs of the NSF will be strengthened. NSF's programs to explore the interactions between fundamental biology, biochemistry, and engineering, and its program to investigate the molecular properties of biological materials, will be accelerated. An important effort at the NIH will be the investigation of the structure, function, and design of molecules and processes for use in health care.

Research needs for manufacturing/bioprocessing include (1) understanding the relationships among enzyme structure, function, and energetics so that proteins can be engineered for particular end uses; (2) modeling techniques for drug and biomaterial design, and for understanding the interaction of proteins with their environment and at the biomaterial–host surface interface; and (3) better techniques for tissue engineering, cell culture, and especially stem cell culture, in order to produce biomaterials and replacement tissues.

Finally, other areas of strategic importance to biotechnology research, development, and commercialization include interdisciplinary training, information science, social impact research, and technology transfer. If biotechnology research is to continue to progress, it will need a continuing supply of new scientists trained in both fundamental research disciplines and interdisciplinary approaches to research. To meet these cross-discipline research needs, physical plants and specialized instrumentation must be designed and developed.

Equally important is the development, management, and cataloging of databases and information resources that are essential for biotechnology research. For example, the nucleic acid and protein sequence databases are more than mere repositories of information—they are unique resources amenable to repeated examinations which will continue to yield valuable new insights, discoveries, and technical breakthroughs.

Social impact research seeks to understand the social, cultural, ethical, economic, and legal implications of biotechnology research and its

numerous applications. For example, there are currently social impact research programs sponsored by the NIH Human Genome Project, the Recombinant Advisory Committee, and the NSF. Biotechnology is likely to have ramifications well beyond its techniques and products, including effects in such diverse areas as: education and communication; personal and cultural beliefs; professional behavior; research practices; issues of privacy and confidentiality; patenting and intellectual property; technology transfer; the economic impact of regulatory processes on industries; and international competitiveness.

Lastly, the FCCSET has recognized the need to establish and maintain mechanisms that will facilitate the timely transfer of information form Federally supported biotechnology laboratories to the private sector. The Technology Information Working Group has been formed to learn more about existing barriers to the movement of technology. A survey of biotechnology trade associations will be used to develop a strategy for fostering technology transfer. A centralized, publicly available database of information on Federally supported biotechnology research will be established, perhaps as part of the current services operated by the National Technical Information Service. The formation of a National Technology Transfer Center is also being considered.

All Federal agencies participating in the FCCSET Biotechnology Crosscut Initiative support programs commensurate with their mission. Because of their important responsibilities in regulatory decisionmaking, technology transfer, and biomedical research support, the programs of the FDA, NIST, NSF, and NIH are described briefly in the appendix.

Coordination and Cooperation Among Government, Academe, and Industry

The FCCSET Biotechnology Initiative has much in common with other FCCSET Initiatives such as the Materials Crosscut. To address the needs and opportunities in materials, the Federal government initiated in FY 93 the Advanced Materials and Processing Program (AMPP) to increase the effectiveness of the Federal research and development program in Materials Science and Technology. The AMPP is a multiyear, interagency effort involving ten Federal agencies coordinated by FCCSET. This program is based on the recognition that materials science and technology are crucial to the U.S. future. The goal of the AMPP is to improve the manufacture and performance of materials to enhance the U.S. quality of life, national security, industrial productivity and economic growth.

Much of the background for this government-wide initiative came from the private sector through a series of comprehensive and broad-based studies. The 1989 report by the National Research Council, "Materials Science and Engineering for the 1990s: Maintaining Competitiveness in the Age of Materials" [15] and the four regional meetings concerned with implementation of that study, had strong industrial, academic, and government input. In 1991 an in-depth cross-cut analysis of the Federal materials research and development effort was conducted by the Committee on Industry and Technology (CIT) of FCCSET. These concerted efforts within and outside of government resulted in the formation of the AMPP.

The AMPP is a goal-oriented program built upon a planning framework of designated research components, strategic objectives, and implementing priorities. These priorities include planning Federal research and development to address problems of interest to industry, as well as promoting the application of advanced materials and processing through cooperative efforts. Success in these endeavors will require cooperation among government, academia and industry.

