FEDERAL RESERVE SYSTEM

Formations of, Acquisitions by, and Mergers of Bank Holding Companies

The companies listed in this notice have applied to the Board for approval, pursuant to the Bank Holding Company Act of 1956 (12 U.S.C. 1841 *et seq.*) (BHC Act), Regulation Y (12 CFR Part 225), and all other applicable statutes and regulations to become a bank holding company and/or to acquire the assets or the ownership of, control of, or the power to vote shares of a bank or bank holding company and all of the banks and nonbanking companies owned by the bank holding company, including the companies listed below.

The applications listed below, as well as other related filings required by the Board, are available for immediate inspection at the Federal Reserve Bank indicated. The application also will be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing on the standards enumerated in the BHC Act (12 U.S.C. 1842(c)). If the proposal also involves the acquisition of a nonbanking company, the review also includes whether the acquisition of the nonbanking company complies with the standards in section 4 of the BHC Act (12 U.S.C. 1843). Unless otherwise noted, nonbanking activities will be conducted throughout the United States. Additional information on all bank holding companies may be obtained from the National Information Center website at www.ffiec.gov/nic/.

Unless otherwise noted, comments regarding each of these applications must be received at the Reserve Bank indicated or the offices of the Board of Governors not later than June 8, 2001.

A. Federal Reserve Bank of Philadelphia (Michael E. Collins, Senior Vice President) 100 North 6th Street, Philadelphia, Pennsylvania 19105–1521:

1. Chester Valley Bancorp, Inc., Downingtown, Pennsylvania; to become a bank holding company by acquiring 100 percent of the voting shares of First Financial Savings Assocoation, Downingtown, Pennsylvania.

2. Franklin Financial Services Corporation, Chambersburg, Pennsylvania; to acquire 15.8 percent of the voting shares of American Home Bank, National Association, Lancaster, Pennsylvania.

B. Federal Reserve Bank of Atlanta (Cynthia C. Goodwin, Vice President) 104 Marietta Street, NW., Atlanta, Georgia 30303–2713:

1. Hancock Holding Company, Gulfport, Mississippi; to merge with Lamar Capital Corporation, Purvis, Mississippi, and thereby indirectly acquire voting shares of Lamar Bank, Purvis, Mississippi.

Board of Governors of the Federal Reserve System, May 9, 2001.

Jennifer J. Johnson

Secretary of the Board.

[FR Doc. 01–12167 Filed 5–14–01; 8:45 am]

BILLING CODE 6210–01–S

FEDERAL RESERVE SYSTEM

Sunshine Act Meeting

AGENCY HOLDING THE MEETING: Board of Governors of the Federal Reserve System.

TIME AND DATE: 11 a.m., Monday, May 21, 2001.

PLACE: Marriner S. Eccles Federal Reserve Board Building, 20th and C Streets, NW., Washington, DC 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.

2. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION: Michelle A. Smith, Assistant to the Board; 202–452–3204.

SUPPLEMENTARY INFORMATION: You may call 202–452–3206 beginning at approximately 5 p.m. two business days before the meeting for a recorded announcement of bank and bank holding company applications scheduled for the meeting; or you may contact the Board's Web site at http://www.federalreserve.gov for an electronic announcement that not only lists applications, but also indicates procedural and other information about the meeting.

Dated: May 11, 2001.

Robert deV. Frierson,

Associate Secretary of the Board.

[FR Doc. 01–12316 Filed 5–11–01; 12:27 pm]

BILLING CODE 6210–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Committee on Vital and Health Statistics: Meeting

Pursuant to the Federal Advisory Committee Act, the Department of Health and Human Services announces the following advisory committee meeting.

Name: National Committee on Vital and Health Statistics (NCVHS), Subcommittee on Standards and Security.

Time and Date: 9 a.m. to 5 p.m., May 31, 2001; 9 a.m. to 2 p.m., June 1, 2001.

Place: Room 705A, Hubert H. Humphrey Building, 200 Independence Avenue, SW., Washington, DC 20201.

Status: Open.

Purpose: At this hearing, the subcommittee will hear testimony regarding the process and outcomes for assessing requests for changes to the transaction standards designated under HIPAA, as well as assess industry progress in identifying a consensus standard for electronic signatures.

Notice: In the interest of security, the Department has instituted stringent procedures for entrance to the Hubert H. Humphrey building by non-government employees. Thus, persons without a government identification card will need to have the guard call for an escort to the meeting.

Contact Person for More Information: Substantive program information as well as summaries of meetings and a roster of committee members may be obtained from J. Michael Fitzmaurice, Ph.D., Senior Science Advisor for Information Technology, Agency for Health Care Research and Quality, 2101 East Jefferson Street, #600, Rockville, MD 20852, phone: (301) 594–3938; or Marjorie S. Greenberg, Executive Secretary, NCVHS, National Center for Health Statistics, Centers for Disease Control and Prevention, Room 1100, Presidential Building, 6525 Belcrest Road, Hyattsville, Maryland 20782, telephone (301) 458–4245. Information also is available on the NCVHS home page of the HHS website: *http://www.ncvhs.hhs.gov/* where an agenda for the meeting will be posted when available.

Dated: May 7, 2001.

James Scanlon,

Director, Division of Data Policy, Office of the Assistant Secretary for Planning and Evaluation.

[FR Doc. 01–12211 Filed 5–14–01; 8:45 am]

BILLING CODE 4151–05–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Reports and Guidance Documents; Availability, etc.: Ethical and Policy Issues in International Research; Clinical Trials in Developing Countries

SUMMARY: Notice of Publication of the Executive Summary of the report, ''Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries'', by the National Bioethics Advisory Commission (NBAC)

SUPPLEMENTARY INFORMATION: The President established the National Bioethics Advisory Commission (NBAC) on October 3, 1995 by Executive Order 12975 as amended. The functions of NBAC are as follows:

(a) Provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

(1) The appropriateness of departmental, agency or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

(2) applications, including the clinical applications, of that research.

(b) Identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

(c) Shall not be responsible for the review and approval of specific projects.

