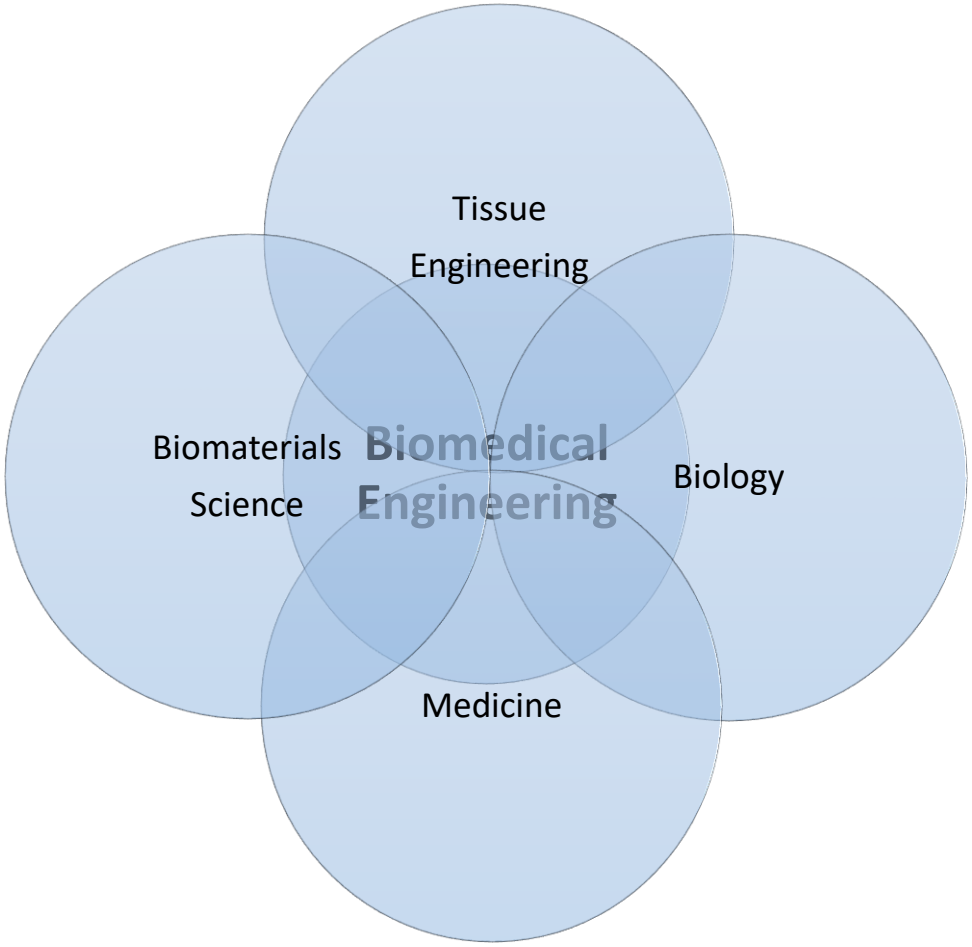
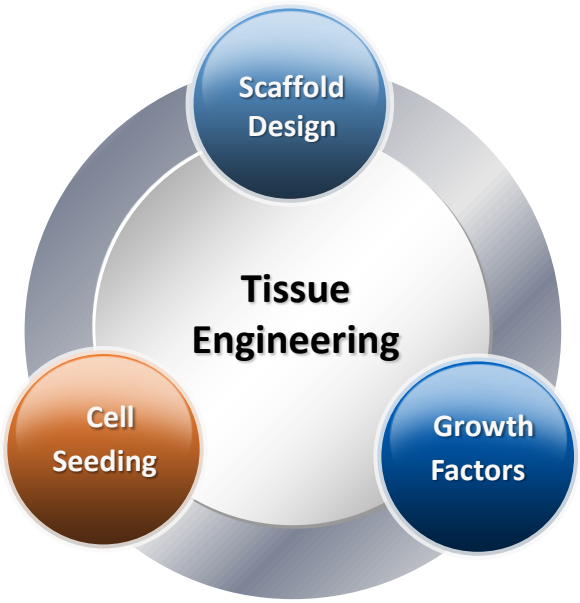
MME 4506 Biomaterials

