The United States Holocaust Memorial Museum commemorates the fiftieth anniversary of
The Doctors Trial (the Medical Case of the Subsequent Nuremberg Proceedings)

THE NUREMBERG CODE [from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Nuremberg, October 1946–April 1949. Washington, D.C.: U.S. G.P.O, 1949–1953.]

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Of the ten principles which have been enumerated our judicial concern, of course, is with those requirements which are purely legal in nature — or which at least are so clearly related to matters legal that they assist us in determining criminal culpability and punishment. To go beyond that point would lead us into a field that would be beyond our sphere of competence. However, the point need not be labored. We find from the evidence that in the medical experiments which have been proved, these ten principles were much more frequently honored in their breach than in their observance. Many of the concentration camp inmates who were the victims of these atrocities were citizens of countries other than the German Reich. They were non-German nationals, including Jews and "asocial persons", both prisoners of war and civilians, who had been imprisoned and forced to submit to these tortures and barbarities without so much as a semblance of trial. In every single instance appearing in the record, subjects were used who did not consent to the experiments; indeed, as to some of the experiments, it is not even contended by the defendants that the subjects occupied the status of volunteers. In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. In many cases experiments were performed by unqualified persons; were conducted at random for no adequate scientific reason, and under revolting physical conditions. All of the experiments were conducted with unnecessary suffering and injury and but very little, if any, precautions were taken to protect or safeguard the human subjects from the possibilities of injury, disability, or death. In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death, either as a direct result of the experiments or because of lack of adequate follow-up care.

Obviously all of these experiments involving brutalities, tortures, disabling injury, and death were performed in complete disregard of international conventions, the laws and customs of war, the general principles of criminal law as derived from the criminal laws of all civilized nations, and Control Council Law No. 10. Manifestly human experiments under such

conditions are contrary to "the principles of the law of nations as they result from the usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience."

Whether any of the defendants in the dock are guilty of these atrocities is, of course, another question.

Under the Anglo-Saxon system of jurisprudence every defendant in a criminal case is presumed to be innocent of an offense charged until the prosecution, by competent, credible proof, has shown his guilt to the exclusion of every reasonable doubt. And this presumption abides with the defendant through each stage of his trial until such degree of proof has been adduced. A "reasonable doubt" as the name implies is one conformable to reason — a doubt which a reasonable man would entertain. Stated differently, it is that state of a case which, after a full and complete comparison and consideration of all the evidence, would leave an unbiased, unprejudiced, reflective person, charged with the responsibility for decision, in the state of mind that he could not say that he felt an abiding conviction amounting to a moral certainty of the truth of the charge.

If any of the defendants are to be found guilty under counts two or three of the indictment it must be because the evidence has shown beyond a reasonable doubt that such defendant, without regard to nationality or the capacity in which he acted, participated as a principal in, accessory to, ordered, abetted, took a consenting part in, or was connected with plans or enterprises involving the commission of at least some of the medical experiments and other atrocities which are the subject matter of these counts. Under no other circumstances may he be convicted.

Before examining the evidence to which we must look in order to determine individual culpability, a brief statement concerning some of the official agencies of the German Government and Nazi Party which will be referred to in this judgment seems desirable.

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opening page

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WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the

patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

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Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

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The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004

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THE BELMONT REPORT
ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfillingthis part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

MEMBERS OF THE COMMISSION

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.
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*** Deceased.

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ETHICAL PRINCIPLES & GUIDELINES FOR RESEARCH INVOLVING HUMAN SUBJECTS

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

PART A: BOUNDARIES BETWEEN PRACTICE & RESEARCH

A. BOUNDARIES BETWEEN PRACTICE AND RESEARCH

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergoreview for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.
When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical

practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

PART B: BASIC ETHICAL PRINCIPLES

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The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in

research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and

position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

PART C: APPLICATIONS

C. APPLICATIONS

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended

to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research

entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research,

based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

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(45 CFR 46)
Revised June 18, 1991 (Effective August 19, 1991)
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RESEARCH

[*45 CFR 164.501, 164.508, 164.512(i)*]
[See also *45 CFR 164.514(e), 164.528, 164.532*]

Background

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule as, "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." See 45 CFR 164.501. A covered entity may always use or disclose for research purposes health information which has been de-identified (in accordance with 45 CFR 164.502(d), and 164.514(a)-(c) of the Rule) without regard to the provisions below.