(d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC may also identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council. The members of NBAC are as follows:

Harold T. Shapiro, Ph.D., Chair
Patricia Backlar
Arturo Brito, M.D.
Alexander Morgan Capron, LL.B.
Eric J. Cassell, M.D., M.A.C.P.
R. Alta Charo, J.D.
James F. Childress, Ph.D.
David R. Cox, M.D., Ph.D.
Rhetaugh G. Dumas, Ph.D., R.N.
Laurie M. Flynn
Carol W. Greider, Ph.D.
Steven H. Holtzman
Bernard Lo, M.D.
Lawrence H. Miike, M.D., J.D.
Thomas H. Murray, Ph.D.
William C. Oldaker, LL.B.
Diane Scott-Jones, Ph.D.

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries; Executive Summary

Introduction

In recent years, the increasingly global nature of health research, and in particular the conduct of clinical trials involving human participants (1), has highlighted a number of ethical issues, especially in those situations in which researchers or research sponsors from one country wish to conduct research in another country. The studies in question might simply be one way of helping the host country address a public health problem, or they might reflect a research sponsor's assessment that the foreign location is a more convenient, efficient, or less troublesome site for conducting a particular clinical trial. They might also represent a joint effort to address an important health concern faced by both parties.

As the pace and scope of international collaborative biomedical research have increased during the past decade, long-standing questions about the ethics of designing, conducting, and following up on international clinical trials have reemerged. Some of these issues have begun to take center stage because of the concern that research conducted by scientists from more prosperous countries in poorer nations that are more heavily burdened by disease may, at times, be seen as imposing ethically inappropriate burdens on the host country and on those who participate in the research trials. The potential for such exploitation is cause for a concerted effort to ensure that protections are in place for all persons who participate in international clinical trials.

As with other National Bioethics Advisory Commission (NBAC) reports, several issues and activities prompted the Commission's decision to address this topic. First, several members of the public suggested that NBAC's mandate to examine the protection of the rights and welfare of human participants in research extends to international research conducted or sponsored by U.S. interests. In this respect, one particular dimension of research conducted internationally has attracted a great deal of attention, namely whether the existing rules and regulations that normally govern the conduct of U.S. investigators or others subject to U.S. regulations remain appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects.

A second circumstance—the changing landscape of international research—also is relevant. Increasingly, scientists from developing countries are becoming more involved as collaborators in research, as many of the countries from which these investigators come have developed their capacity for technical contributions to research projects and for appropriate ethical review of research protocols. Although the source of funding for such collaborative research is likely to continue to be the wealthier, developed countries, collaborators from developing countries are seeking—justifiably—to become fuller and more equal partners in the research enterprise. Finally, the current landscape of international research also reflects the growing importance of clinical trials conducted by pharmaceutical, biotechnology, and medical device companies. Some observers believe that market forces have pressured private companies to become more efficient in the conduct of research, which may—absent vigilance—compromise the protection of research participants. Although the extent, relevance, and force of these pressures are widely debated, it is clear that such pressures can exist regardless of the funding source.

Scope of This Report

This report discusses the ethical issues that arise when research that is subject to U.S. regulation is sponsored or conducted in developing countries, where local technical skills and other key resources are in relatively scarce supply. Within this context, the Commission's attention was focused on the conduct of clinical trials involving competent adults, in particular those trials—such as Phase III drug studies—that can lead to the development of effective new treatments. Complex and important ethical concerns are likely to be more pressing in clinical trials than in many other types of research investigations; thus, the focus of this report has been limited accordingly. Although much of the discussion in this report is relevant to other types of research, the particular characteristics of research endeavors other than clinical trials probably merit their own ethical assessment.

This report centers on the principal ethical requirements surrounding the conduct of clinical trials conducted by U.S. interests abroad, and in particular the need for such trials to be directly relevant to the health needs of the host country. Other major topics addressed include ethical issues surrounding the choice of research designs, especially in situations where a placebo control is proposed when an established effective treatment is known to exist; issues arising in the informed consent process in cultures whose norms of behavior differ from those in the United States; what benefits should be provided to research participants and by whom after their participation in a trial has ended; and what benefits, if any, should be made available to others in the host community or country. Finally, it makes recommendations about the need for developed countries to assist developing countries in building the capacity to become fuller partners in international research. Until this goal can be met, however, recommendations are made regarding how the United States should

proceed in settings in which systems for protecting human participants equivalent to those of the United States have not yet been established.

Essential Requirements for the Ethical Conduct of Clinical Trials

Many of the ethical concerns regarding the treatment of human participants in international research are similar to those raised in conjunction with research conducted in the United States (2). They include, among others, choosing the appropriate research question and design; ensuring prior scientific and ethical review of the proposed protocol; selecting participants equitably; obtaining voluntary informed consent; and providing appropriate treatment to participants during and after the trial. These concerns are consistent with principles endorsed in many international research ethics documents.

NBAC believes that two types of ethical requirements—substantive and procedural—must be carefully considered and distinguished when human research is conducted, regardless of the location. The principles embodied in the ''Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research'' serve as a foundation for the substantive ethical requirements incorporated into the system of protection of human participants in the United States. The ''Belmont Report'' sets forth three basic ethical principles, which provide an analytical framework for understanding many of the ethical issues arising from research involving human participants: respect for persons, beneficence, and justice. NBAC believes that in order to be ethically sound, research conducted with human beings must, at a minimum, be consistent with the ethical principles underlying the ''Belmont Report''. In addition, ethically sound research must satisfy a number of important procedural requirements, including prior ethical review by a body that is competent to assess compliance with these substantive ethical principles. U.S. research regulations also set forth more specific rules to guide ethics review committees (3) (and researchers) in their work. NBAC believes that when conducting clinical trials abroad, U.S. researchers and sponsors should comply with these substantive ethical requirements for the protection of human research participants.

Recommendation 1.1 lists protections that should be provided for individuals participating in U.S. government-sponsored clinical trials, whether conducted domestically or abroad (4). Although existing U.S. law and regulations impose limits on the extent to which non-federally funded research is subject to oversight, the Commission believes that these requirements should extend to all clinical trials, regardless of who sponsors or conducts them.