Highlights of the technical milestones for the current AMPP initiatives in Biomaterials and Biomolecular Materials are incorporated in this Viewpoint. Additional program-specific milestones are listed in the FCCSET publication "Advanced Materials and Processing: The Fiscal Year 1993 Program" [16].

STRATEGIES FOR THE FUTURE

Cooperation of public and private sector groups in developing the Workshop on Biotechnology Applications in Biomaterials has proved to be a good beginning for articulating the needs and developing the strategies for future interaction between government agencies, academia, technical societies, and industry in the field of biotechnology-derived biomaterials. Such cooperative programs will contribute to the full realization of the novel products of these emerging technologies. These efforts will yield a variety of clinical products and devices that will fulfill important clinical needs. The FCCSET Initiatives

in Biotechnology and Materials Science together with the Workshop on Biotechnology Applications in Biomaterials represent the beginning of an ongoing dialogue among scientists, administrators, and policymakers.

As an outgrowth of the Workshop on Biotechnology Applications in Biomaterials, the Biotechnology Special Interest Group of the Society for Biomaterials is developing initiatives related to the safety and effectiveness issues of biotechnology-derived biomaterials. Future symposia and industry/regulatory/scientific societies networks are being established to codify this new science and to highlight the significant issues. Some of the strategies for the future will be developed with this group.

The issues identified in the Workshop and articulated in this report must be resolved if novel biotechnological approaches are to be transferred into products in a timely and effective manner. It is recommended that a series of conferences be initiated to further the goals and develop consensus on issues identified in this Workshop. The establishment of an Advisory Task Force, made up of representatives of relevant private and public sector groups, might help in fostering these goals. This task force would (1) facilitate dialogue about advances in biotechnology and their applications in biomaterials and their effect on regulation and standards setting; (2) propose regulatory guidance for evaluating safety and effectiveness; and (3) propose policies regarding performance evaluation criteria, quality assurance, and post-market surveillance. Once established, the Advisory Task Force could serve as a coordinating body among the participating groups for future scientific and regulatory policy development in the field of biotechnology biomaterials.

REFERENCES

1. U.S. Congress, Office of Technology Assessment (1984): "Commercial Biotechnology: An International Analysis." OTA-BA-218, Washington, DC: U.S. Government Printing Office, p 3.
2. Olson S: "Biotechnology: An Industry Comes of Age." Washington, DC: National Academy of Sciences, National Academy Press, 1986.
3. Ernst and Young (1993): "Biotech '94: Long-Term Value, Short-Term Hurdles."
4. Putting Biotechnology to Work (1992): Bioprocess Engineering; Report of the Committee on Bioprocess Engineering. Washington, DC: National Academy of Sciences.
5. Biotechnology for the 21st Century (1993): Realizing the Promise, A Report by the Committee on Life Sciences and Health of the Federal Coordinating Council for Science, Engineering and Technology. A Supplement to the President's Fiscal Year 1994 Budget, June 1993. U.S. Government Printing Office, Superintendent of Documents, Mail Stop. Washington, DC: SSOP.
6. Biotechnology for the 21st Century (1992): A Report by the Committee on Life Sciences and Health of the Federal Coordinating Council for Science, Engineering and Technology, February 1992. U.S. Government Printing Office, Superintendent of Documents, Mail Stop. Washington, DC: SSOP.
7. Edgington SM (1992): 3-D Biotech: Tissue Engineering. Bio/Technology 10:855–860.
8. Bell E (1991): Tissue Engineering: A Perspective. J Cell Biochem 45:239–241.
9. Food and Drug Administration (1991): "FDA Points to Consider in Human Somatic Cell and Gene Therapy." Rockville, MD: FDA.
10. Kessler DA, Siegel JP, Noguchi PD, Zoon KC, Frieden KL, Woodcock J (1993): Regulation of somatic cell therapy and gene therapy by the Food and Drug Administration. N Engl J Med 329:1169–1173.
11. Federal Register Notice (1993): Docket No. 93N-0173. Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products. Vol. 58, No. 197, pp 53248–53251.
12. Food and Drug Administration (1993): "Final Report of the Committee for Clinical Review." Rockville, MD: FDA.
13. Biotechnology for the 21st Century (in press): New Frontiers. A Report by the Committee on Fundamental Science of the National Science and Technology Council.
14. Technology for Economic Growth (1993): President's Progress Report.
15. Mueller EP, Barenberg SA (1989): Biomaterials in an Emerging National Materials Science Agenda, in National Research Council Report, Materials Science and Engineering for the 1990s: Maintaining Competitiveness in the Age of Materials. Washington, DC: National Academy Press, pp 86–87.
16. Advanced Materials and Processing: The Federal Program in Materials Science and Technology, A Report by the Committee on Industry and Technology of the Federal Coordinating Council for Science, Engineering, and Technology, A Supplement to the President's Fiscal Year 1993 Budget, 1993, Committee on Industry and Technology/COMAT, % National Institute of Standards and Technology, Room B309, Materials Building, Gaithersburg, Maryland 20899.
17. J Biomech Eng 113(2): 1991.
18. Langer R, Vacanti JP (1993): Tissue engineering. Science 260:920–926.
19. Skalack R, Fox CF (eds) (1988): "Tissue Engineering" UCLA Symposia on Molecular and Cellular Biology, New Series. New York: Wiley-Liss.
20. J Cell Biochem 45:239–283.
21. J Cell Biochem 45:317–365.