The Privacy Rule also defines the means by which individuals will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them held by covered entities. Where research is concerned, the Privacy Rule protects the privacy of individually identifiable health information, while at the same time ensuring that researchers continue to have access to medical information necessary to conduct vital research. Currently, most research involving human subjects operates under the Common Rule (45 CFR Part 46, Subpart A) and/or the Food and Drug Administration's (FDA) human subject protection regulations (21 CFR Parts 50 and 56), which have some provisions that are similar to, but separate from, the Privacy Rule's provisions for research. These human subject protection regulations, which apply to most Federally-funded and to some privately funded research, include protections to help ensure the privacy of subjects and the confidentiality of information. The Privacy Rule builds upon these existing Federal protections. More importantly, the Privacy Rule creates equal standards of privacy protection for research governed by the existing Federal human subject regulations and research that is not.

How the Rule Works

In the course of conducting research, researchers may obtain, create, use, and/or disclose individually identifiable health information. Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances set forth in the Privacy Rule.

Research Use/Disclosure Without Authorization. To use or disclose protected health information without authorization by the research participant, a covered entity must obtain one of the following:

- Documented Institutional Review Board (IRB) or Privacy Board Approval. Documentation that an alteration or waiver of research participants' authorization for use/disclosure of information about them for research purposes has been approved by an IRB or a Privacy Board. See 45 CFR 164.512(i)(1)(i). This provision of the Privacy Rule might be used, for example, to conduct records research, when researchers are unable to use de-identified information, and the research could not practicably be conducted if research participants' authorization were required.

A covered entity may use or disclose protected health information for research purposes pursuant to a waiver of authorization by an IRB or Privacy Board, provided it has obtained documentation of *all* of the following:

- Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
- A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
- A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
- A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
- The signature of the chair or other member, as designated by the chair, of the IRB or the Privacy Board, as applicable.

The following three criteria must be satisfied for an IRB or Privacy Board to approve a waiver of authorization under the Privacy Rule:

- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  - an adequate plan to protect the identifiers from improper use and disclosure;
  - an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
  - adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except

as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

- The research could not practicably be conducted without the waiver or alteration; and
- The research could not practicably be conducted without access to and use of the protected health information.

- Preparatory to Research. Representations from the researcher, either in writing or orally, that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, *and* representation that protected health information for which access is sought is necessary for the research purpose. See 45 CFR 164.512(i)(1)(ii). This provision might be used, for example, to design a research study or to assess the feasibility of conducting a study.

- Research on Protected Health Information of Decedents. Representations from the researcher, either in writing or orally, that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, *and*, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought. See 45 CFR 164.512(i)(1)(iii).

- Limited Data Sets with a Data Use Agreement. A data use agreement entered into by both the covered entity and the researcher, pursuant to which the covered entity may disclose a limited data set to the reserchер for research, public health, or health care operations. See 45 CFR 164.514(e). A limited data set excludes specified direct identifiers of the individual or of relatives, employers, or household members of the individual. The data use agreement must:

  - Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or disclosure that would violate the Rule if done by the covered entity;
  - Limit who can use or receive the data; and
  - Require the recipient to agree to the following:
    - Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
    - Use appropriate safeguards to prevent the use or disclosure of the

information other than as provided for in the data use agreement;
- Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware;
- Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
- Not to identify the information or contact the individual.

Research Use/Disclosure With Individual Authorization. The Privacy Rule also permits covered entities to use or disclose protected health information for research purposes when a research participant authorizes the use or disclosure of information about him or herself. Today, for example, a research participant's authorization will typically be sought for most clinical trials and some records research. In this case, documentation of IRB or Privacy Board approval of a waiver of authorization is not required for the use or disclosure of protected health information.

To use or disclose protected health information with authorization by the research participant, the covered entity must obtain an authorization that satisfies the requirements of 45 CFR 164.508. The Privacy Rule has a general set of authorization requirements that apply to all uses and disclosures, including those for research purposes. However, several special provisions apply to research authorizations:

- Unlike other authorizations, an authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the "end of the research study;" and

- An authorization for the use or disclosure of protected health information for research may be combined with a consent to participate in the research, or with any other legal permission related to the research study.