Recommendation 1.1

The U.S. government should not sponsor or conduct clinical trials that do not, at a minimum, provide the following ethical protections:

(a) prior review of research by an ethics review committee(s);

(b) minimization of risk to research participants;

(c) risks of harm that are reasonable in relation to potential benefits;

(d) adequate care of and compensation to participants for injuries directly sustained during research;

(e) individual informed consent from all competent adult participants in research;

(f) equal regard for all participants; and

(g) equitable distribution of the burdens and benefits of research.

Recommendation 1.2

The Food and Drug Administration should not accept data obtained from clinical trials that do not provide the substantive ethical protections outlined in Recommendation 1.1.

Responsiveness of the Research to the Health Needs of the Population

Sponsoring or conducting research in developing countries often poses special challenges arising from the combined effects of distinctive histories, cultures, politics, judicial systems, and economic situations. In addition, in countries in which extreme poverty afflicts so many, primary health care services generally are inadequate, and a majority of the population is unable to gain access to the most basic and essential health products and services. As a result of these difficult conditions, the people in these countries are often more vulnerable in situations (such as clinical trials) in which the promise of better health seems to be within reach.

Whether the research sponsor is the U.S. government or a private sector organization, some justification is needed for conducting research abroad other than a less stringent or troublesome set of regulatory or ethical requirements. Moreover, when the United States (or any developed country) proposes to sponsor or conduct research in another country when the same research could not be conducted ethically in the sponsoring country, the ethical concerns are more profound, and the research accordingly requires a more rigorous justification.

To meet the ethical principle of beneficence, the risks involved in any research with human beings must be reasonable in relation to the potential benefits. Plainly, the central focus of any assessment of risk is the potential harm to research participants themselves (in terms of probability and magnitude), although risks to others also are relevant. The potential benefits that are weighed against such risks may include those that will flow to the fund of human knowledge as well as to those now and in the future whose lives may be improved because of the research. In addition, some of the benefits must also accrue to the group from which the research participants are selected. NBAC understands the principle of justice to require that a population, especially a vulnerable one, should not be the focus of research unless some of the potential benefits of the research will accrue to that group after the trial. Thus, in the context of international research—and particularly when the population of a developing country has been sought as a source of research participants—U.S. and international research ethics require not merely that research risks are reasonable in relation to potential benefits, but also that they respond to the health needs of the population being studied. This is because, according to the principles of beneficence and justice, only research that is responsive to these needs can offer relevant benefits to the population.

Recommendation 1.3

Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country.

Choosing a Research Design and the Relevance of Routine Care

Making a determination about the appropriate design for a clinical trial depends on various contextual considerations, so that what might be an ethically acceptable design in one situation could be problematic in another. For example, it might be unethical to conduct a clinical trial for a health condition in a country in which that condition is unlikely to be found. In comparison, the same trial might be quite appropriately conducted where the trial results could be important to the local population. A more challenging question is whether a research design that could not be ethically implemented in the sponsoring country can be ethically justified in a host country when the health problem

being addressed is common to both nations.

In this report, NBAC is especially interested in exploring the following question: Can a research design that could not be ethically implemented in the sponsoring, developed country be ethically justified in the country in which the research is conducted? In all cases, there is an ethical requirement to choose a design that minimizes the risk of harm to human participants in clinical trials and that does not exploit them. Because the choice of a study design for any particular trial will depend on these and other factors, it would be inappropriate—indeed wrong—to prescribe any particular study design as ethical for all research situations. Nevertheless, under certain, specified conditions, one or another design can be held to be ethically preferable.

Recommendation 2.1

Researchers should provide ethics review committees with a thorough justification of the research design to be used, including the procedures to be used to minimize risks to participants.

Providing Established Effective Treatment as the Control

From the perspective of the protection of human participants in research, one of the most critical issues in clinical trial design concerns the use and treatment of control groups, which often are an essential component in methodologies used to guard against bias. Although placebos are a frequently used control for clinical trials, it is increasingly commonplace to compare an experimental intervention to an existing established effective treatment. These types of studies are called active-control (or positive control) studies, which are often extremely useful in cases in which it would not be ethical to give participants a placebo because doing so would pose undue risk to their health or well-being.

Within the context of active treatment concurrent controls, it is useful to consider whether, and if so under what circumstances, researchers and sponsors have an obligation to provide an established effective treatment to the control group even if it is not available in the host country. This report adopts the phrase an established effective treatment to refer to a treatment that is established (it has achieved widespread acceptance by the global medical profession) and effective (it is as successful as any in treating the disease or condition). It does not mean that the treatment is currently available in that country.

Investigators must carefully explain and ethics review committees must cautiously scrutinize the justification for the selection of the research design, including the level of care provided to the control group. If in a proposed clinical trial the control group will receive less care than would be available under ideal circumstances, the burden on the investigator to justify the design should be heavier. Furthermore, representatives of the host country, including scientists, public officials, and persons with the condition under study, should have a strong voice in determining whether a proposed trial is appropriate.

Recommendation 2.2

Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.

Community Involvement in Research Design and Implementation

Over the past three decades, researchers increasingly have deliberately involved communities in the design of research. In addition, research participants, health advocates, and other members of the communities from which participants are recruited have requested, and in some cases demanded, involvement in the design of clinical trials. By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to health needs of the community involved.

In addition, community consultation can improve the informed consent process and resolve problems that arise in this process because of the use of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study is considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation is particularly important when the researcher does not share the culture or customs of the population from which research participants will be recruited.

Recommendation 2.3

Researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects. Researchers should describe in their proposed protocol how this will be done, and ethics review committees should review the appropriateness of this process. When community representatives will not be involved, the protocol presented to the ethics committee should justify why such involvement was not possible or relevant.

Fair and Respectful Treatment of Participants

The requirement to obtain voluntary informed consent from human participants before they are enrolled in research is a fundamental tenet of research ethics. It was the first requirement proclaimed in the Nuremberg Code in 1947, and it has appeared in all subsequent published national and international codes, regulations, and guidelines pertaining to research ethics, including those in many developing countries.