Ethics in Biomaterials Science


Tissue
Engineering
Biomaterials
Science
Biomedical
Engineering
Biology
Medicine


Scaffold
Design
Tissue
Engineering
Cell
Seeding
Growth
Factors

To understand the factors that have enabled the emergence and rapid growth of tissue engineering, it is helpful to examine its roots in the context of historical developments

Scientific roots of medicine have emerged from the development of the scientific method in the Western tradition

When tissues and organs are damaged by infection, disease, or injury, the first priority has always been the development of methods to salvage life

Infection could be controlled by only drainage of pus until the revolution of antibiotic therapy

With the nineteenth-century scientific understanding of the germ theory of disease and the introduction of sterile technique, modern surgery has emerged

The advent of anesthesia by the mid-ninteenth century enabled the rapid evolution of many surgical techniques

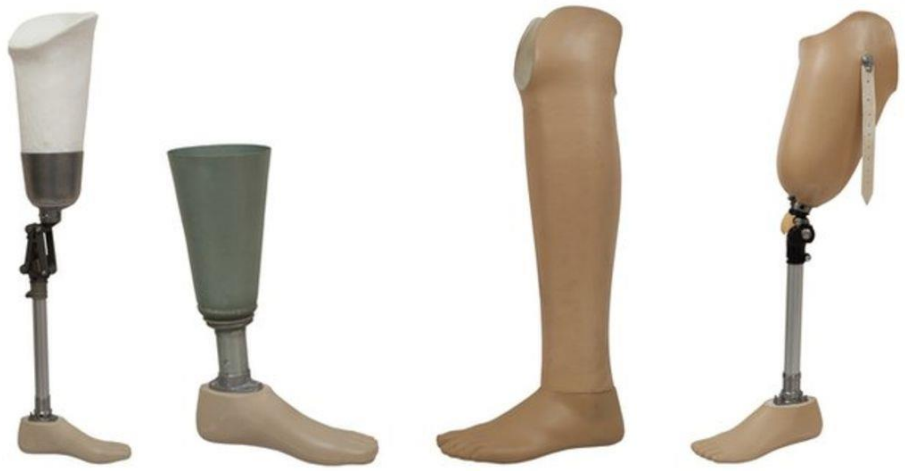
Initially the surgical techniques were primarily destructive

For example, removal of tumors, bypass of the bowel in the case of intestinal obstruction, and repair of life-threatening injuries

Maintenance of life, without regard to the crippling effects of tissue loss or the psychosocial impact of disfigurement, was not an acceptable goal

Techniques that resulted in the restoration of function through structural replacement became integral to the advancement of human therapy

Artificial or prosthetic materials for replacing limbs, teeth, and other tissues resulted in the partial restoration of lost function



The concept of using one tissue as a replacement for another was developed in the same era

With the advent of modern concepts of sterility and anesthesia, whole fields of reconstructive surgery have emerged to improve the quality of life by replacing missing function through rebuilding body structures

In our current era, modern techniques of transplanting tissue from one individual into another have been revolutionary and lifesaving

The molecular and cellular events of the immune response have been understood sufficiently to suppress the response in the clinical setting of transplantation and to produce prolonged graft survival and function in patients

New problems have emerged with new solutions. Techniques using implantable foreign body materials have produced dislodgment, infection at the foreign body/tissue interface, fracture and migration over time

Techniques moving tissue from one position to another position have produced biologic changes because of the abnormal interaction of the tissue at its new location

For example, diverting urine into the colon can produce fatal colon cancers 20–30 years later.

Making esophageal tubes from the skin can result in skin tumors 30 years later.

Using intestine for urinary tract replacement can result in severe scarring and obstruction over time.