Accounting for Research Disclosures. In general, the Privacy Rule gives individuals the right to receive an accounting of certain disclosures of protected health information made by a covered entity. See 45 CFR 164.528. This accounting must include disclosures of protected health information that occurred during the six years prior to the individual's request for an accounting, or since the applicable compliance date (whichever is sooner), and must include specified information regarding each disclosure. A more general accounting is permitted for subsequent multiple disclosures to the same person or entity for a single purpose. See 45 CFR 164.528(b)(3). Among the types of disclosures that are exempt from this accounting requirement are:

- Research disclosures made pursuant to an individual's authorization;

- Disclosures of the limited data set to researchers with a data use agreement under 45 CFR 164.514(e).

In addition, for disclosures of protected health information for research purposes without the individual's authorization pursuant to 45 CFR164.512(i), and that involve at least 50 records, the Privacy Rule allows for a simplified accounting of such disclosures by covered entities. Under this simplified accounting provision, covered entities may provide individuals with a list of all protocols for which the patient's protected health information may have been disclosed under 45 CFR 164.512(i), as well as the researcher's name and contact information. Other requirements related to this simplified accounting provision are found in 45 CFR 164.528(b)(4).

Transition Provisions. Under the Privacy Rule, a covered entity may use and disclose protected health information that was created or received for research, either before or after the compliance date, if the covered entity obtained any one of the following prior to the compliance date:

- An authorization or other express legal permission from an individual to use or disclose protected health information for the research;

- The informed consent of the individual to participate in the research; or

- A waiver of informed consent by an IRB in accordance with the Common Rule or an exception under FDA's human subject protection regulations at 21 CFR 50.24.

However, if a waiver of informed consent was obtained prior to the compliance date, but informed consent is subsequently sought after the compliance date, the covered entity must obtain the individual's authorization as required at 45 CFR 164.508. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization would be required before the covered entity could use or disclose protected health information for the research after the waiver of informed consent was no longer valid.

The Privacy Rule allows covered entities to rely on such express legal permission, informed consent, or IRB-approved waiver of informed consent, which they create or receive before the applicable compliance date, to use and disclose protected health information for specific research studies, as well as for future unspecified research that may be included in such permission.

History of the FDA

By John P. Swann, Ph.D.
FDA History Office
(adapted from George Kurian, ed., *A Historical Guide to the U.S. Government* (New York: Oxford University Press, 1998))

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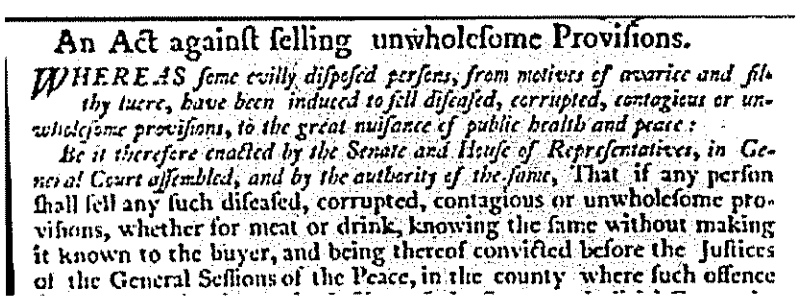
The U S. Food and Drug Administration is a scientific, regulatory, and public health agency that oversees items accounting for 25 cents of every dollar spent by consumers. Its jurisdiction encompasses most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer, medical, and occupational use, cosmetics, and animal feed. The agency grew from a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately 9,100 employees and a budget of $1.294 billion in 2001, comprising chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, D. C. area, staffing over 150 field offices and laboratories, including five regional offices and 20 district offices. Agency scientists evaluate applications for new human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs. Also, the FDA monitors the manufacture, import, transport, storage, and sale of about $1 trillion worth of products annually at a cost to taxpayers of about $3 per person. Investigators and inspectors visit more than 16,000 facilities a year, and arrange with state governments to help increase the number of facilities checked.