Nevertheless, discussion is ongoing about the value and importance of particular procedural approaches to informed consent in other countries. Problems involving the interpretation and application of the requirement to obtain voluntary informed consent—and its underlying ethical principles—arise for researchers, ethics review committees, and others. In some countries, the methods used in U.S.-based studies for identifying appropriate groups for study, enrolling individuals from those groups in a protocol, and obtaining informed voluntary consent might not succeed because of different cultural or social norms. Meeting the challenge of developing alternative methodologies requires careful attention to the ethical issues involved in recruiting research participants and obtaining their consent, which is necessary in order to ensure justice in the conduct of research and to avoid the risk of exploitation.

Recommendation 3.1

Research should not deviate from the substantive ethical standard of voluntary informed consent. Researchers should not propose, sponsors should not support, and ethics review committees should not approve research that deviates from this substantive ethical standard.

Disclosure Requirements

The basic disclosure requirements for satisfying the informed consent provisions in U.S. research regulations focus on the information needed by a potential participant in order to decide whether or not to participate in a study. Requirements for disclosure of information in the research setting usually exceed those for disclosure in clinical contexts. Indeed, the extent of disclosure of medical information to patients in clinical settings differs among cultures and can influence judgments about the amount and kind of information that should be disclosed in research settings. In the United States, the requirements for disclosure of information to potential participants in research are specific and detailed (45 CFR 46.116). The Commission has found some evidence that disclosures relating to diagnosis and risk, research design, and possible post-trial benefits are not always clearly presented in clinical trials conducted in developing countries, even though the current U.S. regulations include such requirements. For example, one disclosure requirement in the U.S. regulations focuses on potential benefits: ''a description of any benefits to the subject or to others which may reasonably be expected from the research'' (45 CFR 46.116(a)(1)). Traditionally, such a disclosure has been required to ensure that potential participants understand whether there is any possibility that the intervention itself might benefit them while they are enrolled in the study. There is, however, no specific mention of any possible post-trial benefits in current U.S. regulations. The Commission believes that, because this information is relevant to participants' decisions to participate in the trial, prospective participants should be informed of the potential benefits, if any, that they might receive after the trial is over.

Recommendation 3.2

Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent, with particular attention to disclosures relating to diagnosis and risk, research design, and possible post-trial benefits. Researchers should describe in their protocols and justify to the ethics review committee(s) the procedures they plan to use for disclosing such information to participants.

Recommendation 3.3

Ethics review committees should require that researchers include in the informed consent process and consent documents information about what benefits, if any, will be available to research participants when their participation in the study in question has ended.

Ensuring Comprehension

In some cultures, the belief system of potential research participants does not explain health and disease using the concepts and terms of modern medical science and technology. However, despite this potential barrier to adequate understanding, if they are willing to devote the time and effort to do so, researchers often are often able to devise creative measures to overcome this barrier. Despite the acknowledged difficulties of administering tests of understanding, NBAC supports the idea of incorporating these tests into research protocols.

Recommendation 3.4

Researchers should develop procedures to ensure that potential participants do, in fact, understand the information provided in the consent process and should describe those procedures in their research protocols.

Recommendation 3.5

Researchers should consult with community representatives to develop innovative and effective means to communicate all necessary information in a manner that is understandable to potential participants. When community representatives will not be involved, the protocol presented to the ethics review committee should justify why such involvement is not possible or relevant.

Recognizing the Role of Others in the Consent Process

In some cultures, investigators must obtain permission from a community leader or village council before approaching potential research participants. Yet, it is important to distinguish between obtaining permission to enter a community for the purpose of conducting research and for obtaining individual informed consent. In their reports, NBAC consultants all noted that the role of community leaders or elders is an integral part of the process of recruiting research participants. Although these reports typically use the terminology of consent to refer to the community's permission or a leader's authorization for the researchers to approach individuals, NBAC will use this term to refer to the permission or authorization given by the individual being recruited as a research participant.

The need to obtain permission from a community leader before approaching individuals does not need to compromise the ethical standard requiring the individual's voluntary informed consent to participate in research. Gaining permission from a community leader is no different, in many circumstances, from the common requirement in this country of obtaining permission from a school principal before involving pupils in research or from a nursing home director before approaching individual residents. An ethical problem arises only when the community leader exerts pressure on the community in a way that compromises the voluntariness of individual consent. In NBAC's view, if the political system in a country or the local situation makes it impossible for individuals' consent to be voluntary and that fact is known in advance, then, because U.S. researchers cannot adhere to the substantive ethical standard of informed consent, it would be inappropriate for them to choose such settings.

Recommendation 3.6

Where culture or custom requires that permission of a community representative be granted before researchers may approach potential research participants, researchers should be sensitive to such local requirements. However, in no case may permission from a community representative or council replace the requirement of a competent individual's voluntary informed consent.

Recommendation 3.7

Researchers should strive to ensure that individuals agree to participate in research without coercion or undue inducements from community leaders or representatives.

Family Members

It is customary although not required in some societies for other members of a potential research participant's family to be involved in the informed consent process. For example, in cultures in which men are expected to speak for their unmarried adult daughters and husbands are expected to speak for their wives, a woman may not be permitted to consent on her own behalf to participate in research. In most instances, the need to involve the family is not intended as a substitute for individual consent, but rather as an additional step in the process. In many cases, family members may be

approached before an individual is asked directly to participate in a research project. However, seeking permission from family members without engaging the potential research participants at all clearly departs from the ethical standard of informed consent. On the other hand, potential participants might also choose to involve others, such as family members, in the consent process. Indeed, involving family or community members in the informed consent process need not diminish, and might even enhance, the individual's ability to make his or her own choices and to give informed consent (or refusal).

It is often possible to obtain individual informed consent, which may require and indeed benefit from the involvement of family or community members, while at the same time preserving cultural norms. Such involvement ranges from providing written information sheets for potential participants to take home and discuss with family members to holding community meetings during which information is presented about the research and community consensus is obtained. When the potential participant wishes to involve family members in the consent discussion, the researcher should take appropriate steps to accommodate this desire.