Transplantation from one individual into another, although very successful, has severe constraints:

There is not enough access to tissue and organs for all of the patients who need them. Currently, a million people are on transplant waiting lists in the world, and many will die waiting for available organs

Also, problems with the immune system produce chronic rejection and destruction over time. Creating an imbalance of immune surveillance from immunosuppression can cause new tumor formation

These constraints have produced a need for new solutions to provide needed tissue and tissue engineering has emerged within this context

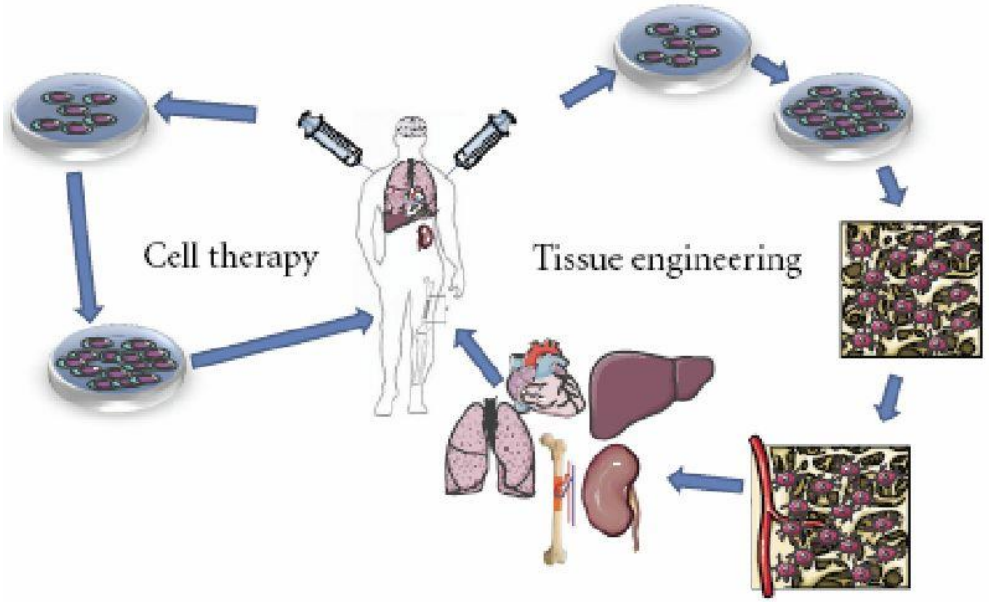
New and functional living tissue is fabricated using living cells, which are usually associated with a matrix or scaffolding to guide tissue development

Living cells can migrate into the implant after implantation or can be associated with the matrix in cell culture before implantation

Conceptually, the application of this new discipline to human health care can be thought of as a refinement of previously defined principles of medicine

Medical doctors have historically treated certain disease processes by supporting nutrition, minimizing hostile factors, and optimizing the environment so that the body can heal itself

In the field of tissue engineering, the same thing is accomplished on a cellular level such that the harmful tissue is eliminated, and cells necessary for repair are then introduced in a configuration optimizing survival of the cells in an environment that will then permit the body to heal itself



In addition to scientific problems related to tissue engineering and human therapy, fundamental issues that are economic, social, and ethical in nature arise

A general problem is funding. Can capitalist dollars be accessed for the purposes of potential new human therapies?

Will industry recognize the potential for commercialization and invest heavily? If this occurs, will the focus be changed from that of a purely academic endeavor?

What role do governmental agencies play as the field develops?

How will the field be regulated to ensure its safety and efficacy prior to human application?

Is a new, engineered tissue to be considered transplanted tissue and, therefore, not subject to regulation, or is it a pharmaceutical that must be subjected to the closest examination by regulatory agencies?

If lifesaving, should the track of regulatory investigation be accelerated toward human trials?

As new knowledge is gained, what becomes ownable through patents?

Who owns the cells that will be sourced to provide the living part of tissue fabrication?