Beginning as the Division of Chemistry and then (after July 1901) the Bureau of Chemistry, the modern era of the FDA dates to 1906 with the passage of the Federal Food and Drugs Act; this added regulatory functions to the agency's scientific mission. The Bureau of Chemistry's name changed to the Food, Drug, and Insecticide Administration in July 1927, when the nonregulatory research functions of the bureau were transferred elsewhere in the department. In July 1930 the name was shortened to the present version. FDA remained under the Department of Agriculture until June 1940, when the agency was moved to the new Federal Security Agency. In April 1953 the agency again was transferred, to the Department of Health, Education, and Welfare (HEW). Fifteen years later FDA became part of the Public Health Service within HEW, and in May 1980 the education function was removed from HEW to create the Department of Health and Human Services, FDA's current home. To understand the development of this agency is to understand the laws it regulates, how the FDA has administered these laws, how the courts have interpreted the legislation, and how major events have driven all three.

States exercised the principal control over domestically produced and distributed foods and drugs in the 19th century, control that was



An Act againſt ſelling unwholeſome Proviſions.

WHEREAS ſome evilly diſpoſed perſons, from motives of avarice and filthy lucre, have been induced to ſell diſeaſed, corrupted, contagious or unwholeſome proviſions, to the great nuiſance of public health and peace:

Be it therefore enacted by the Senate and Houſe of Repreſentatives, in General Court aſſembled, and by the authority of the ſame, That if any perſon ſhall ſell any ſuch diſeaſed, corrupted, contagious or unwholeſome proviſions, whether for meat or drink, knowing the ſame without making it known to the buyer, and being thereof convicted before the Juſtices of the General Seſſions of the Peace, in the county where ſuch offence

markedly
inconsistent from state to state. The illustration at right shows an act passed by Massachusetts, which led the way in state-sponsored food and drug laws. The Vaccine Act of 1813, though short-lived, was the first federal law dealing with consumer protection and therapeutic substances. Federal authority was limited mostly to imported foods and drugs. Adulteration and misbranding of foods and drugs had long been a fixture in the American cultural landscape, though the egregiousness of the problems seemed to have increased by the late 19th century (or at least they became more identifiable). By this time science had advanced significantly in its ability to detect this sort of fraud. Also, legitimate manufacturers were becoming more concerned that their trade would be undermined by purveyors of deceitful goods. Quinine-containing cinchona bark powder could be made less therapeutically effective--and much more profitable--by cutting it with just about anything, alum and clay masked poor wheat flour and thus netted a heftier return for the unethical company, and sufferers of any number of serious or self-limited diseases were relieved only of their finances by vendors of worthless nostrums. Even the so-called ethical drug firms were guilty of this practice.

The Division of Chemistry began investigating the adulteration of agricultural commodities as early as 1867. When Harvey Washington Wiley arrived as chief chemist in 1883, the government's handling of the adulteration and misbranding of food and drugs took a decidedly different course, which eventually helped spur public indignation at the problem. Wiley expanded the division's research in this area, exemplified by *Foods and Food Adulterants,* a ten-part study published from 1887 to 1902. He demonstrated his concern about chemical preservatives as adulterants in the highly publicized "poison squad" experiments, in which able-bodied volunteers consumed varying amounts of questionable food additives to determine their impact on health. And Wiley unified a variety of groups behind a federal law to prohibit the adulteration and misbranding of food and drugs, including state chemists and food and drug inspectors, the General Federation of Women's Clubs, and national associations of physicians and pharmacists.

Harvey Wiley, third from right, is photographed with his staff from the Division of Chemistry, U.S. Department of Agriculture, not long after he arrived in Washington in 1883.

Next: The 1906 Food and Drugs Act and Its Enforcement

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The 1906 Food and Drugs Act and Its Enforcement

While Wiley was stumping for a law, muckraking journalists such as Samuel Hopkins Adams exposed in vivid detail the hazards of the marketplace. In fact, the nauseating condition of the meat-packing industry that Upton Sinclair captured in *The Jungle* was the final precipitating force behind both a meat inspection law and a comprehensive food and drug law. (A poster of the 1913 movie adaptation of Sinclair's novel is pictured at right, courtesy of the Sinclair Archives, Lilly Library, Indiana University, through James Harvey Young's *Pure Food: Securing the Federal Food and Drugs Act of 1906.)* Since 1879, nearly 100 bills had been introduced in Congress to regulate food and drugs; on 30 June 1906 President Roosevelt signed the Food and Drugs Act, known simply as the Wiley Act, a pillar of the Progressive era.