Recommendation 3.8

When a potential research participant wishes to involve family members in the consent process, the researcher should take appropriate steps to accommodate this wish. In no case, however, may a family member's permission replace the requirement of a competent individual's voluntary informed consent.

Consent by Women

A strict requirement that a husband must first grant permission before researchers may enroll his wife in research treats the woman as subordinate to her husband and as less than fully autonomous. In reality, it may be impossible to conduct some research on common, serious health problems that affect only women without involving the husband in the consent procedures. In such cases, a likely consequence would be a lack of knowledge on which to base health care decisions for women in that country. The prospect of denying such a substantial benefit to all women in a particular culture or country calls for a narrow exception to the requirement that researchers use the same procedures in the consent process for women as for men, one that would allow for obtaining the permission of a man in addition to the woman's own consent.

Recommendation 3.9

Researchers should use the same procedures in the informed consent process for women and men. However, ethics review committees may accept a consent process in which a woman's individual consent to participate in research is supplemented by permission from a man if all of the following conditions are met:

(a) it would be impossible to conduct the research without obtaining such supplemental permission; and

(b) failure to conduct this research could deny its potential benefits to women in the host country; and

(c) measures to respect the woman's autonomy to consent to research are undertaken to the greatest extent possible.

In no case may a competent adult woman be enrolled in research solely upon the consent of another person; her individual consent is always required.

Minimizing the Therapeutic Misconception

One barrier to understanding the relevant, important aspects of any proposed research is what has been called the therapeutic misconception. This term refers to the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge. The therapeutic misconception has been documented in a wide range of developing and developed countries.

It is important to distinguish the confusion that arises from the therapeutic misconception from a related consideration. In the research setting, participants often receive beneficial clinical care. In some developing countries, the type and level of clinical care provided to research participants may not be available to those individuals outside the research context. It is not a misconception to believe that participants probably will receive good clinical care during research. But it is a misconception to believe that the purpose of clinical trials is to administer treatment rather than to conduct research. Researchers should make clear to research participants, in the initial consent process and throughout the study, which activities are elements of research and which are elements of clinical care.

Recommendation 3.10

Researchers working in developing countries should indicate in their research protocols how they would minimize the likelihood that potential participants will believe mistakenly that the purpose of the research is solely to administer treatment rather than to contribute to scientific knowledge (see also Recommendation 3.2).

Addressing Procedural Requirements in the Consent Process

A number of issues may arise during the process of obtaining informed consent that require careful scrutiny before determining whether voluntary informed consent can be obtained. These include, for example, determining when it is necessary to obtain written consent and when oral consent should be permitted; when, if ever, it is appropriate to withhold important and relevant information from potential participants; the need in some cultures to obtain a community leader's or a family member's permission before seeking an individual's consent; and standards of disclosure for research participants in cultures in which people lack basic information about modern science or reject scientific explanations of disease in favor of traditional nonscientific beliefs.

In light of the cultural variation that might arise in international clinical trials, the Commission was especially interested in problems that may arise from expecting researchers in developing countries to adhere strictly to the substantive and procedural imperatives of the U.S. requirements for informed consent. NBAC was particularly interested in exploring ways of dealing with the situation that arises when cultural differences between the United States and other countries make it difficult or impossible to adhere strictly to the U.S. regulations that stipulate particular procedures for obtaining informed consent from individual participants. In general, it is important to distinguish procedural difficulties from those that reflect substantive differences in ethical standards. Clearly, more research is needed in this area.

Recommendation 3.11

U.S. research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms. Ethics review committees should grant such waivers only if the research protocol specifies how the researchers and others could verify that research participants have given their voluntary informed consent.

Recommendation 3.12

The National Institutes of Health, the Centers for Disease Control and Prevention, and other U.S. departments and agencies should support research that addresses specifically the informed consent process in various cultural settings. In addition, those U.S. departments and agencies that conduct international research should sponsor workshops and conferences during which international researchers can share their knowledge of the informed consent process.

Access to Post-Trial Benefits

Discussions of the ethics of research with human beings usually center on issues regarding research design and approval and how individuals' rights and welfare are protected when they are enrolled in research protocols. The same has been true of the U.S. regulations, which only tangentially address what happens after a research project has ended by requiring that research participants must be informed in advance about what compensation, if any, will be provided if they are injured during the course of the research. Other questions about what should happen after a trial is completed are left unaddressed by U.S. guidelines.

Thus, central questions in the context of international research include the following: What benefits (in the form of a proven, effective medical intervention) should be provided to research participants, and by whom, after their participation in a trial has ended, and what, if anything, should be made available to others in the host community or country? Although these questions are relevant in terms of the ethical assessment of research—regardless of where the research is conducted—they are being posed with special force, especially regarding serious diseases that affect large numbers of people in developing countries. Therefore, the question of what benefits, if any, research sponsors should make available to participants or others in the host country at the conclusion of a clinical trial is particularly significant for those who live in developing countries in which neither the government nor the vast majority of the citizenry can afford the intervention resulting from the research. Of course, this is especially germane when a drug is proven to be effective in a clinical trial.

An ethically relevant feature that distinguishes most developing from developed countries is the lack of access to adequate health care by a large majority of the population. Many developed countries have long provided universal access to primary health care through a national health service or government-based insurance system. However, in the developing world, especially in the poorest countries in Africa and Asia, substantially fewer health care services are available (if any), and where they are available, access is severely limited. Access to health care is an important issue in research ethics, because an ethically appropriate clinical trial design requires an assessment of the level and nature of care or treatment available outside the research context, as well as any possible future health benefits that might arise from the research.