How should regulations change for enhancing biomedical treatments in comparison to preventive therapies?

The challenges in the field of tissue engineering remain significant and success of progress and resolution will rely on the dedication, creativity, and enthusiasm of those who have chosen to work in this exciting field

Biomaterial science can be defined as that branch of biomedical engineering dealing with the material aspects of medical devices and implants

Biomaterial scientists and engineers have played an important role in the design, manufacturing and testing of biomedical devices such as pacemakers, total joint replacement, and artificial organs, all of which have significantly improved the quality of life and the life expectancies of people

However ethical guidelines have been neglected during the technological advancement in biomaterials which caused emergence of new moral and ethical issues

Some of the ongoing ethical issues presented to a biomaterial scientist are:

- allocation of scarce resources
- clinical trials of new devices and implants
- conflicts of interest
- human and animal experimentation

Research issues

Of particular concern to the biomedical engineer are the problems of improper or incomplete testing and product liability, which have resulted in new quality-control standards, institutional review boards and technology assessment requirements being introduced, to prevent danger to the public

Ethical concern in conducting biomaterial research has raised lots of moral issues and is given much importance in the recent years

The scientist involved in research should be aware of their moral responsibilities to the scientific community and to the society

Benefit of patients should be the main motivation in conducting biomedical research in a scientific manner

If ethical duties of a researcher are well defined then regulation of research and conducting it through humane and moral means become possible

A code of bioethics should be embraced in research

The moral code of ethics would serve as a scaffold for the success of a biomedical engineer and would mold the role he plays towards the betterment of the society

Code of ethics is a guide of principles to help professionals conduct their jobs honestly and with integrity

It may outline the mission and values of an organization, how professionals need to approach problems, the ethical principles and the standards to which the professional is held

Two types of codes of ethics are applied in organizations:

- Compliance based: Set out guidelines for conduct and also lay out penalties for violations

In this type professionals usually undergo formal training to learn the rules of conduct and face penalties for failing to follow these because noncompliance can create legal issues for the organization

This type of code of ethics is based on clear-cut rules and well-defined consequences rather than individual monitoring of personal behavior

- Value based: Codes of ethics that are based on the core values of the organization. It discusses standards of responsible conduct as they relate to the larger public good.

This type of ethical codes require a greater degree of self-regulation

The Biomedical Engineering Society Code of Ethics is presented here:
www.bmes.org/files/CodeEthics04.pdf

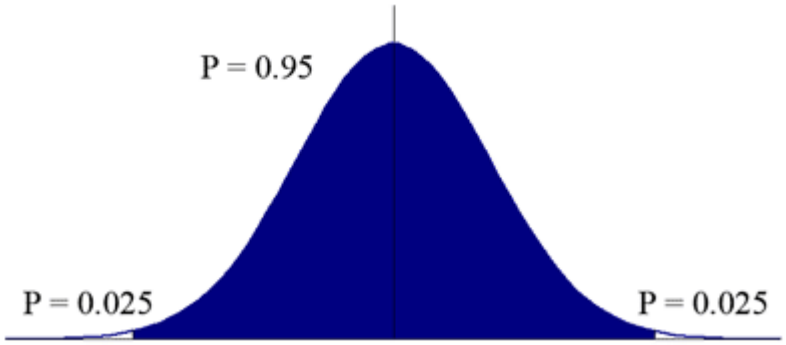
Engineers and scientists are obliged to objectively test the theories, applications and products and to reasonably anticipate all hazards and potential for misuse or accident

A confidence level, a statistically significant level of probability, must be demonstrated within strict standards of research protocol

When engineering studies are submitted for peer review, the methods, data and conclusions are criticized for possible flaws that may cast doubt on the validity of the findings

This same level of scientific idealism is expected for biomaterials scientists too

In fact the rigor of scientific inspection of biomaterials research is intensified due to the application of the engineering advances to patients



Issues related to animal models

A researcher has a moral obligation to provide a degree of humane treatment to animal subjects