This act, which the Bureau of Chemistry was charged to administer, prohibited the interstate transport of unlawful food and drugs under penalty of seizure of the questionable products and/or prosecution of the responsible parties. The basis of the law rested on the regulation of product labeling rather than pre-market approval. Drugs, defined in accordance with the standards of strength, quality, and purity in the *United States Pharmacopoeia* and the *National Formulary,* could not be sold in any other condition unless the specific variations from the applicable standards were plainly stated on the label. Foods were not defined according to analogous standards, but the law prohibited the addition of any ingredients that would substitute for the food, conceal damage, pose a health hazard, or constitute a filthy or decomposed substance. Interpretations of the food provisions in the law led to many, sometimes protracted, court battles. If the manufacturer opted to list the weight or measure of a food, this had to be done accurately. Also, the food or drug label could not be false or misleading in any particular, and the presence and amount of eleven dangerous ingredients, including alcohol, heroin, and cocaine, had to be listed.

The bureau's regulatory emphasis under Wiley centered on foods, which he believed posed a greater public health problem than adulterated or misbranded drugs. Wiley generally held a dim view of chemical additives to foods, championing an approach that considered most to be unnecessary adulterants. On this he clashed often with Secretary of Agriculture James Wilson, and on occasion President Roosevelt himself had to decide government policy on food regulation. Wiley's personal administrative authority under the act was diluted early on when Wilson created a Board of Food and Drug Inspection in 1907 to establish agency policy in enforcing the law. Similarly, the creation of the Referee Board of Consulting Scientific Experts in the following year to

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advise the department on safety issues associated with food additives undercut Wiley's scientific authority. The bureau had been developing informal standards for many foods in collaboration with outside experts since 1903, an activity that continued after the 1906 act. However, courts differed on the role these informal standards could play in cases. Separate laws established standards for some specific foods, such as apples and butter, as well as for canned foods.

Burton J. Howard, chief of the Bureau of Chemistry's microchemical laboratory, is shown in the right foreground in this photo from the 1920s. Howard developed a quantitative method to detect mold in ketchup that proved to be indispensable in establishing food adulteration in court.

After Wiley's resignation in 1912, the bureau devoted more effort to drug regulation, with some emphasis on the so-called patent medicines. While the law was much clearer about drug standards than standards for foods, misbranding was the source of considerable controversy in the regulation of drugs. A year earlier the Supreme Court ruled that the law did not--contrary to the government's interpretation--apply to false therapeutic claims. An amendment in the year of Wiley's resignation attempted to correct the language of the law. But it put the bureau in the difficult position of attempting to prove in court that manufacturers of drugs labeled with false therapeutic claims intended to defraud consumers. The bureau lost several cases against egregious products, but seizures of misbranded and adulterated drugs nevertheless increased in the 1920s and 1930s.

Next: The 1938 Food, Drug, and Cosmetic Act

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The 1938 Food, Drug, and Cosmetic Act

With the election of Franklin Roosevelt and the death in 1930 of the embodiment of the 1906 act--Wiley--the FDA now had a receptive ear to petition for needed changes in the law: legally mandated quality and identity standards for foods, prohibition of false therapeutic claims for drugs, coverage of cosmetics and medical devices, clarification of the FDA's right to conduct factory inspections, and control of product advertising, among other items. A new generation of muckraking journalists and consumer protection organizations aided in pushing a reluctant Congress to sponsor a bill to replace the old law. The FDA itself exemplified the state of affairs in the marketplace by assembling a collection of products that illustrated shortcomings in the 1906 law. It included Banbar, a worthless "cure" for diabetes that the old law protected; Lash-Lure, an eyelash dye that blinded some women (see illustration at right); numerous examples of foods deceptively packaged or labeled; Radithor, a radium-containing tonic that sentenced users to a slow and painful death; and the Wilhide Exhaler, which falsely promised to cure tuberculosis and other pulmonary diseases. A reporter dubbed this exhibit "The American Chamber of Horrors," a title not far from the truth since all the products exhibited were legal under the existing law.