APPENDIX: FEDERAL PROGRAMS IN BIOTECHNOLOGY AND MATERIALS

FOOD AND DRUG ADMINISTRATION

As "gatekeeper" for entry of products into the marketplace, the FDA has an important role in

furthering the commercialization of biotechnology. The FDA, as a scientific regulatory agency, is responsible for ensuring that drugs, biological products, medical devices, and diagnostic products are safe and effective; food is safe and wholesome; cosmetics are safe; the use of radiological products does not result in unnecessary exposure to radiation; and that all of these products are honestly labeled and honestly advertised. To accomplish these activities, FDA maintains up-to-date expertise in many scientific areas with a goal of developing rapid, accurate, sensitive, and reproducible methods that can be applied to evaluation of product safety and effectiveness.

For many FDA research programs, the personnel responsible for laboratory research also perform evaluations of applications to market products. The pharmaceutical, device, and food products of the new biotechnology are rapidly filling the review pipeline at FDA. Biotechnology has had a significant impact on pharmaceuticals and medical device development, resulting in a variety of biotechnology-derived therapeutics and vaccines as well as biomaterial-based and biosensor products, drug delivery, and extracorporeal perfusion devices. Existing and new biomaterials are being increasingly incorporated into medical devices such as implants, prostheses, and biohybrid devices, such as encapsulated cellular transplants. It has been the FDA's view that, to sustain the commercialization of innovative biotechnology products, the agency must continue to maintain and support the necessary science and research base in order to evaluate the safety, effectiveness, and quality of these products.

The FDA is committed to enhancing its research capability in biotechnology and the associated enabling technologies in order to address the safety and effectiveness of existing and emerging products and to provide the information needed for science-based regulatory decision-making regarding both premarket approval and postmarket surveillance of products.

Biotechnology research at FDA focuses on the Agency's regulatory responsibilities in five broad areas: therapeutics, vaccines, diagnostics, devices, and food-borne contaminants and toxins. For example, FDA research programs in certain areas of medical devices have focused on the development of in vitro methodology for assessment of cellular and molecular mechanisms of: (1) biomedical materials degradation and performance, and (2) host system-device interactions. These studies have led to the development and optimization of a unique in vitro method for detecting degradative products generated by host cells in response to biotechnology-derived biomedical materials [5,6]. In addition, studies are also underway to elucidate genetically based human variation in metabolic and immune capabilities with the potential for altering the risk of device biomaterials.

The science base for the regulatory review of state-of-the-art innovative products requires further development. This is essential to ensure that products can be properly evaluated for safety, effectiveness, and quality.

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY

The NIST biomaterials program provides generic measurements, models, standards, and data needed for the development and commercialization of novel biomaterials. The natural lipid and protein components of cell membranes are being studied as potential novel biomaterials in the form of liposomes and planar membranes. These self-assembling biomembranes provide very selective control over the passage of chemicals and electrical signals between compartments. Biomembranes have application as components of electronic and sensing devices and artificial organs and drug delivery systems, and for light energy transduction.