Animal experimentations are most commonly used during the development of new implants and medical devices to show their effectiveness before attempts are made to use them in humans

Our knowledge of human physiology has also been largely derived from animal experimentation

Regulatory governmental organizations such as the National Research Council of USA monitor animal welfare strictly and apply a code of conduct on animal research:
www.grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf
www.nap.edu/read/5140/chapter/1

Every effort should be made to minimize the use of animal subjects, to provide for humane handling of animal subjects and to restrict the use if mammals and other higher species

Most biomedical scientists recognize the usefulness of such animal studies, however several radical activist groups have started an antivivisectionist movement

A claim has been made that animals have rights and value equal to those of human beings This would mean that the health and survival needs of human beings provide no moral justification for inflicting harm or risks on animals

If this view is generally accepted, it would place near-insurmountable burdens on research in biomaterials

This point of view leads to the inevitable conclusion that human beings are not justified in exploiting animals for human benefits such as the use of animals as sources of food, clothing, transportation, etc.

As biomedical research is largely supported by public funds, biomaterial scientists and engineers must point to the public the accomplishments of biomedical science and how animal research has contributed to the improvements in the length and quality of human life

Alternative models to animals like computer models and the use of tissue culture may help reduce the use of animals but will not completely eliminate the need for some animal experimentation

Issues related to clinical trials

The research methods of scientists and engineers emphasize the pursuit of knowledge and accuracy of claims

Practicing medical doctors have an addition concern: providing the best care to an individual patient since trust and confidence is placed on the doctor who is expected to be the ally of the patient

Obligations of the therapeutic alliance and demands of scientific evidence often conflict in clinical trials

Randomized double-blind clinical studies are recommended to minimize these conflicts
There is also debate over when and if studies should be discontinued when there appears to be evidence demonstrating substantial advantage or harm

Important considerations in the design of a study are
How and when to obtain informed consent for a study,
The design of a termination strategy into a clinical trial to protect patients,
The right of self-determination of individual patients in their medical care,
The need to have accurate assessment for safe and effective care of larger numbers of people

Biomaterial research is controlled by regulatory organizations such as FDA to ensure protection of human subjects

Institutional review boards are required to determine the risks of subjects, whether the risk/benefit ratio is reasonable and selection of subject equitable
Also a documented informed consent from the subject or his/her legal representative is required, confidentiality of the subject is respected

When using human subjects in research, four basic concepts need to be considered:

- Beneficience – Does the research do good for the individual and all people?

Benefits arising out of the research must outweigh potential harm

- Non-maleficience – Does the research do no harm to the individual or other people?

Benefits should be balanced against potential harm

- Autonomy – Does the individual have the right to make his/her own decisions?

The individual must be told all the information required to make an informed decision, withholding information removes the right to autonomy

- Justice – Does the research treat everyone fairly?

The risks and benefits should be distributed equally among all people

It is seen that rigid guidelines cannot be broadly applied and that studies need to be examined individually in terms of value of the knowledge, available ways for obtaining it, risks involved to the patient subjects, informed consent problems and their impact on the study, and justifications for violating the therapeutic alliance.

Manufacturing issues

A biomaterial may fail in vivo due to numerous reasons varying from engineering defects to biological degradation

Many of the failure mechanisms are not clearly understood. This suggests that adequate warning about the limitations of the product should be well defined

Misuse or reuse of the products should be minimum or if possible should be totally avoided

Biomaterial scientists should evaluate the actual risks involved in the reuse of the implants and should encourage manufacturing companies using them only when appropriate

They should actively contribute towards the reduction of the cost of expensive devices so that the devices could be available to a larger population