Languishing in Congress for five years, the bill that would replace the 1906 was ultimately enhanced and passed in the wake of a therapeutic disaster in 1937. A Tennessee drug company marketed a form of the new sulfa wonder drug that would appeal to pediatric patients, Elixir Sulfanilamide. However, the solvent in this untested product was a highly toxic chemical analogue of antifreeze; over 100 people died, many of whom were children. The public outcry not only reshaped the drug provisions of the new law to prevent such an event from happening again, it propelled the bill itself through Congress. This was neither the first nor the last time Congress presented a public health bill to a president only after a therapeutic disaster. FDR (pictured at left) signed the Food, Drug, and Cosmetic Act on 25 June 1938.

The new law brought cosmetics and medical devices under control, and it required that drugs be labeled with adequate directions for safe use. Moreover, it mandated pre-market approval of all new drugs, such that a manufacturer would have to prove to FDA that a drug were safe before it could be sold. It irrefutably prohibited false therapeutic claims for drugs,

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although a separate law granted the Federal Trade Commission jurisdiction over drug advertising. The act also corrected abuses in food packaging and quality, and it mandated legally enforceable food standards. Tolerances for certain poisonous substances were addressed. The law formally authorized factory inspections, and it added injunctions to the enforcement tools at the agency's disposal.

Next: Drugs and Foods Under the 1938 Act and Its Amendments

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Drugs and Foods Under the 1938 Act and Its Amendments

Enforcement of the new law came swiftly. Within two months of the passage of the act, the FDA began to identify drugs such as the sulfas that simply could not be labeled for safe use directly by the patient--they would require a prescription from a physician. The ensuing debate by the FDA, industry, and health practitioners over what constituted a prescription and an over-the-counter drug was resolved in the Durham-Humphrey Amendment of 1951. From the 1940s to the 1960s, the abuse of amphetamines and barbiturates required more regulatory effort by FDA than all other drug problems combined. Furthermore, the new law ushered in a flood of new drugs applications, over 6,000 in the first nine years, and 13,000 by 1962.

Illegal sales of amphetamines and barbiturates occupied more regulatory concern at FDA than all other drug problems combined from the 1940s to the 1960s. Interdiction in some venues required undercover tactics, as indicated here by these two inspectors posing as truck drivers.

A new drug law in that year, the Kefauver-Harris Amendments, derived in large part from hearings held by Senator Estes Kefauver. As with the 1938 act, a therapeutic disaster compelled passage of the new law; in this case the disaster was narrowly averted. Thalidomide, a sedative that was never approved in this country, produced thousands of grossly deformed newborns outside of the United States. The new law mandated efficacy as well as safety before a drug could be marketed, required FDA to assess the efficacy of all drugs introduced since 1938, instituted stricter agency control over drug trials (including a requirement that patients involved must give their informed consent), transferred from the Federal Trade Commission to the FDA regulation of prescription drug advertising, established good manufacturing practices by the drug industry, and granted the FDA greater powers to access company production and control records to verify those practices. Three years later Congress gave the FDA enhanced control over amphetamines, barbiturates, hallucinogens, and other drugs of considerable abuse potential in the Drug Abuse Control Amendments of 1965. That function was consolidated with similar responsibilities in 1968 under an organization that gave rise to the Drug Enforcement Administration.

The first food standards to be issued under the 1938 act were for canned tomato products; by

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the 1960s about half of the food supply was subject to a standard. As food technology changed and the number of possible ingredients--including fortifying nutrients--grew, the agency developed recipe standards for foods, lists of ingredients that could lawfully be included in a product. A food that varied from the recipe would have to be labeled an imitation.

Following hearings in the early 1950s under Representative James Delaney, a series of laws addressing pesticide residues (1954), food additives (1958), and color additives (1960) gave the FDA much tighter control over the growing list of chemicals entering the food supply, putting the onus on manufacturers to establish their safety. Responding to the proliferation of pesticides after World War II, FDA pharmacologists developed the fly bioassay (pictured at right), a rapid and sensitive test that could be used in conjunction with chromatographic procedures to screen a variety of chemicals. While tolerances could be established for many chemicals, a provision of the 1958 law, the Delaney Clause, banned any carcinogenic additive.