New monomer systems that shrink less, are more resistant to oral fluids and have the potential to bond to teeth and other materials, are the object of intense investigation. These monomers may find their applications in improved dental composite restoratives, adhesives, cements, and maxillofacial prostheses. Durability is assessed by the evaluation of properties such as hardness, flexure strength, and wear resistance following immersion in food-simulating liquids.

Studies of the basic chemistry of calcium phosphate compounds as they relate to mineralization, demineralization and remineralization are being pursued. This work has led to a recent development by the American Dental Association Research Associates that has resulted in the licensing of technology applicable for toothpastes and chewing gums that can remineralize teeth.

The analysis of the failure of ceramic and ceramic-metal restorations is being conducted with the objective of defining tougher material

systems and developing more clinically relevant test methods. It employs fractography coupled with Weibull analysis of failures. Finite-element analysis and modeling of these multicomponent material systems is used to identify the states of stress in restorations and model test systems as aids to help design more clinically reliable systems.

Funding for industry to develop new biomaterials is available from the NIST Advanced Technology Program (ATP), which provides technology development grants to single businesses or industrial joint ventures. The ATP will support development of laboratory prototypes and proof of technical feasibility, but not commercial feasibility. Awards to individual firms are limited to $2 million over 3 years and can be used only for direct research and development costs. Awards to joint ventures can be for up to 5 years and are limited only by available funds. NIST funding to joint ventures must represent less than 50% of the total research and development cost. No direct funding will be provided to universities, government organizations or nonprofit independent research organizations, but they may participate as members of an industry-led joint venture.

NATIONAL INSTITUTES OF HEALTH

Biomaterials research, including the application of biotechnology, is supported by many components of the NIH. The research covers the spectrum from basic studies to clinical applications, often in close collaborations with other Federal agencies.

National Center for Research Resources

The National Center for Research Resources provides resources such as spectroscopic techniques, Fourier transform infrared spectroscopy, laser Doppler anemometers, and electron microprobes to enable investigations of biomaterial surfaces by other NIH units.

The National Eye Institute

The National Eye Institute conducts and supports research on biocompatible materials to replace or enhance ocular structures, including research in polymer chemistry, replacement vitreous and aqueous fluids, and controlled drug delivery systems.

The National Heart, Lung and Blood Institute

The National Heart, Lung and Blood Institute fosters research for biomaterials used in cardiovascular, pulmonary and hematological disorders, such as small diameter vascular grafts, an "organoid" composed of biomaterial lattice coated with genetically engineered cells capable of delivering insulin, a more biocompatible blood-contacting surface for lining of artificial hearts and lungs, and artificial oxygen carriers as an alternative to red cells for transfusion.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institute of Arthritis and Musculoskeletal and Skin Diseases supports research on the nature and optimization of porous material/bone interfaces and in biological repair of large defects in bone and joints. Regional programs are under consideration for fabricating of a new generation of orthopaedic materials, including alloys, absorbable polymers, and ceramics.

The National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases supports research and research training to study new drug delivery systems, silicone-containing implants and injections, and how they affect host/implant reactions.

The National Institute of Child Health and Development

The National Institute of Child Health and Human Development (NICHHD) has a biomaterials program focused on contraceptive research and rehabilitation science. Contraceptive programs are planned that involve various advanced materials as potential drug delivery systems or materials for developing new barrier methods.

The National Center for Medical Rehabilitation Research

The National Center for Medical Rehabilitation Research (NCMRR) was established within the NICHHD in 1991 to serve as a focus for medical rehabilitation research at the NIH. The NCMRR supports exploratory studies leading to the development of novel genetically engineered biomaterials, biological products modified for use in stimulating tissue regeneration, and delivery vehicles to supply gene products that maintain function or reduce further injury. Specific areas include coating materials that render implanted devices such as indwelling catheters or

electrodes biocompatible and less likely to produce infection, modified natural products that can serve as scaffolding for tissue regeneration, and implantable or cutaneous biosensors to detect pressure and skin breakdown.