Implant type	Knowledge gained/lessons learned
Caged ball valves	• Poppets fabricated from industrial silicone absorbed blood lipids and became swollen and brittle • Fragments of degraded heart valve material may embolize to other organs • Thrombosis can occur at stasis points downstream of the ball
Cloth-covered caged ball valves	• Cloth wear can cause hemolysis and cloth emboli • Cloth wear accompanied by silicone poppet wear can precipitate poppet escape • Healing of fabric may be more vigorous in animals than in humans • Quantitation of data (e.g., polymeric poppet weight and dimensions) may facilitate the understanding of a failure mode
Caged disk valves	• Teflon has poor wear resistance as a valve occluder • Poor design features may potentiate thrombosis
Tilting-disk valves	• Thrombosis may initiate downstream to the edge of a partially open disk at a region of stasis • A "minor" change in valve design can result in a new propensity toward failure • Animal implants instrumented with strain gauges can be used to test a hypothetical mechanical failure mechanism • Understanding a failure mode can lead to both new methods for noninvasive diagnosis (e.g., X-ray and acoustic) and modified patient management strategies (e.g., drugs to depress cardiac contractility)
Bileaflet tilting-disk valves	• Cavitation may cause critical materials damage in some valve designs • Thrombosis may be initiated in regions of microstasis at component junctions • Microscopic areas of stasis may be predicted by computer-assisted computation • Animal implant models may fail to predict vulnerability to thrombosis in humans
Bioprosthetic heart valves	• Tissue calcification is a major failure mode • Calcification is most pronounced in areas of leaflet flexion, where deformations are maximal • Calcification is accelerated in young recipients, especially children • Heart valve calcification can be studied outside of the circulation (e.g., subcutaneous implants in rats) • Calcification is initiated principally at cell remnants deep in the tissue
Cryopreserved allograft valves	• These valves are not viable and cannot grow • Failure is not immunologically mediated and, therefore, immunosuppression is inappropriate
Substitution of new materials	• Pyrolytic carbon has favorable clinical durability • Detailed examination of functional (not failed) prostheses may yield worthwhile data

Conflict of interest issues

Successful biomedical research and applications have brought exponential growth in this research field
Demand and intensified activity have led to an increased need for funds for research
As government funding can not meet the needs of academic researchers, industry funding began, bringing with it ethical issues for the biomedical engineer

The company or the investigator having financial gain from a research can be biased

To avoid this possibility, double-blind studies should be carried out whenever possible

Controversy over conflict of interest issues raised by corporate sponsorship has recently led to disclose funding resources on publications
This requirement has been extended by some journals to include revealing any other associated financial interest and additional bias such as religion

The ability to distinguish right from wrong should be clearly practiced

Biomedical societies should develop guidelines to avoid bias and conflicts of interest between the research investigators and the company involved in such investigation

AdvaMed
Advanced Medical Technology Association

CODE OF ETHICS
ON INTERACTIONS WITH HEALTH CARE PROFESSIONALS

ADOPTED BY THE ADVANCED MEDICAL TECHNOLOGY ASSOCIATION

I. Preamble: Goal and Scope of AdvaMed Code

The Advanced Medical Technology Association ("AdvaMed") represents companies that develop, produce, manufacture, and market medical products, technologies and related services and therapies used to diagnose, treat, monitor, manage and alleviate health conditions and disabilities ("Medical Technologies") in order to enable patients to live longer and healthier liv (collectively "Companies," and individually "Company"). AdvaMed is dedicated to the advancement of medical science, the improvement of patient care, and, in particular, the contributions that high quality, innovative Medical Technologies make toward achieving these goals. AdvaMed recognizes the obligation to facilitate ethical interactions between Companies and those individuals or entities involved in the provision of health care services and/or items t patients, which purchase, lease, recommend, use, arrange for the purchase or lease of, or prescribe Companies' Medical Technologies in the United States ("Health Care Professionals").