Recognizing that it is sometimes difficult to distinguish research from treatment when routine health care is inadequate or nonexistent, it cannot be denied that it may be difficult for participants, whose health status may be altered by their participation in a clinical trial, to distinguish between participating in research and receiving clinical care. Consequently, if all interventions by the research team cease at the end of a trial, participants may experience a loss and feel that the researchers in their clinical role have abandoned them. This sense of loss can take several forms, the starkest of which arises when participants are left worse off at the conclusion of the trial than they were before the clinical trial began. Being worse off does not mean that they were harmed by the research. It can simply mean that their medical condition has deteriorated because they were in what turned out to be the less advantageous arm of the protocol. Such an outcome—particularly when participants are worse off than they would have been had they received standard treatment or if they had been in the other arm of the trial—underlines the extent to which any research project can depart from the Hippocratic goal of ''first, do no harm,'' despite the best intentions and efforts of all concerned. When such a result occurs, efforts to restore participants at least to their pretrial status could be regarded as attempts to reverse a result that would otherwise be at odds with the ethical principles of nonmaleficence and beneficence.

Ironically, people who have benefited from an experimental intervention may also experience a loss if the intervention is discontinued when the project ends. It might be said that this is a risk the participant accepted by enrolling in the trial. But participants who are ill when they enter the research protocol may not be able to appreciate fully how they will feel when they face a deterioration in their medical condition (once the trial is completed) after having first experienced an improvement, even if the net result is a return to the status quo ante. One of the ways to mediate or reduce the burden of such an existential loss (the experience of loss as perceived by the research participant) and to sustain an appropriate level of trust between potential participants and the research enterprise is to continue to provide to research participants an intervention that has been shown to be efficacious in the clinical trial if they still need it once the trial is over.

Recommendation 4.1

Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.

Providing Benefits to Others

Once it is recognized that research projects should sometimes arrange to provide post-trial benefits to participants, a question arises about the justice of differentiating between former trial participants and others in the host community who need similar medical treatments. Is the distinction between former research participants and those who were not merely arbitrary? Applying a competing concept of justice, typically referred to as the principle of fairness—treat like cases alike, and treat different cases differently—to this situation requires a consideration of whether family members (or others) who suffer from the same illness as the participants should be treated as ''like cases'' with respect to receiving an effective treatment. Similarly, are the claims to treatment of people who were eligible for and willing to participate in a clinical trial but who for any number of reasons were not selected comparable to the claims of those who were selected? Or are such cases not sufficiently similar because participants undertook the risks and experienced the inconveniences of the research?

In NBAC's view, the relevant distinction between research participants and these other groups of

individuals is that research participants are exposed to the risks and inconveniences of the study. Moreover, a special relationship exists between participants and researchers that does not exist for others. These are the ethical considerations that support the argument to provide effective interventions to research participants after a trial is completed.

On what basis then can one justify an ethical obligation to make otherwise unaffordable (or undeliverable) effective interventions available to members of the broader community or host country? Given that global inequities in wealth and resources are so vast, expecting governmental or industrial research sponsors to seek to redress this particular global inequity is unfair and unrealistic, especially when no such requirement exists in other spheres of international relationships. Typically, it is not the primary purpose of clinical trials to seek to redress these inequities.

Recommendation 4.2

Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves. Where applicable, the investigator should describe any pre-research negotiations among sponsors, host country officials, and other appropriate parties aimed at making such interventions available. In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.

These concerns prompt the question of whether research sponsors should consider implementing arrangements, such as prior agreements (arrangements made before a clinical trial begins that address the post-trial availability of effective interventions to the host community and/or country after the study has been completed), that would allow some of the fruits of research to be available in the host country when the research is over. Such arrangements would be responsive to the health needs of the host country. The parties to these agreements usually include some combination of producers, sponsors, and potential users of research products. Although only a limited number of prior agreements, either formal (legally binding) or informal, are in place in international collaborative research today, it is useful to consider what role such agreements should play in the future.

Recommendation 4.3

Wherever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.

Mechanisms to Ensure the Protection of Research Participants in International Clinical Trials

The two principal approaches used to ensure the protection of human participants in international clinical trials are (1) relying on assurance processes and reviews by U.S. Institutional Review Boards (IRBs) to supplement and enhance local measures or determining that a host country or host country institution has a system of protections in place that is at least equivalent to that of the United States and (2) helping host countries build the capacity to independently conduct clinical trials and to conduct their own scientific and ethical review. In addition, a regulatory provision permits the substitution of foreign procedures that afford protections to research participants that are ''at least equivalent'' to those provided in the Common Rule. Clarification of the scope and limits of these mechanisms and their use would increase public confidence that a valid system of protections is in place for participants in clinical trials conducted abroad.

Negotiating Assurances of Compliance

U.S. researchers or sponsors and their collaborators often encounter difficulties with some of the procedural and administrative aspects of the U.S. research regulations or their implementation and at times perceive U.S. regulations as unnecessarily rigid. Among the many concerns NBAC heard were those relating to the process of negotiating assurances. An assurance is a document that commits an institution to conduct research ethically and in accordance with U.S. federal regulations. An approved assurance is a prerequisite to federally conducted or sponsored research.

In December 2000, the U.S. Office of Human Research Protections (OHRP) launched a new Federalwide Assurance (FWA) and IRB registration process. The process for filing institutional assurances with OHRP for protecting human research participants has been simplified by replacing Single, Multiple, and Cooperative Project Assurances with the FWA, one for domestic research and one for international research. Each legally separate institution must obtain its own FWA, and assurances approved under this process would cover all of the institution's federally supported human research. The proposed system eliminates the assurance documents now in place and replaces them with either a Federalwide Domestic Assurance or a Federalwide International Assurance, covering all federally supported human research.

NBAC was encouraged that OHRP is taking these steps to revise and simplify the current assurance process. It is not clear at this writing, however, whether the new FWA process will eliminate the problems and inconsistencies that exist among agencies such as the Department of Health and Human Services (DHHS), the Agency for International Development, and the Food and Drug Administration (FDA), or the difficulties expressed by researchers who are familiar with the previous assurance system. Moreover, it should be noted that the assurance process itself does not provide a failsafe system of protections. Because weaknesses in this system have been noted in failures at U.S. research institutions, care should be taken not to rely too heavily on this single mechanism to achieve protections abroad, especially when it is not clear that OHRP will provide a visible presence in the host country (through, for example, site visits). However, it will be important to evaluate the success of these new initiatives.

Recommendation 5.1

After a suitable period of time, an independent body should comprehensively evaluate the new assurance process being implemented by the Office for Human Research Protections.