The National Institute of Dental Research

The National Institute of Dental Research conducts research to develop new and improved biomaterials, methods, and technologies for the treatment of dental disease and restoration of dental function, including restorative fillings materials, bonding agents, tooth surface sealants, adhesives coatings and cements, bone augmentation materials, and materials for improved endodontic therapy.

The National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases supports biomaterials research to improve survival and function of transplanted pancreas islet cells, liver cells, bone marrow cells, and ultimately to the development of newly constructed organs from cultured cells and tissue. This Institute is also considering the support of research in biosensing.

The National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke supports biomaterials research in neural prosthetic implants designed to interact closely with neural tissue in the brain and peripheral nervous system to restore function to neurologically impaired individuals. Cochlear implants are being improved by developing electrodes that are smaller and more biocompatible.

THE NATIONAL SCIENCE FOUNDATION

The NSF supports basic research on biomolecular materials encompassing the physical, chemical and self-assembly properties of macromolecules, amphiphiles, metal–organic complexes, as well as composite materials of biological or biomimetic origin. The NSF has an ongoing foundation-wide effort to support research in biomolecular materials in the following areas: (1) genetic or other modification of natural synthetic pathways to produce materials with novel structures, and optical, mechanical, or electrical properties; (2) biomolecular self-organization and phase behavior to develop new materials not found in nature; (3) novel catalyst, sensor, or transducer materials based on biochemical and biophysical processes; (4) materials aspects of in vivo processing of biopolymers and other naturally occurring materials; and (5) complex molecular structures that mimic naturally occurring composites such as bone, muscle, and photoreceptor arrays as well as materials that are biodegradable or recyclable.

The NSF supports research in tissue engineering primarily through the Bioengineering Program within the Engineering Directorate. Much of this is an outgrowth of a NSF sponsored UCLA Symposia Workshop on Tissue Engineering held at Granlibakken, Lake Tahoe, California, in 1988. Subsequently, NSF has sponsored UCLA/Keystone Symposia on a biennial basis, most recently in 1994. Information reported at these meetings has been published in a number of sources ([7,8], [13,14], [19–21]).

ADVANCED MATERIALS AND PROCESSING

To address the critical need for biomaterials that provide longer-term clinical benefit and fewer complications for patients requiring acute and chronic medical implants, the following are recommended: (1) in FY 93, begin development of a National Implant Data Retrieval and Analysis System; and (2) continue in FY 93 with the development of resins systems for dental restoratives with improved properties. Develop a cooperative integrated research and development program to produce the next generation of restorative materials.

To address the need for understanding and developing the production of structural and functional biomaterials using biological organisms, such as bioceramics, biopolymers and fibers (such as silk), bioadhesives, biosensors, and functional molecular arrays (such as light-transducing materials), the following are recommended: (1) the development of new expression systems (including plant systems) to improve both the quality and quantity of "designer biomolecular materials," and improved existing yeast, baculovirus, and vaccinia systems; (2) the establishment of new interdisciplinary research groups at universities; incorporating provisions for coordination and liaison with industry partners; (3) the development of new biosensor and transduction materials using immobilized enzymes (such as bacteriorhodopsin); establishing their feasibility in applications such as information storage technology and in situ monitoring of cell function; and (4) focusing efforts on molecular details of bioceramic nucleation at surfaces and interfaces in

nature; within 5 years, determination of key structural details present in naturally occurring nucleation molecules for application to analogous bioceramic materials; and initiation of studies of long-term stability and efficacy of bioceramic coatings for orthopedic implants.

ACKNOWLEDGMENTS

The authors thank the following individuals for descriptions of Federal agency programs in biotechnology and materials science: Lura Powell, National Institute of Standards and Technology (NIST), Gaithersburg, Maryland 20899; John T. Watson and Danuto Krotoski, National Heart, Lung, and Blood Institute, (NHLBI) (J.T.W.) and National Institute of Child Health and Human Development (NICHHD) (D.K.) National Institutes of Health, Bethesda, Maryland 20892; Fred Heineken, National Science Foundation (NSF), Arlington, Virginia 22230; and Edward P. Mueller, Advanced Materials and Processing Program (AMPP), Center for Devices and Radiological Health, U.S. Food and Drug Administration, Rockville, Maryland 20852.