Medical Technologies

Medical Technologies are often highly dependent upon "hands on" Health Care Professional interaction from beginning to end—unlike drugs and biologics, which act on the human body b pharmacological, immunological or metabolic means. For example, implantable Medical Technologies are often placed in the human body to replace or strengthen a body part. Surgica Medical Technologies often serve as extensions of a physician's hands. In other circumstances Medical Technologies are noninvasive reagents, instrumentation and/or software to aid in the diagnosis, monitoring and treatment decisions made by Health Care Professionals. Some Medical Technologies work synergistically with other technologies, or are paired with other products that deploy devices in the safest and most effective manner. Many Medical Technologies require technical support during and after deployment.

Interactions with Health Care Professionals

The scope of beneficial interactions between Health Care Professionals and Companies is broa and includes interactions intended to:

- *Promote the Advancement of Medical Technologies.* Developing and improving cutting edge Medical Technologies are collaborative processes between Companies and Health Care Professionals. Innovation and creativity are essential to the development and evolution of Medical Technologies, which often occur outside a Company's laborator

- *Enhance the Safe and Effective Use of Medical Technologies.* The safe and effective of sophisticated electronic, *in vitro* diagnostic, surgical, or other Medical Technologie often requires Companies to provide Health Care Professionals appropriate instructio education, training, service and technical support. Regulators often require this type training as a condition of product approval.

- *Encourage Research and Education.* Companies' support of *bona fide* medical resea education, and enhancement of professional skills improves patient safety and increas access to Medical Technologies.

- *Foster Charitable Donations and Giving.* Companies make monetary and Medical Technology donations for charitable purposes, such as supporting indigent care, as w as patient and public education. This increases access to—as well as the quality of— and treatment in patient populations that may not otherwise be reached.

The Purpose of the Code of Ethics

AdvaMed recognizes that Health Care Professionals' first duty is to act in the best interests o patients. Companies can serve the interests of patients through beneficial collaborations with Health Care Professionals. To ensure that these collaborative relationships meet high ethica standards, they must be conducted with appropriate transparency and in compliance with applicable laws, regulations and government guidance. AdvaMed recognizes the obligation facilitate ethical interactions between Companies and Health Care Professionals in order to ensure that medical decisions are based on the best interests of the patient. The ethical princ that govern these interactions are the subject of this Code of Ethics.[1] To that end, AdvaMed restates and amends its Code of Ethics and Frequently Asked Questions (collectively "Code Ethics" or "Code"), effective July 1, 2009.

II. Code of Ethics Compliance

All Companies are strongly encouraged to adopt this Code and to implement an effective compliance program – one which includes policies and procedures that foster compliance wi the Code with respect to their interactions with Health Care Professionals related to Medical Technologies. A Company that adopts the Code is strongly encouraged to submit to AdvaM an annual certification that the Company has adopted the Code and has implemented an effe compliance program. This certification must be signed by the Company's Chief Executive Officer and Chief Compliance Officer or individuals with equivalent responsibilities within t certifying Company. AdvaMed will publish on its website a list of those Companies that hav submitted the annual certification.

[1] The principles of the Code are derived from a variety of authorities, including the federal Anti-kickback Statu Throughout the Code, we refer to the concept of an "unlawful inducement" to reflect Anti-kickback Statute prohibitions.

FREQUENTLY ASKED QUESTIONS

REGARDING ADVAMED'S CODE OF ETHICS ON INTERACTIONS WITH HEALTH CARE PROFESSIONALS

SECTION I: PREAMBLE AND GENERAL QUESTIONS

Q1 Why did AdvaMed develop a code distinct from the PhRMA Code on Interactions with Health Care Professionals?

The AdvaMed Code of Ethics is intended to address the unique interactions that occur between Companies and Health Care Professionals, just as the PhRMA Code reflects the nature of interactions between pharmaceutical companies and Health Care Professionals. Distinguishing features in AdvaMed's Code arise primarily from the fact that Companies interact with Health Care Professionals because of the complexity and "hands on" nature of Medical Technologies and the importance of having Health Care Professionals understand how to use the technologies safely and effectively.

Q2 Who are "Health Care Professionals"? Does the term include non-clinical people who make Medical Technology purchasing decisions? Does it include decision-makers within GPOs?