Ethics Review

It is now widely accepted that research involving human participants should be conducted only after an appropriate ethics review has occurred. When research is sponsored or conducted in accordance with U.S. research regulations (and within the boundaries of these regulations), an appropriately constituted and designated IRB is empowered to make these assessments. However, spokespersons from developing countries have maintained that those who live in the countries in which the research is to be conducted are in the best position to decide what is appropriate, rather than those who may be unfamiliar with local health needs

and culture. It is argued that committees that are familiar with the researchers, institutions, potential participants, and other factors associated with a study are likely to provide a more careful and fully informed review than a committee or other group that is geographically displaced or distant and that only local committees can exercise the kind of balanced and reasoned judgment required to review research protocols. The concept of local review has been a cornerstone of the U.S. system for protecting human participants. Whether this standard can or should be applied to research sponsored or conducted abroad was a focus of Commission deliberations.

NBAC found that the requirement for local review is occasionally tested and sometimes weakened when research is conducted in developing countries. In some cases, review by a local committee raises the potential for conflict of interest—or at least a heightened interest in approving research—when it means that valuable research funds would flow to a local institution. Although several developing countries have instituted national research ethics guidelines, and in some countries, ethics review is becoming more established, many difficulties and challenges to local review remain, including lack of experience with and expertise in ethics review principles and processes; conflict of interest among committee members; lack of resources for maintaining the committees; the length of time it can take to obtain approvals; and problems involved with interpreting and complying with U.S. regulations.

In NBAC's view, efforts to enhance collaboration in research must take into account the capacity of ethics review committees in developing countries to review research and the need for U.S. researchers and sponsors to ensure that their research projects, at the very least, are conducted according to the same ethical standards and requirements applied to research conducted in the United States. This has led NBAC to conclude that when clinical trials involve U.S. and foreign interests, these protocols must still be reviewed and approved by a U.S. IRB and by an ethics review committee in the host country, unless the host country or host country institution has in place a system of equivalent substantive ethical protections.

Ideally, equivalent (although not necessarily identical) systems for providing protections to research participants in developing countries would exist at both the national and institutional levels. In countries in which a system equivalent to the U.S. system exists at the national level, some institutions may be incapable of conducting research in accordance with that system. However, it is difficult to conceive of institutional systems being declared equivalent in the absence of an equivalent national system, although it may be possible in a few extremely rare cases. When multiple sponsors are participating in research, possibly all from developed countries, determining which ethics review committees (and how many) are required poses additional complexities. Because there may be legitimate reasons to question the capacity of host countries to support and conduct prior ethics review, NBAC believes that with respect to research sponsored and conducted by the United States, it will be necessary for an ethics review committee from the host country and a U.S. IRB to conduct a review. The FDA's regulatory provisions for accepting foreign studies not conducted under an investigational new drug application or an investigational device exemption do not address whether the foreign nation's system must meet U.S. ethical standards.

Recommendation 5.2

The U.S. government should not sponsor or conduct clinical trials in developing countries unless such trials have received prior approval by an ethics review committee in the host country and by a U.S. Institutional Review Board.

However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.

Recommendation 5.3

The Food and Drug Administration should not accept data from clinical trials conducted in developing countries unless those trials have been approved by a host country ethics review committee and a U.S. Institutional Review Board. However, if the human participants protection system of the host country or a particular host country institution has been determined by the U.S. government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.

Lack of Resources as a Barrier to Ethics Review

Ethics review committees in developing countries may have difficulty complying with U.S. regulations because they lack the funds necessary to carry out their responsibilities. In previous reports, NBAC has recognized that there are costs to providing protection to human participants in research, and researchers and institutions should not be put in the position of having to choose between conducting research and protecting participants. Therefore, an additional means of enhancing international collaborative research is to make the necessary resources available for conducting ethics reviews.

Recommendation 5.4

Federal agencies and others that sponsor international research in developing countries should provide financial support for the administrative and operational costs of host country compliance with requirements for oversight of research involving human participants.

Equivalent Protections

Although many countries have promulgated extensive regulations or have officially adopted international ethical guidelines invoking high standards for research involving human participants, the former Office for Protection from Research Risks (OPRR) never determined that any guidelines or rules from other countries—even countries such as Australia and Canada, where research ethics requirements closely parallel (and to some extent exceed) those of the United States'afford protections equal to those provided by U.S. regulations. If these variations cannot be mediated by joint efforts, difficulties may arise in international research that will prevent important and ethically sound research from going forward.

In June 2000, OHRP became the agency responsible for making determinations of equivalent protections for DHHS. However, to date, OHRP has not provided criteria for determining what constitutes equivalent protections or made any such determinations about other countries' guidelines. In lieu of having developed a process for making equivalent protections determinations, in the past OPRR relied on its usual process for negotiating assurances with foreign institutions to ensure the adequate protection of human participants.

Because the number of U.S.-sponsored studies undertaken in

collaboration with other countries is increasing (including many studies that have different procedural requirements), there is a need to enhance the efficiency of those efforts through increased harmonization and understanding, without compromising the protection of research participants. A way must be found to adhere to widely accepted substantive ethical principles while at the same time avoiding the undue imposition of regulatory procedures that are peculiar to the United States.

Recommendation 5.5

The U.S. government should identify procedural criteria and a process for determining whether the human participants protection system of a host country or a particular host country institution has achieved all the substantive ethical protections outlined in Recommendation 1.1.

Building Host Country Capacity To Review and Conduct Clinical Trials

A unique feature of international collaborative research is the degree to which economically more prosperous countries can enhance and encourage further collaboration by leaving the host community or country better off as a result. The kinds of benefits that could be realized as a result of the collaboration would depend on local health conditions, the state of economic development, and the scientific capabilities of the particular host country. The provision of post-trial benefits to participants or others in the form of effective interventions is one option. The appropriateness of providing a benefit other than the intervention will depend on the nature of the benefit and on the economic and technological state of development of the host country. In most cases, offering assistance to help build local research capacity is another viable option. These two options are not, of course, mutually exclusive. But no matter what form the benefit takes, the ultimate goal of providing it is to improve the welfare of those in the host country.