FDA pursued numerous cases of food misbranding in the 1950s and 1960s, most deriving from false nutritional claims and unscientific enrichment, with mixed success in the courts. In 1973, following hearings the agency convened to address the vitamin fortification of foods and the claims made for dietary supplements, the FDA issued regulations for special dietary foods, including vitamins and minerals. The public response to these regulations helped lead Congress in 1976 to prohibit the FDA from controlling the potency of dietary supplements, although the agency maintained authority to regulate enriched foods.

Next: Regulating Cosmetics, Devices, and Veterinary Medicine After 1938

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Regulating Cosmetics, Devices, and Veterinary Medicine After

Cosmetics and medical devices, which the Post Office Department and the Federal Trade Commission had overseen to a limited extent prior to 1938, came under FDA authority as well after 1938. While pre-market approval did not apply to devices, in every other sense the new law equated them to drugs for regulatory purposes. As the FDA had to deal with both increasing medical device quackery and a proliferation of medical technology in the post-World War II years, Congress considered a comparable device law when it passed the 1962 drug amendments.

Quack products were the subject of most of FDA's device regulatory actions until the 1960s. Pictured here are assorted versions of orgone accumulators, developed by psychiatrist Wilhelm Reich to collect what he believed was an ethereal substance in the atmosphere vital to health and longevity.

The legislation having failed to develop, the Secretary of HEW commissioned the Study Group on Medical Devices, which recommended in 1970 that medical devices be classified according to their comparative risk, and regulated accordingly. The 1976 Medical Device Amendments, coming on the heels of a therapeutic disaster in which thousands of women were injured by the Dalkon Shield intrauterine device, provided for three classes of medical devices, each requiring a different level of regulatory scrutiny--up to pre-market approval.

The 1938 act required colors to be certified as harmless and suitable by the FDA for their use in cosmetics. The 1960 color amendments strengthened the safety requirement for color additives, necessitating additional testing for many existing cosmetics to meet the new safety standard. The FDA attempted to interpret the new law as applying to every ingredient of color-imparting products, such as lipstick and rouge, but the courts rebuffed this proposal.

Another agency responsibility, veterinary medicine, had been stipulated since the 1906 act; foods included animal feed, and drugs included veterinary pharmaceuticals. Likewise, animal drugs were included in the provisions for new drugs under the 1938 law and the 1962 drug amendments. However, the Food Additives Amendment of 1958 had an impact too, since drugs used in animal feed were also considered additives--and thus subject to the provisions of the food additive petition process. The Delaney Clause prohibiting carcinogenic food additives was modified by the DES

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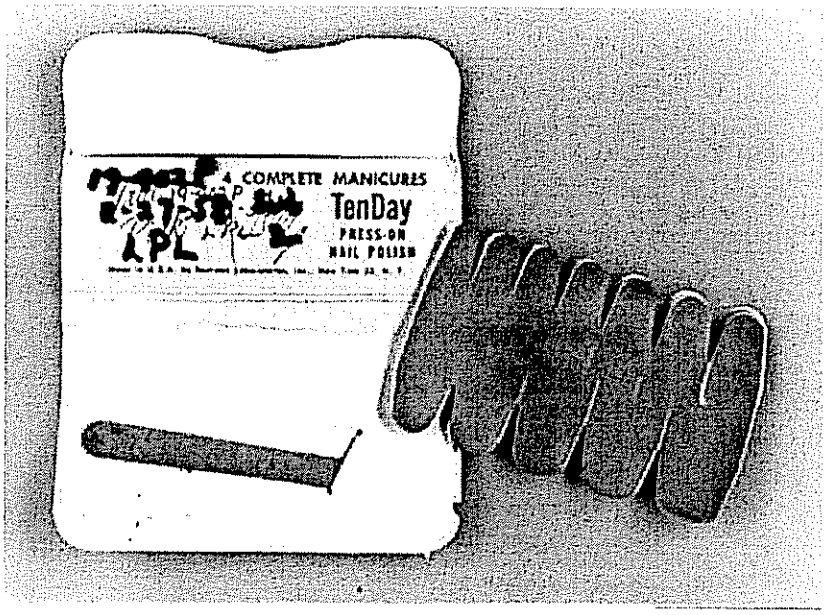
proviso in 1962, named for diethylstilbestrol, a hormone used against miscarriages in humans and to promote growth in food-producing animals. The proviso permitted the use of possible carcinogens in such animals as long as residues of the product did not remain in edible tissues. The Animal Drug Amendments of 1968 combined veterinary drugs and additives into a unified approval process under the authority of the Bureau of Animal Drugs in the FDA.