The phrase "Health Care Professionals" is intended to be a broad one. It includes individuals or entities: 1) which are involved in the provision of health care services and/or items to patients; and 2) which purchase, lease, recommend, use, arrange for the purchase or lease of, or prescribe Companies' Medical Technologies in the United States. The phrase Health Care Professional includes both persons providing services (such as licensed physicians) and persons who do not provide services directly but who are involved in the decision to purchase, lease, or recommend a Medical Technology. These individuals include, for example, purchasing agents, physician's practice managers and management within group purchasing organizations ("GPOs").

Q3 Does the Code apply to gifts, meals, refreshments, and other benefits provided by Companies to government employees?

Yes, the Code applies to gifts, meals, refreshments, and other benefits provided by Companies to government employees if the employees are Health Care Professionals. Companies also should be aware that there may be specific legal restrictions on providing gifts and other benefits to government employees, and that these restrictions may, in some cases, be more restrictive than the Code.

Q4 Does the Code cover interactions with Health Care Professionals whose primary place of work is outside the U.S.? Does it cover interactions outside the U.S. with Health Care Professionals who work in the U.S.?

The Code applies to interactions with Health Care Professionals to the extent that they provide services or Medical Technologies in the United States. This would include interactions with Health Care Professionals who work in the United States, even if the interaction occurs outside

Regulation of medical devices

Frequent medical device failures in USA was prevented in 1976 by the Medical Device Amendment

This amendment defined a medical device and empowered the FDA to regulate the devices at all stages of their development and use

A classification system provided a means for the FDA to impose different controls on devices according to the amount of risk presented

- Class I involved products of least risk such as adhesive bandages and manually adjustable hospital beds
- Class II products such as oxygen masks, blood-pressure cuffs, powered wheelchairs were of intermediate risk
- Class III devices are of highest risk such as artificial heart valves or other implants

In addition to governmental regulation, there are other prominent organizations that have developed guidelines for the design and testing of biomaterials (ASTM, ANSI, etc)

These organizations form voluntary consensus standards. Conformation to these standards are voluntary but useful as a direction and tools for self-regulation

Members of governmental bodies who are tasked with approval for new medical devices need to encourage advancement, set aside possible loyalties, avoid conflicts of interests, and evaluating a new product for safety and effectiveness

FDA regulations provide that, based on “valid scientific evidence,” a device shall be found to be “safe”
…when it can be determined…that the probable benefits to health from use of the device for its intended uses and conditions of use…outweigh any probable risks

and that a device shall be found to be “effective”
… when it can be determined … that in a significant portion of the target population, the use of the device for its intended uses and conditions of use…will provide clinically significant results.

As a rule, the FDA requires a sponsor of a new medical product to submit a formal application for approval to market the product after the completion of preclinical studies and phased clinical trials that demonstrate to the agency’s satisfaction that the product is safe and effective. The form and review of that request to initiate human trials and the subsequent marketing application vary according to the classification of the product with reference to categories

The highest category, Class III, includes those devices for which premarket approval is or will be required to determine the safety and effectiveness of the device

Case study

An engineer is being asked by management to suppress data on a product that may delay or prevent FDA approval

The engineer has been asked to do something that violates his responsibility to scientific integrity and public safety which is also illegal

What must he/she do?

a) Inform the manager about the legal and ethical concerns raised by his order to suppress data
b) Inform the higher administrator in the organization
c) Inform the FDA

Although the engineer has a duty to protect public safety that supersedes company loyalty, he/she should weigh and consider possible solutions to the problem that may best meet his responsibilities to all affected parties

The approach to ethical problem solving is to treat the situation as a practical matter that requires a solution

The goal would be to determine a plan that best addresses all conflicting loyalties and obligations

Ethics is not just about judging behaviors as moral or immoral, it also has to do with determining the best course of action

This implies that there is not just one possible right answer

There clearly are wrong answers, but the challenge is more than rejecting these