Approaches to capacity building are related to, but not fully dependent on, the clarification and improvement of current U.S. procedures for ensuring the protection of research participants in international clinical trials. Progress can and should occur simultaneously in both realms. Capacity building to conduct research could include activities undertaken by investigators or sponsors during a clinical trial to enhance the ability of host country researchers to conduct research (e.g., training and education) or to provide research infrastructure (e.g., equipment) so that future studies might proceed. Building capacity to conduct scientific and ethics review of studies, on the other hand, is primarily a matter of providing training and helping to establish systems designed to review proposed protocols and sustain mutually beneficial partnerships with other more experienced review bodies, including U.S. IRBs.

To enhance research collaborations between developing and developed nations, it is important to increase the capacity of resource-poor countries to become even more meaningful partners in international collaborative research. Making the necessary resources available for improving the technical capacity to conduct and sponsor research, as well as the ability to carry out prior ethics review, is one way to move forward in this effort.

Recommendation 5.6

Where applicable, U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing, reviewing, and conducting clinical trials in developing countries. Projects should specify plans for including or identifying funds or other resources necessary for building such capacity.

Recommendation 5.7

Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international collaborative research.

Conclusions

The ethical standards that NBAC is recommending for conducting research in other countries are minimum standards. Host countries might find it worthwhile to adopt human research participant protections that go beyond the protections that are currently provided under the U.S. system if these higher standards further promote the rights, dignity, and safety of research participants as well as the credibility of research results.

Ethical behaviors and commitments are not barriers to the research enterprise. Indeed, ethical behavior is not only an essential ingredient in sustaining public support for research, it is an integral part of the process of planning, designing, implementing, and monitoring research involving human beings. Just as good science requires appropriate research design, consideration of statistical factors, and a plan for data analysis, it must also be based on sound ethical principles. Only then can research succeed in being efficient and cost-effective, while at the same time embodying appropriate protections for the rights and welfare of human participants. Researchers and sponsors should strive to conduct research in the United States and abroad in a way that furthers these aspirations, even though, regrettably, financial, logistical, and public policy obstacles often stand in the way of immediately achieving this goal.

Although the recommendations in this report focus principally on clinical trials conducted by U.S. researchers or sponsors in developing countries, it will be important to consider their application to other areas of research. However, even though many ethical issues that arise in clinical trials also arise in other types of research, the relevance, scope, and implications of NBAC's recommendations in other types of studies may be very different. Similarly, many of the issues and recommendations discussed in this report may equally apply to research conducted in the United States.

The relationships and, ultimately, the level of trust established among individuals, institutions, communities, and countries are determined by complex and often contradictory social, cultural, political, economic, and historical factors. It is essential, therefore, that sponsors, the countries from which they come, and researchers work together to enhance these collaborations by creating an atmosphere that is based on trust and respect. Finally, because attention will continue to focus on the ethical and policy issues that arise in international research in general and regarding clinical trials in particular, this report provides another opportunity for ongoing public dialogue about how to provide appropriate protection to all research participants.

Notes

1. In past reports, the Commission has used the term human subject to describe an individual enrolled in research. This term is widely used and is found in the Federal Policy for the Protection of Human Subjects (45 CFR 46). For many, however, the term subject carries a negative image, implying a diminished position of those enrolled in research in relation to the researcher. NBAC recognizes that merely changing terminology cannot achieve the desired goal of true participation by individuals who volunteer for research, and NBAC does not imply that a truly participatory role is always the case. Nevertheless, for purposes of simplicity and from a desire to encourage a more equal role for research volunteers, in this report the term participants is adopted to describe those who are enrolled in research.

2. An upcoming NBAC report on the oversight of research conducted with human

participants in the United States will address the implications of the findings and conclusions of this report in the context of domestic research.

3. In the United States, committees that review the ethics of human research protocols are referred to in regulation and practice as Institutional Review Boards (IRBs). In other countries, different names might be used, such as research ethics committees or ethics review committees. In this report, references and recommendations that are specific to the United States will refer to these committees as IRBs. References and recommendations that refer to such committees generally regardless of their geographic location will call them ethics review committees.

4. Although these protections are generally meant to apply to all research involving more than minimal risk, there are exceptions in certain guidelines for informed consent to be waived in research involving minimal risk.

FOR FURTHER INFORMATION ABOUT THE REPORT CONTACT: Eric M. Meslin, Ph.D., Executive Director, National Bioethics Advisory Commission, or to obtain copies of the report contact the NBAC office at 6705 Rockledge Drive, Suite 700, Bethesda, Maryland 20892–7979, telephone number (301) 402–4242, fax number (301) 480–6900. Copies may also be obtained through the NBAC website: www.bioethics.gov.

Dated: May 9, 2001.

Eric M. Meslin,

Executive Director, National Bioethics Advisory Commission.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00E–1413]

Determination of Regulatory Review Period for Purposes of Patent Extension; Xenical

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for Xenical and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent that claims that human drug product.

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Regulatory Policy Staff (HFD–007), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product Xenical (orlistat). Xenical is a lipase inhibitor indicated for obesity management that acts by inhibiting the absorption of dietary fats. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for Xenical (U.S. Patent No. 4,598,089) from HLR Technology Corporation, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated August 7, 2000, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of Xenical represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for Xenical is 3,969 days. Of this time, 3,091 days occurred during the testing phase of the regulatory review period, while 878 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) became effective*: June 12, 1988. The applicant claims June 24, 1988, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND effective date was June 12, 1988, which was 30 days after FDA receipt of the IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505 of the act*: November 27, 1996. The applicant claims November 26, 1996, as the date the new drug application (NDA) for Xenical (NDA 20–766) was initially submitted. However, FDA records indicate that NDA 20–766 was submitted on November 27, 1996.

3. *The date the application was approved*: April 23, 1999. FDA has verified the applicant's claim that NDA 20–766 was approved on April 23, 1999.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 1,824 days of patent term extension.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Dockets Management Branch (address above) written comments and ask for a redetermination by July 16, 2001. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by November 15, 2001. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch. Three copies of any information