TenDay Press-On Nail Polish generated at least 700 consumer complaints in 1957, including several cases in which the nails broke off or split down to the quick. In February 1958, following an FDA press release warning against these synthetic nails, the manufacturer launched a nationwide recall of the goods.

Next: Trends in the Last Quarter-Century

History of the FDA

Trends in the Last Quarter-Century

In the late 1960s and 1970s the FDA lost some of its responsibilities but acquired many more. Shortly after the FDA became a part of the Public Health Service, the Department of Health, Education, and Welfare transferred several functions administered by other PHS agencies to the FDA, including regulation of food on planes and other interstate travel carriers, control over unnecessary radiation from consumer and professional electronic products, and pre-market licensing authority for therapeutic agents of biological origin. The latter originated under the predecessor of the National Institutes of Health in the Biologics Control Act of 1902, which followed the deaths of thirteen children from a tetanus-tainted batch of diphtheria antitoxin in St. Louis, and nine pediatric fatalities from similar circumstances in Camden, New Jersey. (At right, a scientist in FDA's Center for Biologics and Research is conducting research on the organism that causes the childhood disease pertussis.) Congress had authorized the FDA to regulate consumer products such as potential poisons, hazardous toys, and flammable fabrics in a number of laws dating back to 1927, but this function was transferred to the Consumer Product Safety Commission in 1973.

Changes in the work of the FDA have come rapidly in the past 20 years, shaped at least in part by political pressure, consumer activism, and industry involvement. Patient advocacy groups influenced a law to stimulate industry interest in developing so-called orphan drugs for rare diseases, and they played a role in the agency's development of accelerated techniques for drug approval, beginning with drugs for AIDS. Congress passed a law that simultaneously extended patent terms to account for time consumed by the drug approval process and facilitated the approval of generic human and animal drugs to offer a lower-cost alternative to brand name pharmaceuticals. Also, Congress instituted procedures for industry to reimburse the FDA for review of drugs and biologics to speed the agency's evaluations.

Other laws have mandated reporting of adverse reactions to medical devices, post-market monitoring of implants and other devices that pose a serious health risk, recall authority for the FDA over medical devices, and certification and annual inspection of mammography facilities. Among food regulatory issues in the past two decades, Congress issued a singular prohibition against the FDA's banning saccharin under the Delaney Clause on the grounds that the sweetener had been shown to cause cancer in laboratory animals; instead, saccharin would have to carry a label warning. In 1990 Congress passed the Nutrition Labeling and Education Act, which completely

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reformulated the way food products convey basic nutritional information. Four years later, after intense lobbying by the dietary supplement industry, Congress permitted supplements to carry substantiated statements about the role of such products in health, provided they issued a disclaimer that FDA had not evaluated the statements. Moreover, the FDA rather than industry had the burden of proving that a dietary supplement was misbranded or adulterated.

The burgeoning interest in reinventing government and regulatory reform in the 1990s very much included the FDA, with the greatest interest focusing on the agency's time spent in evaluating therapeutic and other products. These were by no means original developments, at least as far as FDA was concerned. Numerous Congressional investigations, external and internal committee reports, independent fact-finding missions, and other venues of inquiry have studied the agency's mission and needs through much of the past century: precisely what one would expect for one of the oldest consumer regulatory agencies in the government, with such a broad responsibility for the public health, sometimes covering issues that have polarized large segments of American society. Such issued included sodium benzoate, sulfur dioxide, and other food preservatives during the Wiley era; Banbar in the 1930s; aminotriazole-tainted cranberries in the 1950s; vitamins in the 1970s; and breast implants in the 1990s. But these and other high visibility cases were just a small fraction of the agency's work, arcane to most of the public, but nevertheless a key ingredient in 20th century U.S. history.

Representatives from FDA and the state of Virginia jointly inspect Chesapeake Bay oysters in this photo from the mid-1980s.

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